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September 7–10, 2019 | Barcelona, Spain

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Abstracts

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INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
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2019 World Conference on Lung Cancer

September 7–10, 2019 | Barcelona, Spain

Conquering Thoracic Cancers Worldwide

Invited Speaker Sessions

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NSCLC Lunch Symposium at the IASLC 2019 World Conference on Lung Cancer

MEDICAL CROSSFIRE®

Leveraging the Lung Cancer Team in Stage III NSCLC With Immuno-Oncology Strategies

Sunday, 8 September 2019
Registration and Lunch: 11:30 – 12:00
Program: 12:00 – 13:30

Conference Main Entrance:
Fira de Barcelona – Gran Via
Hall 8 – North Access
Foc, 37
08038 Barcelona

Program Location:
Hall 6
Barcelona (2005)

Chair

Naiyer A. Rizvi, MD
Professor of Medicine
Director, Thoracic Oncology
Co-Director, Cancer Immunotherapy Program
Price Chair, Clinical Translational Research
Columbia University Medical Center
New York, New York, USA

Faculty

Keith M. Kerr, FRCPath
Aberdeen University Medical School
Scotland, United Kingdom

Suresh Senan, MRCP, FRCR, PhD
Amsterdam University Medical Center
Amsterdam, Netherlands

Prof. Dr. Rolf Stahel
University Hospital Zurich
Zurich, Switzerland

Agenda Topics:

- Assessing Treatment Standards for Patients With Unresectable Stage III NSCLC
- **Medical Crossfire®** #1: Applying the Data to Patients With Stage III NSCLC
- **Medical Crossfire®** #2: Practical Concepts and Best Practices With Novel Immunotherapies for Management of Immune-Related Adverse Events
- **Medical Crossfire®** #3: Future Applications for Immunotherapy in Stage I-III NSCLC

Overview:

Medical Crossfire®: Leveraging the Lung Cancer Team in Stage III NSCLC With Immuno-Oncology Strategies will feature expert perspectives on the application of immunotherapy as a component of treatment with curative intent in patients with non–small cell lung cancer (NSCLC). This program will feature a multidisciplinary faculty, including world-renowned experts in medical oncology, radiation oncology, and surgery. Current standards of care in patients with unresectable stage III NSCLC will be addressed, including the role of biomarkers and management of immune-related adverse events. Potential future roles for immunotherapy in stage I-III NSCLC will also be discussed, including incorporation into combined modality regimens and perioperative immunotherapy in patients with resectable disease. Throughout the program, expert **Medical Crossfire®** discussion panels will illustrate how experts address challenges in the implementation of immunotherapy for patients with locally advanced NSCLC. Be sure to join us for this exciting opportunity to improve your practice.

Accreditation/Credit Designation

The **Medical Crossfire®: Leveraging the Lung Cancer Team in Stage III NSCLC with Immuno-Oncology Strategies**, Barcelona, Spain, 08/09/2019-08/09/2019 has been accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 2 European CME credits (ECMEC®s). Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the Union Européenne des Médecins Spécialistes and the American Medical Association, physicians may convert EACCME® credits to an equivalent number of *AMA PRA Category 1 Credits™*. Information on the process to convert EACCME® credit to AMA credit can be found at www.ama-assn.org/education/earn-credit-participation-international-activities.

Live educational activities, occurring outside of Canada, recognised by the UEMS-EACCME® for ECMEC®s are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

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Plenary Sessions

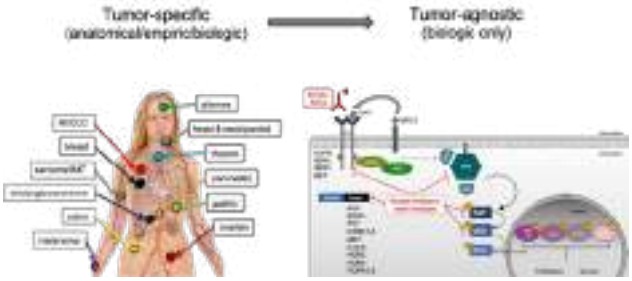
PL01 NEW QUESTIONS WITH IMAGINATIVE ANSWERS
SUNDAY, SEPTEMBER 8 08:15–09:45

PL01.01 TUMOR-AGNOSTIC BIOLOGICALLY DRIVEN TREATMENTS: AN ENDLESS DREAM?

R. Doebele

University of Colorado, Aurora/United States of America

The identification of several oncogenes in non-small cell lung cancer (NSCLC) along with the development of cognate, targeted tyrosine kinase inhibitors (TKIs) has revolutionized the treatment approach for patients with this disease. Several oncogene targets have been successfully deployed in other malignancies, including melanoma (BRAF), GIST (KIT), CML (BCR-ABL) and other malignancies. However, until recently, the conventional wisdom has said that targeted therapies will not have similar efficacy for the same class of oncogenes across different tumor histologies. This point of view was likely largely grounded in two perceptions: 1) certain oncogenes are heavily associated with certain tumor histologies (e.g., BCR-ABL in CML or EGFR in NSCLC) and 2) based on the differential activity of BRAF/MEK inhibition in melanoma compared to colorectal cancers (CRC) harboring BRAF V600E mutations. Since then, BRAF +/- MEK inhibition has demonstrated remarkable response rates in NSCLC, anaplastic thyroid cancer, and hairy cell leukemia suggesting that CRC may be the exception rather than the rule. In 2012, we identified the first NTRK1 fusion in NSCLC,1 and while prior reports of NTRK gene fusions existed, 2 there were no therapies developed for this oncogene. Preclinical *in vitro* and in vivo models suggested that ATP-competitive inhibitors had activity irrespective of NTRK1/2/3 gene (TRKA/B/C kinases) and also irrespective of tumor histology.3 Clinical trial data with the two lead TRK inhibitors, larotrectinib4 and entrectinib, 5 confirmed both of these preclinical findings of activity in NTRK1/2/3 across tumor histologies, validating the concept of tumor (or tissue) agnostic therapeutic strategies in cancer. Similar to NTRK gene fusions, ALK, ROS1 and RET gene fusions have not only been identified in NSCLC, but also in other tumor histologies. Clinical data suggest similar opportunities for these oncogene targets. For examples, entrectinib generated a robust and durable response in a patient with GOPC-ROS1 fusion melanoma6 and similar responses have been noted in ROS1 fusion IMT.7 Basket clinical trials of ROS1 inhibitors are now ongoing. RET gene fusions are targetable alterations in NSCLC as well as other malignancies, and now improved, highly RET-selective inhibitors under development with encouraging activity.8 NRG1 gene fusions represent another opportunity for a tumor agnostic development. Although first described in NSCLC (specifically, invasive mucinous adenocarcinomas),9 these novel fusion genes that signal via HER2/HER3 heterodimers have been described across numerous tumor types, including pancreatic, ovarian, and other cancers, albeit at a low estimated frequency of 0.2%.10 This low frequency is a common reason cited to not pursue such strategies, but given the immense heterogeneity of cancer it is likely that we will further fragment cancer types based on their underlying biology. Additional tumor agnostic targets include ALK gene fusions, HER2 mutations, EGFR mutations (including exon 20 insertions), FGFR1/2/3 fusions, BRAF fusions, MET (exon 14 skipping, gene amplification, and fusions), and others. Indeed, several KRAS mutant selective inhibitors are under development and may open the flood gates for tumor agnostic trials given the frequency of mutations in this oncogene. Success of tumor agnostic strategies will be dictated by appropriate biomarker selection, which may differ for each tumor types, robust testing methods that capture the majority of oncogenic variants (NRG1 is a good example that is not currently covered on many assays), and implementation of panel-based next generation sequencing applications in more routine practice. While it is likely that we already have the testing capability and even the appropriate drugs to to target these tumor agnostic oncogenes, infrastructure changes at institutions may need to be enacted to allow for clinical trial teams that enroll from many disease types, similar to existing phase I teams. The NSCLC community of oncologists, researchers, pathologists, patient advocates, and commercial partners has had immense success in realizing the dream of precision oncology strategies and can lead the way to distribute the knowledge gained over the last decade in precision oncology strategies



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Keywords: oncogene, precision oncology, agnostic

PL01 NEW QUESTIONS WITH IMAGINATIVE ANSWERS
SUNDAY, SEPTEMBER 8 08:15–09:45

PL01.02 THE EVOLUTION OF TISSUE TESTING FOR IMMUNOTHERAPY - WHERE NEXT?

K. Kerr

University of Aberdeen, School of Medicine and Dentistry, Aberdeen/United Kingdom

Biomarkers have, to date, had an uneasy relationship with immunotherapy in lung cancer, a conflict between the degree of biomarker expression (largely PD-L1) being related to treatment efficacy, and a desire to give these drugs to everyone, either as monotherapy or, increasingly, in combination with other drugs. PD-L1 immunohistochemistry (IHC) is well established as a companion or complementary diagnostic, depending on indication, and tumour mutational burden (TMB) is an item of interest, with a surrogate, MSI-high, approved by the FDA in a tumour-type agnostic setting for second/greater line therapy. Where is PD-L1 testing going? PD-L1 IHC will remain a useful test. PD-L1 IHC scoring in cytology-type samples has been validated outside clinical trials and will become accepted in daily practice. New IHC clones will challenge the place of existing ones, hopefully validated by comparative study and EQA. Data are emerging on the clinical validity of PD-L1 scoring on small amounts of tumour (the heterogeneity issue), how few cells can be used, and the clinical impact of scoring PD-L1 on insufficient material. Tumour Mutational Burden Difficulties with the PD-L1 IHC biomarker drove the search for alternatives and TMB, as a several times removed surrogate of tumour immunogenicity, emerged. The place for TMB in the diagnostic algorithm remains uncertain but clinical trials looking at tumour tissue or blood TMB continue to provide promising, if confusing, results. Many of the issues with PD-L1 IHC are also in play with TMB. There is no consensus about what is 'high TMB'? TMB is another biological continuum, like PD-L1 expression, so the creation of a binary high vs low categorization potentially ignores

relative biological significance of different levels. There is huge variability in the methodology used to derive or predict TMB, the amount of the genome screened, different definitions of a 'mutation', different next generation sequencing platforms, different contexts (tumour tissue vs blood) and a lack of published data on how these different TMB assessment approaches vary. Anecdotal reports so far indicate substantial variation. As a predictive biomarker in this setting, TMB works; it enriches a treatment group for benefit. But we have seen relatively little comparative data to suggest superiority over any other singular biomarker in this treatment area. TMB is a crude predictor of tumour neo-antigenicity and perhaps we should look to more specific measures of this aspect of sensitivity to immunotherapy. It is possible to predict probable neo-antigenicity from deep analysis of sequencing data. Neo-antigens should be clonal, rather than subclonal, to maximize their immune impact. Are their particular genes whose alteration would predict greater (or lesser) tumour 'visbility' to the immune system, be they involved in DNA repair, maintaining genome stability or integrity, antigen processing and presentation, or more likely to generate immunogenic proteins? Other factors such as loss of heterozygosity at MHC coding genes may also provide useful information. So, it may well be possible to refine our assessment of TMB into a more specific and meaningful metric. This then raises the question of whether it is practical to do so, and whether this provides clinically useful information. Tumour inflammation For immune checkpoint inhibitors (ICI) to work, a tumour specific immune response must be 'available' and somehow inhibited by the checkpoints being therapeutically targeted. Assessments of tumour inflammation, as a presumptive sign of such an available but inhibited immune response, have been successfully used to enrich a treatment group for benefit from ICI therapy. In lung cancer, these assessments of inflammation have been relatively complex assays of immune gene signature expression using mRNA extracted for fresh/frozen tumour tissue. Initially large panels of immune response-related genes have been reduced to single digit-sized panels. Interferon gamma seems to be important as is, unsurprisingly, PD-L1. The same questions arise with respect to immune gene signatures. Is this any better than a more simplistic approach such as PD-L1 IHC? Evidence is at best marginal, that it would be superior. Is this practical and affordable in a daily practice setting? Probably not. Are there alternative ways to derive the same information? Probably yes. In other tumour sites, a morphological assessment of tumour inflammation has been more keenly pursued than in lung cancer. This approach has tended to focus on the presence and location of the immune cell infiltrate and to some extent, on the nature of the infiltrating cells. When tumour sample area allows, immune cell activity at the tumour-stromal interface, and the presence of CD8-expressing T cells have been associated with better responses to ICI. There is much more that could be investigated, especially in relation to other immune-active or immune-suppressive cell types and their location within the tumour and its microenvironment (TME). Immunohistochemistry is readily available, but in order to understand the complexity of this process and find new biomarkers, in limited tissue samples, multiplex IHC and digital pathology analysis tools will almost certainly be required. These tools already exist but the challenge will be generating the data in relation to clinical response and then deployment in daily practice. Other regulation in the TME Other factors in the TME, such as tissue hypoxia and lactate dehydrogenase, are relevant biomarkers, indicating an immune-suppressive environment, and potential resistance to ICI therapy. Other factors like IDO, and other immune checkpoints like LAG3 and TIM3 may also confer resistance to current ICI therapy and provide new therapeutic targets. Conclusion There is much more to be learned about factors that regulate responsiveness to ICI therapy. The multifactorial complexity of the immune response suggests that combinations of biomarkers are more likely to provide better prediction of therapeutic benefit. Many of these factors are more likely to be continuous variables rather than binary metrics, and oncology will have to learn to deal with this situation, perhaps more akin to a complementary rather than a companion diagnostic, leading to more nuanced therapeutic decisions. It remains to be seen whether oncology, regulatory authorities or industry has an appetite for such an approach. References Blank CU et al. Science 2016;352,658 Camidge DR et al. Nat Rev Clin Oncol 2019;16,341

Keywords: immunotherapy, biomarkers

PL01 NEW QUESTIONS WITH IMAGINATIVE ANSWERS
SUNDAY, SEPTEMBER 8 08:15–09:45

PL01.03 WILL THE IMMUNOTHERAPY WITH NEWER BIOMARKERS, COMBINATION THERAPY OR NEW TECHNOLOGY EVENTUALLY CURE LUNG CANCER?

T. Mitsudomi

Kindai University Faculty of Medicine, Osaka-Sayama/Japan

The recent introduction of immune checkpoint therapy has greatly changed the clinical practice of non-small cell lung cancer (NSCLC). A battery of clinical trials showed the superiority of either PD-1 antibody monotherapy or PD-1/L1 antibody combined with chemotherapy as a first-line treatment of NSCLC over standard platinum doublet chemotherapy that has long been a standard of care. Hence, most if not all of NSCLC patients receive PD-1/L1 antibodies unless contraindicated due to coexisting immune-related comorbidities. The recent update of the Keynote-001 trial showed that 5-year survival of the high expressors of PD-L1 treated with pembrolizumab as a first-line treatment was 23%. Especially, the 5-year survival rate of patients who received the first-line pembrolizumab more than 2 years was 79%. This really indicates that at least some of the NSCLC patients may be cured by monotherapy of PD-1 antibodies. Conversely, about three fourth of patients, even with high expression of PD-L1 cannot survive for more than 5 years. This is natural considering the complexity of immunologic mechanisms against cancer. To be eliminated effectively by PD-1/L1 treatment, cancers should express their unique antigens typically generated by somatic mutations in the context of MHC. Therefore, the adequate quantity as well as the adequate quality of somatic mutations and intact antigen presentation, are prerequisite for immune response. When abnormal peptide is recognized by immune cells, adaptive expression of PD-L1 on the tumor cells occurs by secretion of interferon γ by T cells as a negative feedback that dampens antitumor immunity, Upon binding of PD-L1 with PD-1 on T cells downregulates T cell function. This tumor microenvironment (TME) is the best candidate for anti-PD-1/PD-L1 therapy. However, not all cancer has this TME. Besides PD-1/L1 systems, there are many other molecules such as CTLA4, TIGIT, TIM3, LAG3, etc. that negatively regulate the immune response. Regulatory T cells and myeloid-derived suppressor cells (MDSC) are also major players of immunosuppressive TME To overcome these immunologic evasions, many strategies are being extensively sought. To enhance immune recognition of mutations and to prime new response, polypeptide or RNA-based vaccines that contain mutation-derived epitopes are being tested. For tumor cells that lost HLA molecules, enhancement of NK cell activities through NKG2A antibody or anti KIR antibody may be effective. To overcome adaptive immune resistance by molecules other that PD-1, use of blocking antibodies against above-mentioned other co-inhibitory molecules or agonistic antibodies against co-stimulatory molecules such as ICOS, GITR, 4-1BB, OX40, etc. is a rational way. Finally, to reverse immune suppressive TME, use of antibodies against CSF-1R and CCR4 to suppress MDSC and regulatory T cells, respectively, may be effective. Antagonists for immunosuppressive molecules such as adenosine A2AR, IDO, TGFb, etc are also expected to enhance tumor immunity. Will the Immunotherapy eventually cure lung cancer? Currently, I have to say "Yes, for some but not sure for every patient". In this talk, I would like to discuss ongoing efforts to further improve outcomes of immune-therapy of lung cancer and future perspectives.

Keywords: future strategy, Immunotherapy, new combination

PL01 NEW QUESTIONS WITH IMAGINATIVE ANSWERS
SUNDAY, SEPTEMBER 8 08:15–09:45

PL01.04 ARTIFICIAL INTELLIGENCE, BIG DATA AND LUNG CANCER: READY TO IMPLEMENT?

H. Aerts

Harvard-DFCI, Boston/United States of America

A critical barrier present in cancer research and treatment today is when and how to act based on the information provided from tumor data. One important reason for the slow progress in the fight against cancer, is the fact that cancer is a "moving target". It is constantly evolving and diversifying, changing its phenotype, its genomic composition, and through metastatic spread, even its location. This

is even more true when subjected to the pressure of therapeutic intervention, where cancer evolution rapidly explores and exploits resistance mechanisms, potentially even aided by the mutagenic nature of cancer treatments, leaving the treating oncologist chasing a constantly changing disease. Artificial Intelligence (AI) and Deep Learning technologies have recently led to revolutionary advances in areas ranging from computer vision to speech recognition - tasks that up to a few years ago could only be done by humans. AI has the potential to fundamentally alter the way medicine is practiced, as it excels in recognizing complex patterns in medical data and provides a quantitative, rather than qualitative, assessment of clinical conditions. AI-powered radiographic-biomarkers ("radiomics") may quantify non-invasive information of the cancer phenotype that is clinically actionable, and may further improve diagnosis, characterization, and longitudinal tracking through therapy. AI methods are precise and allow specific quantification of features not otherwise quantifiable by human experts. Radiomic-analysis is performed on the entire tumor as compared to just a small sample for molecular analysis and provides a non-invasive window into internal growth pattern of the tumor (including internal textural heterogeneity, macroscopic necrosis, and viable tumor mass). Radiomics can thus quantify the phenotypic state of a tumor within its evolutionary process, thereby sidestepping issues relating to biopsies. This is particularly important for patients with cancer, where different cancer lesions can express different microenvironments that could ultimately lead to heterogeneous response patterns. Despite the remarkable success of novel cancer therapies, the clinical benefit remains limited to a subset. Cancer therapies are often expensive and could bring unnecessary toxicity, there is a direct need to identify beneficial patients, but this remains difficult in the clinic today. Radiomics biomarkers could provide this information on a lesion and patient level using standard-of-care CT scans. Unlike biopsy assays that - by definition - only represent a sample within the tumor, imaging can depict a full picture of the entire tumor burden, providing information of each cancer lesion within a single non-invasive examination. Another field that will be impacted by AI and big data is radiation oncology. Radiation oncology as a therapeutic specialty presents itself as an exemplary field that will be impacted by AI automation. Especially as much of the current radiation therapy work flow requires time-consuming, manual labor by both radiation oncologists and a team of medical staff including medical physicists, certified medical dosimetrists, and radiation therapists. The growing complexity of the human-machine and human-software interactions in conjunction with the increasing incidences of cancer have created a workforce shortage throughout the world. In fact, variations in the radiation treatment planning process can lead to significant differences in the quality of care, and negatively impact overall survival even in clinical settings where extra care is given to standardizing segmentation and planning approaches. Furthermore, the knowledge and experience gap between more developed and under-resourced health care environments poses an enormous public health challenge and represents one of the great global inequities in cancer care. In this talk, Dr. Aerts will discuss recent developments from his group and collaborators performing research at the intersection of artificial intelligence big data, and oncology. Also, he will discuss recent work of building a computational image analysis system to extract deep learning algorithms and use these to build radiomic signatures. The presentation will conclude with a discussion of future work on building integrative systems incorporating both molecular and phenotypic data to improve cancer therapies.

Keywords: Radiology, Artificial Intelligence, Lung cancer

PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.02 LUNG CANCER SCREENEE SELECTION BY USPSTF VERSUS PLCOM2012 CRITERIA – INTERIM ILST FINDINGS

S. Lam[1], R. Myers[2], M. Ruparel[3], S. Atkar-Khattra[2], E. Stone[4], R. Manser[5], A. Mcwilliams[6], P. Fogarty[7], D. Lam[8], J. Yee[9], J. Mayo[10], C. Berg[11], S. Janes[12], K. Fong[13], M. Tammemagi[14]

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This abstract is under embargo until September 9 10:15 CET

PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.03 EARLY DETECTION OF CANCER OF THE LUNG SCOTLAND (ECLS): TRIAL RESULTS

F. Sullivan[1], S. Schembri[2]

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PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.04 BLOOD MICRORNA AND LDCT REDUCE UNNECESSARY LDCT REPEATS IN LUNG CANCER SCREENING: RESULTS OF PROSPECTIVE BIOMILD TRIAL

U. Pastorino[1], M. Boeri[2], S. Sestini[1], F. Sabia[1], M. Silva[1], P. Suatoni[1], C. Verri[2], A. Cantarutti[3], N. Sverzellati[4], G. Corrao[3], A. Marchianò[5], G. Sozzi[2]

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PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.06 IN HOSPITAL CLINICAL EFFICACY, SAFETY AND ONCOLOGIC OUTCOMES FROM VIOLET: A UK MULTI-CENTRE RCT OF VATS VERSUS OPEN LOBECTOMY FOR LUNG CANCER

E. Lim[1], T. Batchelor[2], J. Dunning[3], M. Shackcloth[4], V. Anikin[5], B. Naidu[6], E. Belcher[7], M. Loubani[8], V. Zamvar[9], T. Brush[10], L. Dabner[10], R. Harris[10], D. Phillips[10], C. Beard[10], H. Mckeon[10], S. Paramasivan[10], D. Elliott[10], A. Realpe Rojas[10], E. Stokes[11], S. Wordsworth[11], J. Blazeby[10], C. Rogers[10], T. Violet Trialists[1]

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PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.08 REGISTRATIONAL RESULTS OF LIBRETTO-001: A PHASE 1/2 TRIAL OF LOXO-292 IN PATIENTS WITH RET FUSION-POSITIVE LUNG CANCERS

A. Drilon[1], G. Oxnard[2], L. Wirth[3], B. Besse[4], O. Gautschi[5], S.W.D. Tan[6], H. Loong[7], T. Bauer[8], Y.J. Kim[9], A. Horiike[10], K. Park[11], M. Shah[12], C. Mccoach[13], L. Bazhenova[14], T. Seto[15], M. Brose[16], N. Pennell[17], J. Weiss[18], I. Matos[19], N. Peled[20], B.C. Cho[21], Y. Ohe[22], K. Reckamp[23], V. Boni[24], M. Satouchi[25], G. Falchook[26], W. Akerley[27], H. Daga[28], T. Sakamoto[29], J. Patel[30], N. Lakhani[31], F. Barlesi[32], M. Burkard[33], V. Zhu[34], V. Moreno Garcia[35], J. Medioni[36], M. Matrana[37], C. Rolfo[38], D.H. Lee[39], H. Nechushtan[40], M. Johnson[41], V. Velcheti[42], E. Olek[43], J. Kherani[43], K. Ebata[43], E. Zhu[43], M. Nguyen[43], X. Huang[43], S. Cruickshank[43], S. Rothenberg[43], B. Solomon[44], K. Goto[45], V. Subbiah[46]

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PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.09 NATIONAL LUNG MATRIX TRIAL (NLMT): FIRST RESULTS FROM AN UMBRELLA PHASE II TRIAL IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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PL02 PRESIDENTIAL SYMPOSIUM INCLUDING TOP 7 RATED ABSTRACTS
MONDAY, SEPTEMBER 9 08:00–10:15

PL02.11 OVERALL SURVIVAL WITH DURVALUMAB PLUS ETOPOSIDE-PLATINUM IN FIRST-LINE EXTENSIVE-STAGE SCLC: RESULTS FROM THE CASPIAN STUDY

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This abstract is under embargo until September 9 10:15 CET

PL03 RELEVANT ASPECTS OF LUNG CANCER MANAGEMENT
TUESDAY, SEPTEMBER 10 09:15–10:45

PL03.01 ESTABLISHING A NURSE LED FOLLOW-UP SERVICE FOR PATIENTS WIH RESECTED EARLY STAGE LUNG CANCER

J. Mitchell, E. Belcher

Oxford University Hospitals NHS Foundation Trust, Oxford/United Kingdom

This abstract is under embargo until September 10 10:45 CET

PL03 RELEVANT ASPECTS OF LUNG CANCER MANAGEMENT
TUESDAY, SEPTEMBER 10 09:15–10:45

PL03.02 BRINGING IMMUNOTHERAPY INTO THE CURATIVE SETTING: EMERGING DATA ON NEOADJUVANT STRATEGIES

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Immunotherapy with checkpoint inhibitors targeting PD-1 and PD-L1, as monotherapy or in combination with chemotherapy, have become standard of care in all patients with advanced lung cancer who do not have an actionable oncogene or contraindication.1, 2 Similarly patients with unresectable stage III non-small cell lung cancer who do not progress through concurrent chemoradiotherapy have improved progression free and overall survival with anti-PD-L1 consolidation therapy.3 In early-stage disease, four randomized phase 3 studies are evaluating the role of adjuvant immunotherapy following standard of care chemotherapy. As is the nature of adjuvant investigation, these studies require years of clinical follow-up and will not mature until sufficient recurrence and/or death events occur. Neoadjuvant therapy has many advantages to the patient and for the sake of science. As a therapy, preop treatment is better tolerated and can be monitored for efficacy by imaging and pathologic regression. In terms of research, the early pathologic response endpoint may accelerate trial readouts. Investigation into pathologic response as a surrogate for survival in lung cancer is ongoing.4 The true excitement about neoadjuvant investigation with immunotherapy and/or chemo-immuno combinations, is the theoretical therapeutic superiority of this approach over an adjuvant approach. This is hypothesized to be due to the tumor with its associated mutation specific neoantigens *in situ* during exposure to the PD-1 treatment, enabling a more robust tumor specific immune response. In pre-clinical mouse models, PD-1 monotherapy is more effective when administered neoadjuvantly versus adjuvantly.5 The first experience with neoadjuvant PD-1 therapy in NSCLC was a small pilot study performed for safety and feasibility of this approach. No unexpected safety signals were noted and unanticipated pathologic regression observed.6 Two additional series with neoadjuvant immunotherapy have been presented, the Lung Cancer Mutation Consortiums experience with PD-L1 monotherapy and the MD Anderson study of PD-1 +/- CTLA-4 therapy. Both studies confirmed this approach is both safe and induces pathologic regression (at times pathologic complete response) in some patients.7, 8 Correlative studies to try to identify predictors of response and resistance are ongoing. PD-L1 expression is not as clearly predictive in this patient population as in advanced disease. Shortly after PD-1 monotherapy was demonstrated to be safe and have some anti-cancer efficacy, many other monotherapy and combination studies launched. Two combination studies rapidly accrued. The combination of carboplatin, a taxane, and a PD-1/L1 agent have been demonstrated by two groups to induce major pathologic regression in the majority of patients.9, 10 In the Spanish Lung Cancer Group study, complete pathologic response was seen in more than 50% of resected patients.10 These studies have spurred a tremendous interest in the best neoadjuvant therapy. There are 4 international phase 3 studies enrolling patients to receiving neoadjuvant chemotherapy with or without immunotherapy (NCT03800134, NCT03456063, NCT03425643, NCT02998528). Many of these studies have pre-specified pathologic response co-primary endpoints that will be evaluable well before classic clinical endpoints. These studies will help substantiate the role of immunotherapy in the preoperative setting and pathologic response as a possible surrogate endpoint. As the international adjuvant immunotherapy efforts wrap up, the research community should commit to enrolling patients on neoadjuvant studies. This is our best chance to improve cure rates in early stage lung cancer – to identify effective therapy for those cancers of a clinical stage to justify induction therapy and adjuvant therapy for those incidentally upstaged at the time of surgery. Within these therapeutic studies are essential biomarker efforts. These efforts are poised to be successful and position the research community to extend investigation into the earliest stages of non-small cell lung cancer, looking to improve cure rates for all stages of disease.

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Keywords: neoadjuvant immunotherapy, adjvuant immunotherapy, Non-Small Cell Lung Cancer

PL03 RELEVANT ASPECTS OF LUNG CANCER MANAGEMENT
TUESDAY, SEPTEMBER 10 09:15–10:45

PL03.03 THE DISPARITY OF LUNG CANCER PREVENTION, DIAGNOSIS AND TREATMENT AROUND THE WORLD... WHAT IS THE ROLE OF IASLC

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Lung cancer is a global health problem that results in over 1.8 million deaths globally each year. Diagnosis at an advanced stage, lack of effective treatment options and disabling co-morbid conditions, have all contributed to the poor outlook for patients with lung cancer. However, there is now new hope in the global fight against lung cancer. Improved understanding of the biology of the disease, early diagnosis and effective therapies have contributed to growing optimism. The International Association for the Study of Lung Cancer (IASLC) has been at the forefront of research and education by bringing together committed scientists, physicians, care providers, epidemiologists, nursing staff and patient communities to increase awareness, develop improved staging systems, fund research for early career researchers, promote development of novel therapies, and educate healthcare professionals at all levels. Tobacco smoking contributes to approximately 85-90% of all cases of lung cancer; while the prevalence of smoking has reduced in many developed countries, it appears to be on the upswing in developing nations. More recently, the introduction of electronic nicotine delivery systems (ENDS) has raised the possibility of creating a new generation of the population addicted to nicotine. Any efforts to reduce the burden of lung cancer has to start with educating the public about the health hazards related to smoking, tobacco cessation programs and reducing the access of teenagers and young adults to tobacco products. Early detection by adopting screening programs will be another important strategy to reduce the burden of lung cancer. In recent years, the reduction in mortality related to lung cancer by adopting low dose CT screening in high risk individuals has been proven beyond doubt. Despite this evidence, only a minority of eligible patients are being screened for lung cancer, even in developed nations. To increase adoption of screening, we have to collectively engage in educating the primary care physicians, subjects at risk and the entire health care community. Diagnosis of lung cancer at earlier stages will result in greater likelihood of cure due to the exciting advances that have taken place in the management of patients with stages I, II and III NSCLC. Even for patients diagnosed with advanced stage lung cancer, long term survival is possible; precision therapies directed to oncogenic molecular events, immune checkpoint inhibitors and multi-modality treatment approaches have all contributed to the recent progress. For patients with mutations in the epidermal growth factor receptor and aberrations in the anaplastic lymphoma kinase gene, the median survival for stage 4 disease is now measured in years with the use of specific targeted treatment approaches. There

are at least five genomic targets in lung adenocarcinoma that can be treated with specific tyrosine kinase inhibitors. It is likely that more genomic mutations will join the list of treatable aberrations, thanks to the rapid pace of drug development. Molecular testing remains critical to the ability to personalize therapies for patients with lung cancer. A recent survey conducted by the IASLC across the world noted several barriers to routine adoption of molecular testing. Finally, access to cutting-edge therapies is a major challenge in several parts of the world. Rising costs of healthcare and medicines have resulted in the inability for patients to receive optimal care. Our efforts to improve lung cancer outcomes and reduce the burden of this disease will have to address every one of these issues. The IASLC is launching an ambitious program to double the 5-year survival rate for patients with lung cancer later this year. This will be accomplished by a multi-pronged approach to promote early detection, optimal staging and diagnostic testing and by addressing survivorship issues. A new staging system seeks to integrate molecular knowledge to traditional clinical staging in order to provide precise prognostic information. Investments in improving the sensitivity of CT screening, promoting universal standards for CT imaging and partnering with other societies to increase awareness regarding early detection will all be important components of this strategy. The IASLC has made major contributions to diagnosis of lung cancer by developing a new pathology classification system for lung cancer; it has also conducted original research to improve biomarker testing and promote education on molecular diagnosis. In the upcoming years, the IASLC will seek to study the correlation between major pathological response with neo-adjuvant therapy and overall survival. This will allow for earlier utilization of exciting novel agents to be used as part of curative therapies for early stage NSCLC. The IASLC will also promote research on issues specific to survivorship; as long-term outcomes for lung cancer patients becomes a reality, it is important to learn about coping with physical and emotional challenges that can be related to their journey. Very little work has been conducted to date on this topic. In conclusion, the time is ripe for us to launch a collective campaign to reduce the burden of lung cancer globally. The IASLC will partner with like-minded organizations, and engage its membership to aggressively pursue innovative approaches that will ultimately result in lower number of patients diagnosed with lung cancer, and improved survival and quality of life for patients afflicted with lung cancer.

PL03 RELEVANT ASPECTS OF LUNG CANCER MANAGEMENT
TUESDAY, SEPTEMBER 10 09:15–10:45

PL03.04 LUNG CANCER AND TUBERCULOSIS: PARALLEL LIVES

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It is a Battlefield. Searching for parallelisms, using historical analogies is a well established method in many fields of soft sciences, medical humanities included. A challenge of seemingly repetitive failure patterns and paradigm shift structures are to be answered in the following imaginary experiment. The aim is the creation of a mental model where understanding of developments and mistakes in treatment of tuberculosis might support our fight against lung cancer (1). The two diseases are existing parallely – one mainly for the poor and young and the other for the richer and older. History of tuberculosis follows the classic algorhythm: diagnostic (Villemin, Virchow), casuistic (Koch) and therapeutical (Waksman/ Streptomycin) stages. The therapeutical phase of lung cancer has been reached without identified cause of the disease. Eradication of the macrosocopic focus by physical interference with the involved tissue mass, in both diseases preceeded medical treatment. Causation is not an absolute sine qua non of an effective treatment, as the tuberculosis-lung cancer analogy also proves. While lung cancer seems to be controlled by an emerging array of new drugs, tuberculosis poses a new challenge. Tuberculosis of the lung is a systemic disease, best treated by drugs with additional surgical removal of the focus of the disease as a last option. The disease has a fairly good chance of around 90% of to be cured (2). The prognostic factors include the functional and immunological reserves of the patient. Stage I to III lung cancer is a local manifestation of a systemic disease without sufficiently identified aetiology. Therapy response is understood at cohort level, but it is unpredictable where the individual patient's fate is concerned. For reasons unknown, mechanical eradication offers the best chance for cure in early stages of the tumour. Some parallelism between tuberculosis and lung cancer might be of interest. In Search of a Character If progress takes a standstill categorization, fever takes over. Lymphnodes are the central elements of the Ghon and Ranke complexes.(3) of the tuberculous lung. The TNM system, a topology approach gyrates around the N status as well. (4). The desire to find a strong characteristic prognostic/predictive element resulted in the Gaffky index (5). The number of Koch bacillus in the sputum as a prognostic tool failed to validate the theory. The discussions of stations and size of lymphnodes in lung cancer (6) might share the fate of the Gaffky index. A Burnt out Case? There are disturbing similarities in the phenomenon of a late relapse/recurrence in both diseases. The dormant Koch bacillus vs exogenous reinfection debate (7) is paralleled by the dormant cancer cell hypothesis (8). Journey without Maps Circulating Koch bacillus, and their prognostic value hotly debated in the 1920s, are comparable to the circulating tumor cell question. The bloodstream journey polemic settled down by 1950, the "seed and and soil" theory of cancer cells is subject of intense research. The Heart of the Matter Till the 1960s all tuberculosis cases seemed to be the same, until atypical tuberculosis was identified and the *Mycobacterium xenopi* lost its stigmatising power (95). Certain phenotypes of the adenocarcinoma *in situ* behaves definitely in a more benign way than any other cell type NSCLC. In 2019, we still do not know what is the single causative agent (if it exists at all) of NSCLC (if it exists at all as a single entity). The Copernican revolution in tumour biology is still awaited. The Power and the Glory Tuberculosis taught us, that the disease affects the body and the soul as well, reflecting to the society around the patient as well. Lung cancer treatment also depend on the immune status of the individual as well as on the protective capabilities of the science and the society. Affordability and avaibility of anticancer treatments/ drugs are key words yet not interchangeable (8). Onco-economy is as a powerful factor as gene sequencing. A scalpel for sale Our techniques to treat lung cancer are rooted in surgery for tuberculosis (1). VATS techniques take their origin in Jacobeus' thoracoscopy and Veress needle. Modern thoracic surgical staplers are derivates of the "Russian machines", Petz staplers adjusted to tuberculotic bronchi. Thoracic surgery practiced in local anesthesia for many decades, is genuine awake/non-intubated thoracic surgery of today. The recent debate over neoadjuvant *vs.* adjuvant therapy reflects to the bygone dispute on resection before or after antituberculous medical treatment. The different modalities are no mutually exclusive options, but complementary ones. The End of the Affair: Conclusion. The main message of tuberculosis to present day oncopulmonologists is that no one can forget the interaction between tumour and patient and his/her socioeconomic status around the pathologically identified focus. References 1.) Molnar TF.,Tuberculosis: mother of thoracic surgery then and now, past and prospectives: a review J Thorac Dis 2018;10(Suppl 22):S2628-S2642 2.) Silva VD, Mello FC, Figueiredo SC. Estimated rates of recurrence, cure, and treatment abandonment in patients with pulmonary tuberculosis treated with a ¬four-drug fixed-dose combination regimen at a tertiary health care facility in the city of Rio de Janeiro, Brazil. J Bras Pneumol 2017;43:113-20. 3.) Ober WB. Ghon but not forgotten: Anton Ghon and his complex. Pathol Annu 1983;18:79-85. 4.) Rusch Crowley J, Giroux DJ, et al. 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Keywords: Lung cancer, Tuberculosis, Medical Humanities

PL04 FOOD FOR THOUGHT IN THE MANAGEMENT OF THORACIC MALIGNANCIES
TUESDAY, SEPTEMBER 10 16:15–17:00

PL04.02 WHAT DOES SURVIVORSHIP MEAN IN THE WORLD OF IMMUNOTHERAPY (PHYSICAL AND FINANCIAL)?

M. Turner

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With improvements in diagnostic, therapeutic, and supportive therapies, the number of cancer survivors continues growing with over 20 million cancer survivors worldwide and an estimated 2/3 of adults with a cancer diagnosis who are anticipated to be alive in 5 years[1]. Due to this increase in survivors, major medical societies such as American Society of Clinical Oncology (ASCO), Institute of Medicine (IOM), and the Society for Immunotherapy of Cancer's (SITC) have highlighted the need for strategies to improve the ongoing care of survivors and survivorship plans.[2] The 4 basic tenets of a survivorship plan are surveillance, prevention, intervention and coordination. Surveillance is aimed at monitoring for recurrence, second cancers, and long term toxicities, prevention of these sequelae if possible, intervention if they are found, and lastly coordination between hospital and community-based doctors is essential for this plan to be effective.[3] These needs are typically communicated to the patient's general practitioner (GP)/primary care physician (PCP) by a "care plan" that outlines the patient's oncology treatment course, potential long-term toxicity, the frequency of follow up visits, scans and links to community resources. New cancer therapies such as immunotherapy has resulted in significantly improved overall survivals in many advanced cancers, including those that had formerly been considered refractory.[6,7,8] However, the short-, intermediate-, and long-term complications of these therapeutic agents are still being identified. Immune-mediated events, for example, can occur immediately after therapy initiation or even up to two years post treatment as a consequence of overstimulation of the immune system leading to autoimmunity with the potential for permanent or long-term sequelae.[4,5] References: 1. https://cancercontrol.cancer.gov/ocs/statistics/statistics.html 2. https://www.canceradvocacy.org/ 3. Denlinger, CS et. Al. Survivorship: Introduction and Definition. J Natl Compr Canc Netw. 2014 Jan; 12(1): 34–45. 4. Sheela S, Kim ES, Mileham KF. Moving away (finally) from doublet therapy in lung cancer: immunotherapy and KEYNOTE-189J Thorac Dis. 2018 Sep;10(9):5186-5189. 5. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 2017; 35:785.

Keywords: Immunotherapy, suvivorship, toxicity

PL04 FOOD FOR THOUGHT IN THE MANAGEMENT OF THORACIC MALIGNANCIES
TUESDAY, SEPTEMBER 10 16:15–17:00

PL04.03 THE RELEVANCE OF AN INTERNATIONAL DATABASE FOR THE STUDY OF THYMIC NEOPLASMS

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Introduction: Until the 8th edition of the AJCC/UICC TNM classification of malignant tumours went into effect, no official stage classification was available for thymic malignancies. Some classification systems had been proposed but were generally developed from a limited number of patients and not usually tested in an independent dataset. The system developed by Dr. Akira Masaoka in 1981 did undergo external validation and was widely adopted. However, the adoption of these proposed systems in different institutions and regions was hampered by a lack of uniform nomenclature and varying interpretations of definitions. The current (8thedition) TNM stage classification for thymic malignancies endorsed by AJCC and UICC was informed by a database with 10,808 cases of thymic malignancies from 105 sites worldwide, compiling cases contributed by ITMIG (including patients from North and South America, European, and Korean (KART) and Chinese (ChART) institutions), Japan (JART), and Europe (ESTS) with funding and coordination by IASLC and Cancer Research and Biostatistics (CRAB), with the specific intent of developing a TNM based staging system for these malignancies. Methods and materials The IASLC Stating and Prognostic Factors Committee - Thymic Domain (SPFC-TD) conducted a web-based cross-sectional survey to assess the implementation of the 8thEdition TNM staging system in the thoracic community. The survey was sent to the major thymic organizations (ITMIG, ESTS, KART, ChART, RYTHMIC, JART) in addition to IASLC membership. A new database to inform the 9thedition TMN staging system is under development to provide updated follow-up from the institutions contributing to the 8thedition database, add additional institutions, and add new cases collected prospectively. Results According to the survey results, the TNM stage classification of thymic tumors has gained a reasonable acceptance in the scientific community, while the Masaoka stage system remains widely employed. An increased attention to the N descriptor seems to have been incorporated. There is high awareness of the new staging system. The current efforts of the Thymic Domain of the IASLC Staging and Prognostic Factors Committee focus on expanding and updating the database used for the 8thedition to further refine the stage definitions and includes updated follow-up on patients from Turkey, the ESTS, JART, ChART and KART, plus data collected prospectively from ChART. Conclusion The database created to inform the 9thedition of TNM staging for thymic malignancies will allow for refinement and adjustment of the 8thedition system and attempt to address any perceived deficiencies of the current system. An overview of the current state of the database will be presented at the meeting in Barcelona.

Keywords: database, staging, Thymic malignancies

PL04 FOOD FOR THOUGHT IN THE MANAGEMENT OF THORACIC MALIGNANCIES
TUESDAY, SEPTEMBER 10 16:15–17:00

PL04.04 PROGNOSTIC FACTORS IN MALIGNANT PLEURAL MESOTHELIOMA

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Malignant pleural mesothelioma (MPM) is a disease for which we are facing difficulties and challenges at many levels from diagnosis over treatment selection and prediction of treatment response to prediction of the prognosis of individual patients. Besides the necessities to obtain an accurate and early diagnosis and to be able to predict the response to a specific treatment, it is equally important to be able to estimate the overall prognosis of a patient as this will also affect treatment decisions. Looking at the research efforts of the last two decades, we see an abundance of studies investigating prognostic markers for MPM, yet to date the most reliable predictors of disease outcome are still the clinical and pathological parameters, which have been used in the past. Probably the most accurate prognostic factor for MPM is the histopathological subtype, with epithelioid MPM being associated with the best prognosis followed by the biphasic subtype and sarcomatoid histology. In addition, it is well recognised that patients presenting with less advanced disease, of younger age and female gender are generally doing better. Some of these factors were combined with additional proposed predictors of outcome into scoring systems suggested by the European Organization for Research and Treatment of Cancer (EORTC, [1]) and the Cancer and Leukemia Group B (CALGB, [2]). Both scores have been subsequently validated and still hold true today, over 20 years later. Since then, many studies have attempted to identify additional prognostic biomarkers. One area of extensive research is the investigation of changes in blood cell ratios, which can be linked to the inflammatory and/or nutritional status of the patients [3, 4]. In terms of inflammation-related indicators of poor outcome, elevated C-reactive protein (CRP), a high neutrophil-to-lymphocyte ratio, and a low lymphocyte-to-monocyte ratio (LMR) have been proposed. Some of these inflammatory markers have also been combined with factors reflecting the nutritional status of patients. For example, has the combination of CRP and albumin been suggested to have prognostic value, as shown in the CRP-to-albumin ratio (CAR) and the modified Glasgow Prognostic Score (mGPS). Another proposed combination is that of albumin and lymphocytes into the Prognostic Nutritional Index (PNI). Additionally, radiological factors, such as tumour volume or pleural thickness measured by CT or MRI alone or as part of prognostic scores (e.g. in combination with other factors such as in the multimodality prognostic score [5]), as well as radiomics approaches have shown prognostic potential [6]. While many of these proposed prognostic factors are often routinely collected during standard clinical work-up and blood tests, prospective

testing in a clinical setting has yet to be attempted. A second area of extensive research in the last decade has been molecular factors, namely the expression of proteins, genes, and microRNAs [3]. Initially, the majority of studies focused on the potential prognostic role of protein expression in tumour tissue. Here, rather frequently, the expression of tyrosine kinases such as epidermal growth factor receptor (EGFR) and c-Met has been investigated, due to the additional potential of targeting those using tyrosine kinase inhibitors. In addition, many cell cycle and apoptosis-related proteins such as p21, p53, survivin or PTEN were evaluated, but in many cases these proteins did not reach significance in multivariate analyses, highlighting that they do not represent independent markers. Other proteins, such as ERCC1 and TS, the target of the antimetabolite drug pemetrexed, did not show consistent results between various studies, hence none of these proteins are used routinely in the clinic. On the level of gene expression, already 15 years ago a 4-gene signature was proposed, which was subsequently independently validated, but never in a prospective fashion. In addition to gene expression, microRNAs have also been proposed to hold prognostic value, but again, independent validation is thus far lacking. While many candidate prognostic biomarkers have been proposed, these tend to be dependent on the histological subtype, and the identification of factors predictive of outcome within the individual histological subgroups of MPM patients remains a major challenge. However, with more genetic profiling of larger datasets becoming available also in MPM, investigators have started to address this issue. By aiming to genetically subclassify pathologically purely epithelioid or sarcomatoid tumours, this resulted in the C1/C2 classification [7] and the e-score and s-score classification [8], as well as the 4 cluster iCluster classification generated based on TCGA data [9]. Besides providing potential novel prognostic factors, the molecular characterization of MPM can also provide us with urgently needed deeper insights into the biology of the different subgroups of MPM, which is likely to allow us to identify novel treatment targets together with respective markers predictive of response. Nevertheless, these exciting recent findings remain to be independently validated, most importantly in a prospective fashion. A closer look at the literature of the last two decades, however, shows us that rather than aiming at validation of proposed prognostic factors, we are inclined to identify novel candidates. In order to move these promising novel candidates from the bench to the bedside, international collaboration to increase cohort sizes as well as prospective validation will be crucial.
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Keywords: Mesothelioma, prognosis, biomarkers

Controversy Session

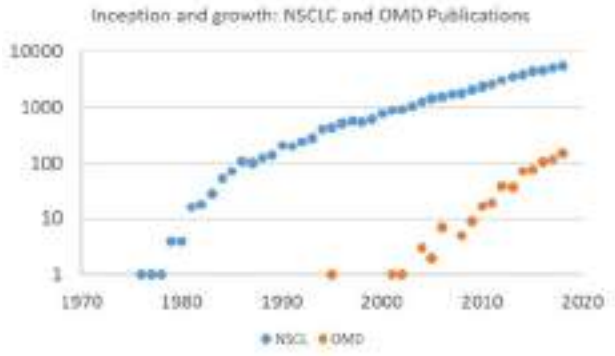
CS01 CONTROVERSIES IN NSCLC OMD
MONDAY, SEPTEMBER 9 11:00–12:30

CS01.01 "HUNTING A GHOST FOR 25 YEARS – WILL WE EVER CATCH OMD?" - NO

T. Treasure

University College London, London/United Kingdom

Oligometastatic disease (OMD) is no more and no less than what it say on the label. It is cancer with few metastases, no more than can be counted on the fingers of one hand. A few metastases can be locally eradicated with surgery, image guided thermal ablation (IGTA) or with stereotactic ablative radiotherapy (SABR) but beyond five it becomes increasingly impractical to attempt local control. Total eradication is unlikely and systemic treatment makes more sense. So five or fewer identified metastases fit a working definition of OMD as treatable by local interventions. 'Framing' disease according to suitability for treatment has always been part of clinical practice. Diagnostic frames shift over time. A classic example is the emergence of 'ESRD' (end stage renal disease) as a diagnosis. 18thC diagnoses depended on clinical descriptions. 'Dropsy' was illness characterised by water retention; what we call oedema. William Withering observed that some of those sick with dropsy were helped by infusions of foxglove. Later Richard Bright discovered protein in the urine of others. At autopsy he found shrivelled kidneys and dropsy had to be reframed, depending on whether it was the heart or the kidneys that were failing. Aetiology, pathophysiology, and histology sequentially framed the many types of kidney disease through the 1960s but effective treatment only became available with dialysis and transplantation. Long-term survival was possible but was too costly for nearly all individuals and their families. In 1972 US Congress passed Public Law 92-603 which framed a new diagnosis: ESRD. Patients with end stage renal disease were entitled to federal funding. In 1974 ESRD appeared for the first time in PubMed in a paper about public financing. ESRD has been used in titles or abstracts 15,282 times since and runs at over a thousand citations a year. Hellman and Weichselbaum proposed the term 'oligometastases' in 1995 to describe a clinical state between freedom from metastases and their 'extensive and widespread' presence. (Figure) A search for <oligometas*> reveals very few publications for about 10 years. Improving resolution of CT, and then PET imaging, allowed the counting of macroscopic metastases by being more confident of the *absence* of further macroscopic metastases. That was a prerequisite to diagnose OMD. Weichselbaum had in mind that "recognition .. of a state of oligometastases is necessary to invite active clinical investigation of new and potentially curative therapeutic strategies". In practical terms it is the therapeutic opportunity that makes OMD a useful working diagnosis, summarised as few enough to 'zap'. In 2015 Joseph Salama surveyed radiation oncologists on their clinical practice and opinions; 99% of 1007 regarded OMD as something for them to treat. It is the feasibility of treatment which characterises OMD. Many diseases are framed and reframed by whether they are amenable to treatment. A familiar example was the emergence of non small-cell lung cancer (NSCLC) as a diagnostic frame. In the 1970s, adenocarcinoma, squamous cell, and large cell anaplastic cancer had 25-30% five-year survival after lobectomy, but surgery for small-cell cancers nearly always failed. Conversely chemotherapy for lung cancer, then associated with modest responses, caused small-cell carcinoma to melt away, if only temporarily. It may seem strange to frame a disease by *what it is not*, but that is how NSCLC was framed. Lung cancer was dichotomised on the basis of response to treatments. We used use 'SBE' for subacute bacterial endocarditis and 'CVA' for cerebrovascular accident. In the modern world of heart surgery and antibiotic resistance, SBE is no longer a serviceable diagnostic frame. We must be specific about organisms, underlying lesions, and prostheses. With therapeutic interventions available for stroke we have to distinguish bleeding from embolism. The catch-all term 'CVA' will no longer serve. In time NSCLC will no doubt be unbundled on the basis of tumour markers, genomics, and targeted treatments. But in an era when we talk of precision medicine, it is remarkable that the 99 patients in SABR-COMET had more than five different primary and secondary sites, bundled as OMD. At Guy's our lung cancer meetings were chaired by a lady radiologist who steered us with incisive clarity. She and I discussed treatment of metastases. She was just back from a trip to the US where she had many similar conversations. "It always ends up with the same question" she told me "Can you charge for it?". So that is the reality. The 1007 radiation oncologists will view the SABR-COMET trial results as the evidence they need. People with ESRD demonstrably survive due to treatment but OMD does no more than identify patients at the tail of the survival distribution, those most likely to live a while longer. Attributing their survival to treatment of a few metastases that can be seen is largely illusory. If sound biological science is the Ghost we seek, we haven't caught it yet.



Keywords: Randomised trials in thoracic oncology, Surgical oncology, Oligometastasectomy

CS01 CONTROVERSIES IN NSCLC OMD
MONDAY, SEPTEMBER 9 11:00–12:30

CS01.02 "HUNTING A GHOST FOR 25 YEARS – WILL WE EVER CATCH OMD?" - YES

J. Belderbos

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The treatment options for NSCLC patients with a limited number of metastases at diagnosis (oligometastatic disease) have increased the past decade. The focus lies at combining systemic- and local radical treatments. With the introduction of oligometastatic disease (OMD) as a separate entity, a more radical treatment approach is increasingly applied. For OMD we distinguish synchronous OMD (in case of OMD at diagnosis) and metachronous OMD (in case of a limited amount of metastases as first event of an initially locally limited disease). There is also the term oligometastatic progression in which case during systemic treatment of a pluri-metastatic disease only few metastases progress. Finally there could be a situation called oligo persistence in case of remaining metastatic lesions. The existing literature is seriously flawed by the lack of consensus on the definition of oligometastatic disease. Often a maximum of 2-3 metastases are referred to as oligometastatic disease, but ≤5 metastases are also selected and considered for radical treatment. Important developments of local consolidative therapies in OMD Since 2016 several retrospective and prospective trials reported favorable progression free survival (PFS) for OMD treated with systemic therapy followed by local consolidative therapy (LCT). The intrathoracic disease is generally locally treated with radical radiotherapy or resection. Treatment of the metastases consists of radical or stereotactic radiotherapy, surgical resection or local ablative therapies. In an observational study radical local treatment for a selected group of NSCLC patients (n=91) with good performance status presenting with synchronous oligometastatic disease resulted in 14 months PFS and 32 months overall survival (OS).These results are comparable to outcomes for stage III NSCLC disease. De Ruysscher et.al. [2] reported a prospective single arm phase II study for synchronous oligometastatic disease treated with radical local treatment (radiotherapy or surgery) after first line chemotherapy. The median PFS and OS in this study were 12.1 months and 13.5 months respectively. After 24 months 15% of the patients did not show disease progression. In a trial Iyengar et al [4] randomized 29 metastatic NSCLC patients with up to 6 sites of extracranial disease (including primary) and a good performance. After induction chemotherapy non-progressive patients were randomized for maintenance chemotherapy or stereotactic

radiotherapy. In an unplanned interim analysis, the median PFS was 9.7 months in the stereotactic radiotherapy arm versus 3.5 months in the maintenance chemotherapy arm. In a randomized phase II trial Gomez included 49 patients with stage IV NSCLC with three or fewer metastases, and no progression after first-line systemic therapy. The trial investigated LCT with stereotactic or conventionally fractionated radiotherapy or surgery versus maintenance therapy or observation. Patients in the LCT arm experienced improved PFS as well as improved OS [5].The trial was closed early because of a significant PFS and OS benefit in the LCT arm. With a median follow-up time of 38.8 months the PFS benefit with additional local therapy was 14.2 months versus 4.4 months in the maintenance therapy/observation arm (p=0.022). They also reported an impressive OS benefit in the LCT arm: 41.2 months versus 17.0 months (p=0.017). This OS benefit was achieved despite the fact that 41% of the patients in the maintenance therapy/observation arm crossed over to the local consolidative therapy arm at the time of progression. No additional grade 3 or greater toxicities were observed. It is important to know that these studies were performed in the pre-immunotherapy era. In patients with metachronous OMD (controlled primary tumour and 1-5 oligometastatic lesions) the effect of LCT on survival, toxicity, and quality of life in 99 patients was recently reported in the SABR-COMET trial: a randomized, phase 2 trial [4]. Patients were randomly assigned (1:2) to receive either palliative standard of care treatments alone (control group), or standard of care plus stereotactic or conventional radiotherapy to all metastatic lesions (SABR group). Median overall survival was 28 months in the control group versus 41 months in the SABR group (p=0.090). Several reasons could explain the benefit by adding LCT for OMD in these trials: 1) LCT potentiates the effects of systemic therapy 2) By reducing the residual tumor burden, LCT delays the growth of distant micrometastatic disease 3) LCT reduced the amount of treatment-resistant lung cancer cells 4) Necrosis caused by LCT allows the immune system to induce an immune-specific reaction that affects distant cancer cells **Conclusion:** The synergy of local consolidative therapies combined with systemic treatments in oligometastatic patients is currently one of the most exciting developments in lung cancer treatment. Ref: 1. Kwint M et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. Lung Cancer. 2017 Oct;112:134-139. doi: 10.1016/j.lungcan.2017.08.006. 2. De Ruysscher D et al. Progression-Free-Survival and Overall Survival beyond 5 years of non-small cell lung cancer patients with synchronous oligometastases treated in a prospective phase II trial (NCT 01282450). JTO 2018 doi: 10.1016/j.jtho.2018.07.098. 3. Iyengar P et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018 Jan 11;4(1):e173501. doi:10.1001/jamaoncol.2017.3501. Epub 2018 Jan 11. 4. Gomez D et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019 Jun 20;37(18):1558-1565. doi: 10.1200/JCO.19.00201. Epub 2019 May 8. 5. Palma D et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial.Lancet. 2019 May 18;393(10185):2051-2058. doi: 10.1016/S0140-6736(18)32487-5. Epub 2019 Apr 11 6. Gu X et al. Cryoablation combined with molecular target therapy improves the curative effect in patients with advanced non-small cell lung cancer J Int Med Res. 2011;39(5):1736-43

Keywords: Local consolidative therapy, oligo metastatic disease, stereotactic radiotherapy,

CS01 CONTROVERSIES IN NSCLC OMD
MONDAY, SEPTEMBER 9 11:00–12:30

CS01.03 TECHNICAL REASONS OF LOCAL TREATMENT DEFINE THE LIMITS OF NSCLC OMD IN TERMS OF NUMBER OF METASTASES, NOT A FIXED NUMBER

M. Scorsetti

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Currently there is no consensus on the definition of oligometastatic disease in NSCLC, with 3 or 5 lesions historically considered as the upper limit [1]. A low number of metastases, indeed, is a good although not perfect surrogate of the biology behind the oligometastatic state. In real life practice, the number of metastatic lesions is often misleading, since it is possible to find patients with more than 5 metastases affected by a slowly progressing disease, potentially taking advantage from local treatments. On the contrary, patients affected by just one or two metastases can progress very rapidly with a dismal prognosis, despite the apparent low disease burden. Since the number of metastases is not a perfect indicator of oligometastatic state and biomarkers really able to identify this disease are lacking, there is a trend favoring the technical feasibility of local treatment over the number of metastases to treat. This approach has pros and cons. On one side, the idea of killing all visible cancer cells independently by their number is appealing and possibly with a positive impact on patient prognosis. On the other side, clinical data supporting such an aggressive local treatment have still a low level of evidence. Moreover, the definition of "technically feasible" is quite vague, particularly in the world of radiation oncology. Indeed, radiotherapy is strongly related to technological development. The innovations in this setting have dramatically increased the possible indications of radiotherapy, also for oligometastases. With state of the art radiotherapy, we are now able to treat virtually all sites in the body and it is becoming really difficult to define an upper limit to the number of lesions that can be treated. However, this is feasible only with advanced technologies, like image guided radiotherapy (IGRT), motion management (4D CT, gating, tracking, etc.), and heavy particles in particular clinical settings (retreatment for instance). This trend is creating a gap between Radiation Therapy Departments, since some treatments are becoming safely deliverable only in well selected Institutions with high expertise in this field. Despite all recent technological achievements, some clinical settings remain in which the risk-benefit ratio should be carefully weighted before delivering ablative dose to a metastatic patient. For instance, there are still uncertainties in the treatment of central lung lesions abutting on the main bronchus [2] or, changing scenario, the amount of remaining healthy liver is still limiting liver metastases treatment in some situations [3]. More importantly, the goal of local treatment of an oligometastatic patient should be to change the natural history of the tumor, independently from the number of metastases we are able to treat. Treating all the metastases, even though safely feasible, remains just a technical exercise if no impact on prognosis, quality of life or symptoms control is achievable. Oligometastatic disease has definitely a different biology, and every effort should be in the direction of identifying this biology [4]. Technologies have developed faster than our clinical and biological knowledge, and this should be kept in mind. In conclusion, the number of metastases remains a good clinical indication of oligometastatic state, but this number should not be an insuperable limit in clinical practice. Technical feasibility of local treatments (as radiotherapy) should be always carefully weighted accounting for risk-benefit ratio. Being able to treat any number of metastases should not be considered as a good reason for doing it indiscriminately. Physicians should always consider the clinical and biological reasons for a local ablative treatment in a metastatic patient, independently by technical issues. [1] Hong JC, Salama JK. The expanding role of stereotactic body radiation therapy in oligometastatic solid tumors: What do we know and where are we going? Cancer Treatment Reviews 52 (2017) 22–32 [2] Videtic GM, Donington J, Giuliani M et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Practical Radiation Oncology (2017) 7, 295-301 [3] Mondlane G, Ureba A, Gubanski M et al. Estimation of the risk for radiation-induced liver disease following photon- or proton-beam radiosurgery of liver metastases. Radiat Oncol. 2018 Oct 22;13(1):206. doi: 10.1186/s13014-018-1151-6 [4] Correa RJ, Salama JK, Milano MT et al. Stereotactic Body Radiotherapy for Oligometastasis Opportunities for Biology to Guide Clinical Management. Cancer J. 2016 Jul-Aug;22(4):247-56.

Keywords: Oligometastases, SBRT, NSCLC

CS01 CONTROVERSIES IN NSCLC OMD
MONDAY, SEPTEMBER 9 11:00–12:30

CS01.04 NSCLC OMD IS DEFINED BY A FIXED MAXIMUM NUMBER OF METASTASES, NOT TECHNICAL REASONS OF LOCAL TREATMENT

G. Wright

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Other than a select group of patients with solitary brain metastases and cT1-2a N0 resectable primary cancers, the idea of aggressively ablating metastatic non-small cell lung cancer (NSCLC) has always been considered unconventional. The resectable solitary cerebral metastasis has traditionally yielded better results than any other

M1b disease, and this has been put down to careful selection and perhaps a different biology in these rare cases. It wasn't until the publication of a large individual patient data meta analysis in 2014[1] that more general treatment of OMD could be benchmarked and taken seriously enough to consider clinical trials. This confirmed that in select populations, long-term survival was achievable by surgical or radio-ablation of a small number of metastases. Only 1.9% of the series had more than 3 metastases and only 3% of the series had multi-organ disease. A main finding of multivariate analysis was that those with any nodal disease (effectively another metastatic site) did poorly. The definition of the oligometastatic disease state (OMD) has always been elusive. In principle, it is defined as M1a-c disease with low metastatic burden (usually up to three or five lesions) and limited organ involvement (usually up to two sites). It is considered an intermediate condition between truly localized disease and widely metastatic disease. The reporting bias of 1-3 metastases seen in so many published treatment series is tacit acknowledgement that OMD only encompasses three or fewer metastases, and probably to just a single organ. Our own IALSC TNM staging system recognizes this in our M1 sub-stages. Unlike oligo-metastatic colorectal carcinoma, sarcoma or renal cell carcinoma, which have reproducibly achieved long term survival after pulmonary metastasectomy (and/or hepatic metastasectomy) for several decades, the pace of disease and apparent inevitability of shortened lifespan in a patient with metastatic NSCLC has led to self-regulation of this practice for our tumour specialty. The relatively poorer average cardio-pulmonary fitness of patients with lung cancer and the maxim of 'first do no harm' largely tempered any enthusiasm. As surgery has become increasingly less invasive/morbid, and therapies such as stereotactic ablative body radiotherapy (SABR) and radiofrequency ablation have become more readily available, the temptation is to expand indications for intervention well beyond their evidence base and/or cost-benefit ratio. The last 5 years has seen a proliferation of publications of eyebrow-raising SABR series outside of any clinical trial protocols. This is a slippery slope that surgeons have been accused of sliding down in pulmonary metastasectomy for colorectal carcinoma[2]. We must not let our enhanced ability to inflict therapy dictate whether or not a condition is appropriate to treat. The definition of OMD cannot be stretched arbitrarily to match our technological capabilities or we will waste huge resources and inevitably cause some harm by way of futile overtreatment. The 'breakthrough' SABR-COMET trial[3] has invigorated discussion and enthusiasm for treating NSCLC oligometastatic disease on the basis that overall survival was superior with ablation of OMD (41 months) compared to the control group treated with palliative measures (28 months). This enthusiasm does need to be tempered by a few salient observations. Firstly, this was a phase 2 trial of mixed histologies with 66 recruits in the treatment arm and 33 in the control arm. In all, only 18 enrolled patients had NSCLC, with 12 in the treatment arm. It is indeterminate from the paper how well these particular NSCLC patients performed and the confidence intervals would be wide. The follow-up tail becomes decidedly 'bushy' after 1 year due to censorship. There were three treatment-related deaths and four other serious adverse effects not seen in the control arm. The control rate was less optimistic than in Rusthoven's phase 1 trial[4], with 75% having no progression in targeted lesions (compared to 49% in the control arm). The most telling information supporting the ≤3 metastasis OMD hypothesis is the number of metastases and number of organs involved in the recruited SABR-COMET patients. Only 7 recruits had more than 3 metastases, with 5 of these receiving SABR. It is not clear if ANY of these had NSCLC, but these are not dissimilar numbers to the aforementioned NSCLC meta analysis[1]. Historically, there is far more data on survival after metastasectomy for series excluding NSCLC. Only 1% of pulmonary metastasectomies in the International Registry of Lung Metastases[5] had NSCLC and some may have been second primaries. Whilst 26% of cases had ≥4 metastases resected, this was largely confined to sarcoma and germ cell tumours, where aggressive resection and re-resection is considered standard of care. Their survival was still inferior to patients with either solitary or 2-3 metastases. This is despite the likelihood that patients with ≥4 metastases are "hyper-selected', based on survival characteristics such as performance status, younger age, excellent fitness, anatomical location and favourable observed tumour behaviour. This creates a false impression that this group is receiving not dissimilar survival benefit as the cohort with ablation of 1-3 metastases. OMD as a hypothesis is very reasonable and deserves to be tested. Diluting the potential benefits by expanding that definition to match our technological wizardry is not. Clinical trial resources would be better mobilized to further study surgical and/or SABR metastasectomy in lung cancer with ≤3 metastases in a single organ before expanding umbrella trials to ≥4 metastases.

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Keywords: Stereotactic, metastasectomy, oligometastasis

Educational Sessions

ES01 WHAT IS THE ROLE OF CHEMOTHERAPY IN THE ERA OF IMMUNOTHERAPY IN ADVANCED NSCLC?
SUNDAY, SEPTEMBER 8 10:30–12:00

ES01.01 CHEMOTHERAPY IS STRICTLY ADDITIVE TO IMMUNOTHERAPY

J. Vansteenkiste, E. Wauters

University Hospitals KU Leuven, Leuven/Belgium

Historically, chemotherapy was the only systemic therapy for advanced NSCLC. Over the last decades, effective targeted therapy has been developed. EGFR is the prime target since 20 years now [1], and is followed by an increasing number of targetable rare oncogenic driver mutations. This decade, the phase I trial of nivolumab – including NSCLC patients – started recruitment on July 1, 2011 [2]. Since then, immunotherapy with immune checkpoint inhibition (ICI) has become the third pillar in our therapeutic armentarium, with a very rapid development for relapsed, and thereafter for untreated advanced NSCLC. Most patients with non-oncogene addicted advanced NSCLC will nowadays have both chemotherapy and ICI, either in a concurrent or sequential way. This raises the question whether their interaction is synergistic or additive, favoring the former versus the latter approach. We will look at this from the perspective of adverse events, mechanistic background, and clinical trial outcomes. There is not much overlap between the typical and common adverse events (AEs) of chemotherapy or ICI. The former are mostly bone marrow inhibition, nausea/vomiting, mucositis, hair loss and neuropathy. ICIs are well tolerated, with no or mild AEs in most patients, but may induce immune related AEs mostly in skin or endocrine organs, liver, lungs or kidneys. Hence, there is little difference in overall adverse event profiles when the chemotherapy+ICI (chemo+ICI) and chemotherapy+placebo (chemo+PL) arms from randomized trials are compared. In the Keynote-189 trial - an example with the anti-PD-1 agent pembrolizumab – overall grade 3 to 5 AEs were present in 67.2% and 65.8% of patients with chemo+ICI and chemo+PL, respectively [3]. Grade 3 to 5 immune-related AEs, as rated by investigators blinded to the assigned therapy, were 8.9% for chemo+ICI, while 4.5% for chemo+PL. AEs leading to discontinuation of all treatment were 13.8% and 7.9%, respectively. Hence, irAEs acted additive to the overall AE profile. The notable exception in this trial was renal toxicity. There was a low frequency of auto-immune nephritis (1.7%), but there was a 5.2% incidence of acute kidney injury in the chemo+ICI arm, compared to 0.5% in the control arm. In the IMpower-133 trial – an example with the anti-PD-L1 agent atezolizumab – overall grade 3 to 5 AEs were present in 67.2% and 63.8% of patients with chemo+ICI and chemo+PL, respectively [4]. All grade immune-related AEs, as rated by investigators blinded to the assigned therapy, were 39.9% for chemo+ICI, and 24.5% for chemo+PL. So, here again a rather additive pattern in AE profile is put forward. Chemotherapy has long time been regarded as immunosuppressive and incompatible with immunotherapy. To improve on the rather low response rate with ICI alone, recent trials focused on the combination of chemo+ICI, trying to exploit the immune modulatory (synergistic) effects of chemotherapy both on the tumor cells and immune cells. The details of this interaction are beyond the scope of this abstract, but a central one is immunogenic cell death (ICD) by chemotherapy. In contrast with necrotic/apoptotic cell death, ICD is characterized by immune-promoting features on dendritic cells and macrophages, by means of inducing calreticulin expression on tumor cells, release of adenosine triphosphate in the extracellular space and of high mobility group box 1 protein from the nucleus of the cancer cell. ICD, however, has been associated with only a limited number of chemotherapeutic agents used in clinical practice, such as doxorubicin, mitoxantrone, oxaliplatin and cyclophosphamide [5]. None of these agents is part of the modern chemotherapeutic armentarium for NSCLC. Recent phase III trials with chemo+ICI versus chemo+PL demonstrated a convincing benefit in response rate, progression-free survival (PFS) and overall survival (OS) with the combination (e.g. [3]). Of note, there are no randomized data comparing the combination of chemo+ICI in a concurrent versus a sequential way. Ideally, such a trial should have several arms: one with the concurrent use of chemo+ICI in all PD-L1 tumors; a sequential one with pembrolizumab followed by chemotherapy in PD-L1 >=50% tumors; and one with the sequential use of a chemotherapy and then ICI in PD-L1 <50% tumors. The primary endpoint preferably should be PFS2 in a intention-to-treat analysis. In the absence of such data, there is no definitive evidence that one or the other strategy is superior, and we can only make speculations about this question. At the meeting, we will present suggested algorithms based on the comparison of PFS from several recent trials. Especially the PFS2 analysis of the Keynote-024 [6,7] and KN-189 [3,8] trials are helpful in this respect. Even if there are many caveats with this approach, it may be helpful to guide clinical practice between concurrent and sequential treatment strategies. References 1. Vansteenkiste J, Wauters E. Tyrosine kinase inhibition of EGFR: A successful history of targeted therapy for NSCLC since 20 years. Ann Oncol 2018; 29 Suppl 1: i1-i2. 2. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-54. 3. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. N Engl J Med 2018; 378: 2078-92. 4. Horn L, Mansfield AS, Szczesna A et al. First-line atezolizumab plus chemotherapy in extensive-stage small cell lung cancer. N Engl J Med 2018; 379: 2220-9. 5. Bezu L, Gomes-de-Silva LC, Dewitte H et al. 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Keywords: Chemotherapy, Immune Checkpoint Inhibition, Additive effect

ES01 WHAT IS THE ROLE OF CHEMOTHERAPY IN THE ERA OF IMMUNOTHERAPY IN ADVANCED NSCLC?
SUNDAY, SEPTEMBER 8 10:30–12:00

ES01.02 CHEMOTHERAPY ENHANCES THE EFFICACY OF IMMUNOTHERAPY

N. Leighl

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Combination chemotherapy with anti-PD-1 therapy has now become standard of care as first-line therapy in patients with advanced NSCLC. Several trials demonstrate the improvement of combination therapy versus chemotherapy alone, but trials comparing immunotherapy +/- chemotherapy are ongoing (e.g. INSIGNA, CCTG BR.34, Checkmate 9LA, Checkmate 227). Several preclinical studies suggest that adding chemotherapy to immunotherapy is additive. Chemotherapy has been shown to disrupt immunsuppressive cell activity, for example regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC) and tumour associated macrophages (TAM) in preclinical studies (reviewed in Yan et al. Frontiers in Immunology, 2018). Chemotherapy may also promote immune responses via induction of tumor cell death, upregulation of MHC Class 1 expression and dendritic cell maturation. Lara et al recently reported activity both preclinically and clinically when combining gemcitabine with anti-PD1 therapy in mesothelioma, despite lack of activity of either as a single agent (Lara et al. Clin Cancer Res 2018). A key question in the first-line setting for those eligible for anti-PD1 monotherapy (PDL1 TPS >=50%) is whether the addition of chemotherapy is of benefit. Keynote 024 demonstrates superior survival, progression-free survival and response in this population compared to platinum doublet therapy, with a response rate of 45%. Overall response rates in the Keynote 189 and 407 trials in the subgroup with PDL1 TPS>=50% were 60% and 63% for chemotherapy plus pembrolizumab. Despite consensus that some patients clearly benefit from combination therapy while others likely can receive anti-PD-1 monotherapy, it is unclear how to select patients for each strategy. Ongoing studies are currently examining this question, such as the US cooperative-group-led INSIGNA trial (NCT03793179). In this study, patients with advanced PDL1 TPS>=1% nonsquamous NSCLC will be randomized to receive either (1) pembrolizumab monotherapy followed by pemetrexed/platinum upon progression; (2) pembrolizumab monotherapy and upon progression, the addition of pemetrexed/

platinum to pembrolizumab; and (3) pembrolizumab/pemetrexed/platinum followed by maintenance pembrolizumab/pemetrexed with investigator's choice of treatment upon progression. It is hoped that this study will provide answers in how to best select patients for either strategy.

Keywords: combination chemoimmunotherapy, Immunotherapy, NSCLC

ES01 WHAT IS THE ROLE OF CHEMOTHERAPY IN THE ERA OF IMMUNOTHERAPY IN ADVANCED NSCLC?
SUNDAY, SEPTEMBER 8 10:30–12:00

ES01.03 CHEMOTHERAPY DIRECTLY TARGETS THE IMMUNE SYSTEM TO IMPROVE EFFICACY

D. Tan

National Cancer Centre Singapore, Singapore/Singapore

Multiple phase III trials support the use of combination chemotherapy with immune checkpoint inhibitors in the first line setting. Yet the exact mechanism of synergy is poorly understood. In this third instalment of three talks dissecting this topic, the focus will be on the impact of chemotherapy on the immune system, ranging from its effect on recognition of tumor antigens, circulating immune cells and/or cytokines, as well as on immune cells in the tumor microenvironment. Elucidating the mechanism of action can delineate more tailored approaches to first line therapy, including the use of single agent checkpoint inhibitors or alternative/ additional combinations that further enhance the immune response.

Keywords: IO combinations, immunotherapy, translational immunology

ES01 WHAT IS THE ROLE OF CHEMOTHERAPY IN THE ERA OF IMMUNOTHERAPY IN ADVANCED NSCLC?
SUNDAY, SEPTEMBER 8 10:30–12:00

ES01.04 IMMUNOTHERAPY, RADIOTHERAPY AND CHEMOTHERAPY COMBINATION: A POTENTIAL NEW STANDARD?

M. Perol

Department of Medical Oncology, Centre Léon Bérard, Lyon/France

The advent of immunotherapy in lung cancer with immune checkpoints inhibitors (CPIs) has first involved stage IV non-small cell lung cancer (NSCLC), recently in combination with cytotoxic chemotherapy in first-line setting. The rationale to combine chemotherapy with CPIs is theoretically based on the chemotherapy-induced immunogenic cell death triggering an immune response and the modification of the tumor microenvironment (TME) by depletion of immunosuppressive cells. Radiotherapy remains one of the main components of the NSCLC treatment, from early stages with stereotactic ablative radiotherapy (SABR) and locally advanced stage III NSCLC in combination with chemotherapy to stage IV disease for the local palliative treatment of metastatic sites. Radiation therapy (RT) techniques have been considerably improved with image-guidance, and technological developments in linear accelerators, allowing now a very precise delivery of radiation. Radiation biology has been mainly concentrated on radiation-induced DNA damage with irreparable double strand break, leading to cell cycle inhibition and cell death. There are also a rationale and a preclinical evidence to expect a synergy between RT and CPIs. RT can also cause immunogenic cell death by direct cytotoxic effects, resulting in the release of tumor-associated antigens (TAAs) and danger signals (DAMPs: damage associated molecular pattern) that can be recognized by toll-like receptors, thus facilitating the presentation of TAAs to CD8+ T cells by MHC I. The dendritic cell activation and up-regulation of interferon pathway also enhance TAAs presentation to immune cells and up-regulate MHC-1 expression on tumor cells. Radiotherapy can therefore act as an auto-vaccine, activating the dendritic cells, broadening up the immune repertoire of T cells and increasing the "visibility" of TAAs. Beside this promotion of priming and activation of cytotoxic T cells, RT upregulates PD-L1 expression in the TME. Nevertheless, the modification of TME induced by RT may be equivocal with on one hand an increase in the CD8+ T cells recruitment by up-regulation of adhesion molecules, but on the other hand, the promotion of immune tolerance via the recruitment of MDSCs and Treg cells. Moreover, RT activates the immunosuppressive TGF-β pathway by reactive oxygen species. In addition to the potential synergism in terms of local control, the RT might also mediate an abscopal effect, describing the tumor regression of lesions distant from the irradiated volume, due to circulating of T cells locally activated by RT. This phenomenon has been experimentally demonstrated in preclinical models and occasionally reported in case reports. In stage IV NSCLC, the impact of RT delivered on a metastatic site or on the primary tumor on CPIs anti-tumor effect has been suggested by the retrospective analysis of the Keynote 001 phase I trial of pembrolizumab showing that patients who received radiotherapy before pembrolizumab had a better overall survival (OS) and progression-free survival (PFS) than those patients who did not receive radiotherapy. Many ongoing trials are exploring the possibility to "boost" the activity of CPIs by the addition of local RT, especially SABR; these trials have to face many challenges in terms of treatment timing, radiation dosing, and minimization of the RT toxicity on local and circulating T-cells. The main advance was brought in stage III NSCLC by the Pacific study which evaluated the impact of a treatment consolidation with durvalumab (anti-PD-L1), administered during 1 year after completion of concurrent chemoradiation therapy. This trial was a double-blinded, 2:1 randomized versus placebo study; randomization was authorized between 1 and 42 days after the end of radiation therapy. PD-L1 status was not required for enrollment. The majority of the 713 included patients were male, smokers and received a dose of radiotherapy between 54 and 66 Gy. The addition of durvalumab after concurrent chemo-RTsignificantly improved both PFS (median 17.2 vs. 5.6 months, HR 0.51 95%CI, 0.41-0.63) and OS at the first interim analysis (median not reached vs. 28.7 months, HR 0.68 99.73%CI, 0.469-0.997). The effect of durvalumab was mainly due to a reduction of metastatic relapses, including brain metastases. Subgroups analysis showed a trend toward a greater magnitude of PFS and OS benefit for patients randomized early after completion of radiotherapy (<14 days). The exploratory analysis of the impact of PD-L1 expression on the magnitude of benefit was planned with a cutoff at 25% for tumor cells. Knowing that 37% patients had no PD-L1 assessment, the analysis showed a PFS benefit in both subgroups of patients and no OS benefit for patients with PD-L1<25%. At the request of EMA, an additional unplanned subgroup analysis at the cutoff of 1% showed no PFS benefit and a trend toward a worse survival with durvalumab for the PD-L1<1% tumors, due to an unexpected very good survival for patients randomized in the placebo group in this small subset of patients. While FDA approval of durvalumab was unrestricted, the European label is limited to the PD-L1≥1% tumors, even if the statistical validity of the subgroup analysis is questionable. The risk of pneumonitis after radiation therapy was slightly increased in the durvalumab arm without significant augmentation of grade ≥3 events. Pacific was the first study demonstrating the potential for CPIs to obtain a potential synergy with radiation therapy, defining a new standard of care for these patients. However, further already ongoing clinical research will have to address the questions of a similar benefit with sequential chemoradiation therapy and of the optimization of this potential synergy by administering immunotherapy concurrently with thoracic radiotherapy as suggested by preclinical data. Potential long term toxicities must also be carefully assessed. Another area of further development of RT and CPIs combinations actually investigated is the incorporation of immunotherapy after SABR in the treatment of early stage NSCLC. The combination of RT and immunotherapy has proven effective in preclinical studies and in stage III NSCLC. A lot of challenges still exist to harness the combination of chemotherapy, RT and CPIs, especially in terms of timing, irradiated volume, fractionation, and dose that likely play a major role in the modulation of the RT different effects on the tumor cells, the immune response and the TME.

Keywords: Immune checkpoint inhibitor, radiotherapy, stage III NSCLC

ES02 MANAGEMENT OF ONCOGENE ADDICTED PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 10:30–12:00

ES02.01 BIOMARKER TESTING IN LA DISEASE

H. Yu

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Routine biomarker testing in metastatic lung cancer has led to enormous improvements in outcomes for our patients with metastatic lung cancers. Oncogene testing has allowed us to identify the 50% of patients with metastatic lung cancer that are eligible for targeted therapies1. Consistently, targeted therapy for EGFR, ALK, ROS1, RET, BRAF have demonstrated superior progression-free survival compared to standard cytotoxic chemotherapy2. Identification of these genomic biomarkers has provided additional treatment options for our patients that are more effective and less toxic than standard treatments. In addition, serial biomarker testing allows us to also identify mechanisms of resistance to targeted therapy which can then inform subsequent treatment decisions. PDL1 testing is also routinely performed in the metastatic setting and assists us in identifying patients that may benefit from immunotherapy alone instead of first-line combination immunotherapy and chemotherapy treatment3. PDL1 testing allows us to predict likelihood of response to immunotherapy and selects patients that we can de-escalate treatment; patients with high PDL1 expression derive benefit from treatment with immunotherapy alone. Routine utilization of biomarker testing in metastatic lung cancer is easily the most importance advancement in this field to date. Current recommendations: Biomarker testing for patients with locally advanced lung cancers is currently not recommended in the NCCN guidelines or any expert guidelines. This is likely because the current management for locally advanced lung cancers do not incorporate the use of biomarkers. Patients currently receive adjuvant durvalumab after concurrent chemoradiation for stage 3 disease irrespective of PDL1 status. Currently, adjuvant targeted therapies after definitive resection or radiation are not recommended in the NCCN or other cancer care guidelines. Oncogene testing: The risk of recurrence for early stage lung cancers remain high. After surgical resection, adjuvant chemotherapy for high risk stage 1B, stage 3 and stage 4 and post-operative radiation for patients with mediastinal lymph node involvement are both recommended are they improve survival. Despite this, there is a large subset of patients that will have recurrent disease. Because of their demonstrated superiority over chemotherapy in the metastatic setting, there is great interest in assessing whether adjuvant targeted therapies would improve outcomes in the locally advanced disease setting. EGFR mutant lung cancer is the largest oncogene subset in which the bulk of previous studies have been done. However, all studies to date have been subsets of larger unselected patients (RADIANT study) or single arm studies (SELECT study). These smaller studies have shown a disease-free survival benefit but have been underpowered to demonstrate a survival benefit. There are several well-designed large studies ongoing that will definitively demonstrate whether adjuvant EGFR inhibitors improve overall survival. The ALCHEMIST study is a phase 3 randomized cooperative group study assessing erlotinib versus observation for patients with stage IB-IIIA resected lung cancers; accrual is ongoing. The ADAURA study is a randomized phase 3 study where patients with stage IB-IIIA resected lung cancers are randomized to osimertinib versus placebo for 3 years with a primary objective of DFS and a secondary objective of overall survival. These studies will help answer the question as to whether adjuvant targeted therapy should be utilized. PDL1 testing: In stage 3 lung cancers, more than 60 percent of patients will ultimately die of their lung cancer4. Adjuvant durvalumab has improved outcomes with a clear improvement in overall survival but many patients still recur and ultimately die of their disease. An unplanned subset analysis of the PACIFIC study suggests that patients with PDL1 0% expression may not derive benefit from durvalumab. Further assessment will be needed to ascertain whether PDL1 expression can be used to select patients who would derive benefit from adjuvant durvalumab. Due to their efficacy in the metastatic setting, there are a significant number of studies looking at immunotherapy as both neoadjuvant and adjuvant treatment for locally advanced disease. Just as we utilize PDL1 as a biomarker that helps select appropriate therapies in the metastatic setting, I see similar use of PDL1 in the future in the locally advanced setting. Future directions: As personalized medicine infiltrates our care of patients with lung cancers, we will need biomarker results for patients with locally advanced lung cancer to better tailor and personalize their care. In particular, if the EGFR TKI studies demonstrate improved overall survival with adjuvant EGFR TKI, we will certainly need to incorporate biomarker testing as standard of care for locally advanced disease. In addition, because a significant portion of patients recur, already having molecular test results available which were done on their surgical sample, makes their care later more stream-lined. We also need to assess whether PDL1 is a useful biomarker to select patients for immunotherapy in the adjuvant setting. Results from ongoing clinical trials will provide definitive answers. Works cited: 1. Jordan, E.J., et al. Prospective Comprehensive Molecular Characterization of Lung Adenocarcinomas for Efficient Patient Matching to Approved and Emerging Therapies. Cancer discovery 7, 596-609 (2017). 2. Sequist, L.V., et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. 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ES02 MANAGEMENT OF ONCOGENE ADDICTED PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 10:30–12:00

ES02.02 MANAGEMENT OF EGFR LA DISEASE

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The standard of care for the locally advanced non-small cell lung cancer(LA-NSCLC) is concurrent chemoradiotherapy(CCRT). Recently, the addition of consolidation immune checkpoint inhibitor following CCRT demonstrated improved outcome and is now recommended as the new standard of care for this heterogeneous group of LA-NSCLC patients. In advanced/metastatic setting EGFR mutation (+), NSCLC cancer patients define a unique subset with a dramatic response to the EGFR TKIs. Currently, molecular profiling of tumor tissue for EGFR mutations (as part of multiplex testing) is a routine procedure at the time of initial diagnosis of patients with recurrent or metastatic NSCLC. For advanced or metastatic EGFR mutant NSCLC patients EGFR TKI therapy is the treatment of choice and the median overall survival is > 30 months. Despite the great success of EGFR TKI in metastatic NSCLC, the role of EGFR TKIs in LA-NSCLC is less well defined and controversial. Early clinical trials in *unselected* NSCLC patients failed to demonstrate the benefits of EGFR-TKIs as an adjuvant treatment. The first prospective randomized phase III trial to investigate the role of EGFR TKI in earlier stage NSCLC includes the SWOG 0023 study (J Clin Oncol 2008;26:2450-6) which failed to support the role of maintenance gefitinib (versus placebo) following definitive chemoradiation in unresectable stage III NSCLC. The CALGB 30106 phase II study also failed to show the benefits of adding gefitinib to sequential or concurrent chemoradiotherapy in unresectable stage III NSCLC (J Thorac Oncol 2010;5:1382-90). And the randomized prospective placebo-controlled adjuvant gefitinib trial in *unselected* patients with stage IB–IIIA resected disease (BR.19) was prematurely closed (J Clin Oncol 2013;31:3320-6). Another randomized double-blind trial in adjuvant NSCLC with tarceva (RADIANT) in patients with completely resected state IB to IIIA NSCLC whose tumors expressed EGFR protein by immunohistochemistry or EGFR amplification by fluorescence in situ hybridization did not show prolonged DFS (J Clin Oncol 2015;33:4007-14). The prognostic or predictive value of EGFR mutation in early stage NSCLC patients is not well defined. In a retrospective single institutional analysis (J Thorac Oncol. 2012;7: 1815–1822), patients with resected stage I–III lung cancers and EGFR mutation have a lower risk of death compared to patients without EGFR mutation. There was a trend toward improvement in DFS among individuals with resected stages I to III lung adenocarcinomas harboring mutations in EGFR exon 19 or 21 who received adjuvant EGFR TKI therapy (J Thorac Oncol 2011;6:569–575). There have been recently reported several *prospective* trials of adjuvant EGFR TKI in early stage NSCLC patients enriched with EGFR mutation. CTONG1104 study (ADJUVANT), a randomized, open-label, phase III trial of adjuvant gefitinib for 24 months versus intravenous vinorelbine plus cisplatin for 4 cycles in patients with completely

resected (R0), stage II–IIIA (N1–N2), EGFR-mutant (exon 19 deletion or exon 21 Leu858Arg) NSCLC, demonstrated that adjuvant gefitinib compared to cisplatin-based chemotherapy significantly increases disease-free survival, diminishes toxic effects, and improves HRQoL in patients with completely resected stage II–IIIA EGFR-mutant NSCLC (Lancet Oncol 2018; 19: 139–48). In the phase II SELECT trial, adjuvant erlotinib for 2 years in patients with resected stage IA to IIIA EGFR-mutant NSCLC after standard adjuvant chemotherapy with or without radiotherapy (J Clin Oncol 2019;37:97-104) showed an improved 2-year DFS. Patients rechallenged with erlotinib after recurrence experienced durable benefits. There are also some neoadjuvant trials of EGFR TKI for locally advanced NSCLC. RTOG 1306, a randomized phase II study of individualized combined modality therapy for stage III NSCLC (12-weeks of either erlotinib hydrochloride or crizotinib followed by chemoradiation therapy in stage III NSCLC with EGFR TK mutations or EML4- ALK fusion). The primary objective was to assess whether patients with unresectable LA-NSCLC treated with EGFR or ALK TK targeted agents based on molecular characteristics have a longer progression-free survival than those treated with standard care therapy alone. The study was, however, unfortunately prematurely terminated due to poor accrual (NCT01822496). CTONG 1103 is an open-label, randomized trial that compared the efficacy and safety of erlotinib versus gemcitabine plus cisplatin neoadjuvant therapy in patients with exon 19 or 21 EGFR mutations and untreated resectable stage IIIA-N2 NSCLC. The study did not meet the primary end point of ORR with 42 days of neoadjuvant erlotinib, but the secondary end point PFS was significantly improved (J Clin Oncol 37. © 2019; published at jco.org on June 13, 2019: DOI https://doi.org/10.1200/JCO.19.00075) There are also several ongoing clinical trials of EGFR TKIs in resected stage IB - IIIA NSCLC with activating EGFR mutations. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is a prospective randomized double-blind placebo-controlled trial to investigate the benefits of the addition of molecularly targeted agents after standard postoperative chemotherapy in patients with resected NSCLC (Clin Cancer Res:2015; 21(24); 5439–44). It is worth noting that the primary objective for the ALCHEMIST adjuvant trials is overall survival (OS). ADAURA, a randomized phase III trial (osimertinib vs. placebo in patients with stage IB-IIIA NSCLC, following complete tumor resection with or without adjuvant chemotherapy; NCT02511106) has been designed to assess the efficacy and safety of adjuvant osimertinib versus placebo in patients with resected stage IB-IIIA EGFR mutation-positive (Ex19Del or L858R) NSCLC. The primary efficacy objective is DFS. In brief, many neoadjuvant/adjuvant EGFR TKI trials in earlier stage of NSCLC have demonstrated its safety and feasibility with an improved DFS esp. in EGFR mutation(+) LA-NSCLC. However, the real question should be "Can we improve the 'overall survival' and thus ultimately the 'cure rate' of locally advanced NSCLC with EGFR mutation?" In order to address this issue, there remain several critical questions to be answered, e.g., who is most likely to benefit from adjuvant EGFR TKI, what is the optimal duration of adjuvant TKI, what is the best regimen, etc. Whether the earlier introduction of EGFR targeted therapy in less advanced NSCLC would lead to improved '*Cure Rate*' remains to be seen in future prospective trials in a larger number of EGFR mutation(+) patients.

Keywords: EGFR mutation, locally advanced, management

ES02 MANAGEMENT OF ONCOGENE ADDICTED PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 10:30–12:00

ES02.03 MANAGEMENT OF OTHER NON EGFR ONCOGENE ADDICTED TUMORS

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Stage III non-small cell lung cancer accounts for heterogeneous group of diseases, due to differences in tumor size, location number of nodes involved, and lymph node station involved. Stage III non-small cell lung cancer comprises 2 distinct stages, stage IIIA and IIIB disease that have different prognosis, and are usually treated differently. Approximately 15% of all patients with newly diagnosed non-small cell lung cancer present with stage III disease. Options for stage III non-small cell lung cancer include surgery, with lobectomy or pneumonectomy depending on the tumor stage, and lymph node involvement. Chemotherapy may be administered in the neoadjuvant, concurrent or adjuvant setting. Radiation therapy can be given in a concurrent, sequential approach, or may be administered in the postoperative fashion. Combination approaches are often used, and due to the significant need of multi-modality therapy, treatment decisions are usually made in a multidisciplinary setting. The optimal therapeutic approach for patients with stage IIIA non-small cell lung cancer remains controversial. For subset of patients with T3 to T4 N0-1 disease, and superior sulcus location, surgery remains a viable and preferred option. However, the optimal treatment for patients with stage III A, with bulky lymph node involvement, or multi station lymph node involvement including N2 disease, remains an area of ongoing controversy. Tri-modality approaches using preoperative chemotherapy, or upfront chemoradiation therapy followed by surgery have been evaluated (1). For patients with surgically unresectable, or medically inoperable disease, concurrent chemoradiation therapy has been established as the standard of care for patients spanning the spectrum of stage IIIA and IIIB disease. Recently, the PACIFIC trial demonstrated an improvement in progression free survival and overall survival with the administration of durvalumab as consolidation therapy (regardless of PDL-1 status) for patients who had not progressed after 2 or more cycles of definitive concurrent platinum-based chemoradiation therapy (2, 3). This approach represents a new paradigm in the management of unresectable NSCLC, and has now been adopted as standard of care. Management of Stage III patients with non EGFR oncogene addicted tumors is an area of active research. ALK or ROS directed oral tyrosine kinase inhibitors (TKIs) are not typically administered in the adjuvant setting outside of a clinical trial. There are several trials evaluating the use of targeted therapies. ALINA, is one such trial, that is a phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive ALK positive NSCLC (4). Another study is comparing adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with ALK positive NSCLC, here the alectinib is administered for 2 years (NCT 03456076). The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing (ALCHEMIST) trial is actively enrolling patients with operable NSCLC and will perform genetic screening of their tumors. Patients with *EGFR* mutation or *ALK* gene rearrangement in their tumor will be randomized to placebo versus erlotinib or crizotinib, respectively (NCT02194738). We await the results of these trials prior to routine incorporation of molecularly directed therapy in the management of locally advanced disease. References: 1. Albain KS, Swann RS, Rusch VW, Turrisi AT, 3rd, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379-86. Epub 2009/07/28. doi: 10.1016/S0140-6736(09)60737-6. PubMed PMID: 19632716; PubMed Central PMCID: PMC4407808. 2. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017;377(20):1919-29. 3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. 2018; 379:2342-2350 4. Solomon BJ, Ahn JS, Barlesi F et al. ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (*ALK*+) non-small cell lung cancer (NSCLC). J Clin Oncol 37, 2019 (suppl; abstr TPS8569)

ES02 MANAGEMENT OF ONCOGENE ADDICTED PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 10:30–12:00

ES02.04 CONCURRENT, SEQUENTIAL AND COMBINATION IMMUNOTHERAPY REGIMENS IN LA-NSCLC

M. Provencio

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Immunotherapy in Oncogenic-Addicted Stage III Patients At diagnosis of non small cell lung cáncer (NSCLC), at least 40% of patients are diagnosed at an advanced stage and a third locally advanced disease (stage III). The results of stage IIIA with induction treatment of clinical practice outside the clinical trial show a median survival of 22 months and a 3-year survival rate of 34%. Concurrent definitive chemoradiation has been established as the standard of care for unresectable stage IIIB (N3 disease) NSCLC, with a median overall survival (OS) of approximately 17 months. Strategies that have been investigated include induction chemotherapy, immunotherapy

(IO), concomitant chemoradiotherapy, intensified radiotherapy and adjuvant treatment. The role of IO in NSCLC with oncogenic-addicted tumors is so far unclear. In EGFR-mutation positive patients there seems to be a worse effect of IO compared to those patients without actionable mutations,; nevertheless, no safe conclusions can be drawn due to the lack of randomized trials addressing this clinical issue. The available information from second lines with IO in patients with actionable mutations, is currently found in 2 meta-analyses[1]. These meta-analyses show OS benefit between EGFR wild-type vs mutated patients with a Hazard Ratio (HR) of 0.67, p< 0.001, consistent in all the trials. There was no OS advantage for those with EGFR mutant tumors, with a HR of 1.11, p=0.54. Of note, data from other studies were not included in these meta-analyses. Study CA209-012 showed patients with EGFR mutation, overall response rate (ORR) 14% mutated vs 30% in wild type and PFS at 24 weeks: 14% vs 51% respectively[2]. In KEYNOTE-001, best ORR based on mutation status was 15.8% in patients with EFGR mutation vs 37.1% without mutation, and 60% were unknown. Overall PD-L1 subgroups, EGFR mutated patients had lower ORR than patients with EGFR-wild type tumors. ORR was 20 % in TPS > 50% and 0% in patients with TPS<1% vs 12.7% in EGFR wild type[3]. An update of this study, and median OS in patients with EGFR mutation was 6 months (mo) (95%CI, 4.4-8.8) and 12 mo (95%CI, 9.2-14.3) in patients wild-type[4]. In the Immunotarget Cohort study, patients with EGFR-mutation had response rates of 12% and PFS of 2.1 mo and with a positive correlation in patients with high expression of PDL1 and response. The BIRCH[5] study, also not included in the meta-analyses, provides us with similar information, with higher response rates in patients with higher expression of PDL1 (31% vs 23%), even achieving similar PFS to wild type patients (7.6 vs 7.7 mo) or OS with 28.5 mo (20.1, NE) in mutant vs 20.1 mo (15.5, 31.1) in wild-type. The phase II ATLANTIC trial testing durvalumab as third-line treatment included the largest cohort of EGFR mutant patients treated with IO after progression of TKI and chemotherapy. According to PD-L1 expression (< 25% or ≥ 25%), durvalumab achieved a response rate (RR) of 3.6% and 14.1%, a similar median PFS 1.9 months and a median OS of 9.9 months and 13.3 months, respectively[6]. Despite improvements in the treatment of stage IV NSCLC with the introduction and dissemination of checkpoint inhibitors, very little progress has been made in the treatment of stage III. The PACIFIC trial was the first study to show a clear benefit for the approach. Patients were enrolled regardless of PD-L1 expression, and those with EGFR mutations were also eligible. The subgroup of patients with EGFR mutations did not clearly benefit from durvalumab maintenance. These patients were equally represented in the durvalumab (6%) and placebo (5.9%) arms. The HR was 0.76 in this setting, and whether because of a small sample size or true lack of efficacy, the findings were not significant (95% CI, 0.35–1.64). In NADIM Study, a Phase II, with neoadjuvant chemotherapy and immunotherapy in stage III, unprecedented pCR rates observed (around 70%) and with down-staging around 90%. We did not include patients with actionable mutations, and we do not have information about other trials using chemo and IO. In KN 189 using combination of chemo and IO in stage IV, no sensitizing EGFR or ALK alteration were included. In the ImPOWER 150 study[7] comparing the use of bevacizumab plus atezolizumab plus carboplatin, plus paclitaxel versus carboplatin plus paclitaxel plus bevacizumab in first-line stage IV, provides interesting results in PFS, with a HR of 0.41 (95% CI: 0.22-0.78), in patients with common mutations (already treated with TKIs) in the arm with atezolizumab plus chemo better than the control arm. In the light of these results, we may conclude that other biomarkers such as a tumor mutational burden (TMB) could be used in the future, but low TMB is especially significant among the oncogenic alterations strongly related with never-smokers, such as EGFR mutation and ALK rearrangements. Therefore, these data suggest a role for actionable mutations testing in the stage III setting and for additional trials specifically targeting EGFR-mutant patients and stage III disease.

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Keywords: Immunotherapy, Stage III, Oncogene-addicted

ES03 BAP-1 AND OTHER NOVEL MOLECULAR AND METABOLIC TARGETS IN MESOTHELIOMA
SUNDAY, SEPTEMBER 8 10:30–12:00

ES03.01 TARGETING ALTERED MICRORNA EXPRESSION IN MESOTHELIOMA

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MicroRNAs (miRNAs) are an important class of noncoding RNA that post-transcriptionally regulate the expression of most protein-coding genes. In addition to central roles in normal biology, their aberrant expression in tumours contributes to all of the hallmarks of cancer. In common with other tumour types, changes in miRNA expression in malignant pleural mesothelioma (MPM) are characterised by a global downregulation, although elevated levels of some miRNAs are also found. While altered expression has been demonstrated for many miRNAs in MPM, relatively few have been functionally characterised. Early studies reported modest tumour suppressive activities of, among others, miR-29c, miR-31 and miR-145. More recently, miR-16, miR-193a and the miR-34 family were shown to have clear tumour suppressor activity; restoring the levels of these miRNAs leads to a range of effects including inhibition of cell growth, induction of apoptosis, reversal of drug resistance and reduced migration and invasion. In the case of miR-16 and miR-193a, targeted delivery of mimics to tumours in a xenograft model led to significant inhibitory effects on tumour growth. These results laid the foundation for the phase I MesomiR-1 trial, investigating the safety and optimal dose of a miR-16-based mimic delivered in anti-EGFR antibody-targeted bacterial minicells. This trial of 27 patients demonstrated safety of the treatment as well as initial signs of activity, with one objective response and stable disease in a further 15 patients. With miR-16 also impacting response to pemetrexed and contributing to PD-L1 regulation *in vitro*, restoration of miR-16 levels in combination with chemo or immunotherapy are potential future applications of this approach. Other miRNAs with pronounced tumour suppressor activity, including miR-137 and miR-193a, are further candidates for clinical development. The lower levels of miR-193a recently found to be associated with shorter overall survival in the TCGA study lend support to this notion. In contrast to the use of mimics to restore levels of miRNAs downregulated in MPM, inhibition of overexpressed miRNAs with antisense oligonucleotides is an alternative strategy for modulating miRNA levels. This approach is attractive as it may be amenable to local delivery, avoiding the problems associated with tumour targeting via systemic administration. While the number of miRNAs found to be consistently overexpressed in MPM is relatively small, recent studies suggest that their inhibition can have profound effects on MPM growth. One such example was the report of the effects of inhibiting the overexpressed miR-182 and miR-183. They are upregulated in MPM cell lines where they promote proliferation and invasion, at least in part due to suppression of FOXO1. Reducing their levels with miRNA inhibitors reversed these effects, with dual inhibition showing additive effects. An oncogenic role for miR-182 was first demonstrated in melanoma, in which this miRNA enhances migration, invasion and metastasis via inhibition of FOXO3 and MITF. Upregulation of miR-182 in melanoma is due to amplification (at 7q31) of a miRNA cluster which also contains the related miR-183 and miR-96. As this region appears to be more frequently lost in MPM, the mechanism for overexpression remains to be determined. Another miRNA with oncogenic activity in MPM is miR-24, which was identified via a screen of polysome-associated miRNAs and is upregulated in cell lines and tumour samples. This miRNA regulates a range of genes involved in cell adhesion and communication, many of which are associated with good prognosis, and miR-24 knockdown reduced migration and invasion *in vitro* and in vivo. Although the targets of miR-24 identified in this study had no obvious link to MPM biology, it is intriguing that in other cancers miR-24 regulates both transcripts produced by the *CDKN2A* locus. Whether other well known oncogenic miRNAs such as miR-155, miR-10b and miR-21

promote MPM tumour progression remains to be seen, but the initial results with miR-182, miR-183 and miR-24 warrant further pre-clinical development. Despite progress in the development of miRNAs as therapeutic targets for MPM, outstanding questions remain. Of particular relevance is the question of the cell of origin of dysregulated miRNAs. As tumour samples consist of a mix of cancer, stroma and immune cells, the source of miRNA contributing to changes in expression is unknown and thus impacts the interpretation of results. For example, altered expression of miR-223 was linked to changes in migratory behaviour of MPM, but in xenograft studies this miRNA is clearly derived from the stroma. Another confounding observation concerns the apparent contradictory findings from studies of the same miRNA. For example, miR-137 has clear tumour suppressor function in MPM cells *in vitro*, but its expression varies widely across MPM lines and is found at higher levels in tumours from patients with shorter survival. Similarly, miR-31 has growth inhibitory activity but higher expression is associated with poor prognosis in sarcomatoid tumours. There are also cases of different miRNAs showing apparent differences in MPM compared with other cancers. A prime example of this is miR-21; an oncomiR in most cancer types, but growth inhibitory when overexpressed MPM cell lines. Finally, because the activity of miRNAs typically leads to modest reductions in target genes, demonstrating in vivo effects is not trivial. In addition, because the miRNA being restored (or inhibited) is usually identical to its endogenous miRNA counterpart, measuring delivery can be difficult. Due to their short size, even novel sequences such as that used in the TargomiR study are difficult to definitively measure by RT-qPCR or RNA-seq. In summary, the changes in miRNA expression in MPM provide avenues to develop new therapetuic approaches. The successful phase I trial of TargomiRs demonstrated that miRNA targeting is feasible in MPM and while the majority of miRNA studies in MPM have focused on miRNA mimics, recent studies suggest that antisense inhibitors have similar potential. Notwithstanding the ongoing difficulties in delivering nucleic acid-based drugs, the recent FDA approval of the first siRNA therapy – together with ongoing clinical trials of a number of miRNA mimic drugs – means that gene silencing drugs have moved from concept to reality. Continued preclinical studies and early phase clinical trials are needed to determine the true potential of miRNA targeting in MPM treatment.

Keywords: therapy, Mesothelioma, microRNA

ES03 BAP-1 AND OTHER NOVEL MOLECULAR AND METABOLIC TARGETS IN MESOTHELIOMA
SUNDAY, SEPTEMBER 8 10:30–12:00

ES03.02 TARGETING CDKN2A IN MESOTHELIOMA

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Interrogation of the genomic landscape in mesothelioma has revealed considerable inter-patient genomic heterogeneity, however development of molecularly targeted stratified therapy is currently in its infancy. Somatic copy number loss involving the chromosome 9p21-3 locus occurs at high frequency (45% deep deletion in the TCGA cohort), and its expression may be further suppressed by DNA methylation. 9p21-3 harbours CDKN2A. Conditional Knockout of CDKN2A is sufficient to initiate mesotheliomas in vivo consistent with a role in tumorigenesis. This is supported by emerging phylogenetic analysis in which 9p21-3 occurs as an early (clonal or truncal) homozygous event during tumour evolution, in around 20% of cases. Late homozygous and heterogzyous losses also occur, with evidence of parallel evolution. Importantly, CDKN2A is a major negative prognostic factor associated with earlier progression following surgical resection. CDKN2A encodes two genes; 1, the inhibitor of cyclin dependent kinases 4 and 6 known as p16ink4A, and 2. MDM2, an inhibitor of the p53-MDM2 interaction. Early preclinical studies showed that re-introducing p16ink4A transgene in a CDKN2A negative mesothelioma exhibited anti-tumour activity. Small molecule inhibition of CDK4/6 essentially phenocopies p16ink4a (in the presence of wild type RB1). Large scale drug-gene interaction studies have revealed CDKN2A dependent sensitivity to CDK4/6 inhibition suggesting a possible strategy in mesothelioma. We have therefore developed the MiST stratified umbrella trial (NCT NCT03654833) is therefore evaluating the CDK4/6 inhibitor abemaciclib in p16ink4a negative relapsed mesothelioma (arm 2) Loss of p14ARF expression promotes MDM2, an E3 ubiquin ligase targeting p53. Given the low mutation rate for p53 in mesothelioma (around 16% in the TCGA), MDM2 inhibitors may, in the context of p14ARF loss, de-repress p53 to mediate tumour suppression. Preclinical data supports this hypothesis which has translational potential. Co-deletion of the gene MTAP with CDKN2A is common, and coincident with around 80% of CDKN2A losses. MTAP (methylthioadenosine phosphorylase) may represent a potential molecular target in 9p21-3 deleted mesothelioma. This tumour suppressor salvages the essential amino acid methionine, as well as adenine, and plays a critical role in the polyamine salvage pathway. Recently it has been shown that loss of MTAP leads to an increase level in its substrate, methylthioadenosine (MTA). This metabolite directly interacts with and inhibits the epigenetic modifier, PRMT5 (protein arginine methyltransferase 5) that mediates symmetrical arginine di-methylation of histone H4 (H4R3me2s). A direct consequence of this is a reduction in the pool of functional PRMT5 enzyme, revealing a vulnerability to 1. Inhibition of PRMT5 expression or 2. Inhibition of PRMT5 substrate (SAM) synthesis via MAT2A (which converts methionine to SAM). 1st generation small molecule PRMT5 inhibitors are currently undergoing phase 1 clinical evaluation, however MTA dependent allosteric antagonism of such inhibitors presents a challenge to achieving efficacy. Small molecule transcriptional suppression may present a solution. Accordingly, using the connectivity map, we have identified quinacine as a PRMT5 transcriptional suppressor capable of suppressing PRMT5 transcription (which is c-jun dependent), mediating MTAP selective loss of viability with commensurate reduction in H4R3me2s, consistent with an on-target effect. In summary, 9p21-3 loss encompassing CDKN2A and MTAP is one of the most common genomic aberrations in mesothelioma. Novel strategies are emerging with significant translational potential to deliver targeted therapies for mesothelioma.

Keywords: CDKN2A MTAP synthetic lethality

ES03 BAP-1 AND OTHER NOVEL MOLECULAR AND METABOLIC TARGETS IN MESOTHELIOMA
SUNDAY, SEPTEMBER 8 10:30–12:00

ES03.03 TARGETING NF2 IN MESOTHELIOMA

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Malignant mesothelioma (MM), which arises from the pleural or peritoneal cavities, is a very aggressive tumor that is highly refractory to conventional therapies. Several key genetic alterations, including mutations of the *CDKN2A/ARF*, *NF2*, and *BAP1* tumor-suppressor genes, are associated with the development and progression of MM. Notably, activating oncogene mutations are very rare; thus, it is difficult to develop effective inhibitors to treat MM. *Neurofibromatosis type 2* (*NF2*) encodes the tumor suppressor protein moesin-ezrin-radixin-like protein (merlin), which is a member of the Band 4.1 family of cytoskeletal linker proteins. NF2-inactivating mutations, deletions, or rearrangements are harbored in 40%–50% of MMs and result in bi-allelic loss of protein function. Somatic *NF2* mutations are also frequently detected in sporadic schwannomas, meningiomas, ependymomas, and to a lesser extent, in other types of solid tumors. Merlin/NF2 primarily localizes to the plasma membrane where it mediates contact-dependent inhibition of proliferation in normal cells. Merlin/NF2 has also been shown to regulate multiple cell-signaling cascades including the Hippo pathway. The Hippo signaling pathway is involved in critical biological processes, including organ size-control, development, differentiation, tissue regeneration (via cell-growth restriction), cell division regulation, apoptosis, and cancer development. The 4 core components in this pathway, MST1/2, SAV1 (also called WW45), MOB1, and LATS1/2, have all been shown to act as tumor suppressors. Since MMs also exhibit genetic or epigenetic inactivation of Hippo pathway components, including MST1/2 and LATS1/2, merlin-Hippo pathway dysregulation is thought to play a key role in MM development and progression. Hippo pathway inactivation results in inactivation of the LATS1/2 kinases, which, in turn, induces constitutive activation (via underphosphorylation) of YAP1 and TAZ transcriptional coactivators. Underphosphorylation stabilizes YAP1 and TAZ and enables them to enter the nucleus where they bind to distinct transcription factors, including TEAD1-4, and regulate transcription of numerous target genes. We, along with other groups, have shown that constitutive activation of YAP1 and TAZ *in vitro* and *in vivo* confer malignant phenotypes in mesothelial cells, whereas their knockdown suppresses these phenotypes. Critical YAP1/TAZ target genes include prooncogenic cyclin D1 (*CCDN1*), forkhead box M1 (*FOXM1*), connective tissue growth

factor (*CTGF*), and cytokine-encoding genes such as *IL1B*, which have also been shown to enhance the malignant phenotypes of MM cells. Currently, several small molecules have been developed to directly target YAP1/TAZ coactivators, including YAP1-TEAD binding inhibitors. Targeting key YAP1/TAZ-inducible downstream genes, such as *IL1B* and *CTGF*, in the dysregulated Hippo pathway may also represent an alternative approach to inhibit MM progression. Furthermore, targeting stimulatory or inhibitory signaling pathways within the Hippo pathway, which include TGF-beta, Wnt, G-protein-coupled receptor (GPCR), mammalian target of rapamycin (mTOR) and mevalonate pathways, may be considered. Collectively, these evidences indicate that the Hippo pathway is a promising therapeutic target for MM treatment, particularly with regard to NF2-Hippo pathway inactivation, and supports the development of new strategies to effectively target YAP1/TAZ activation status as a promising therapeutic modality for this formidable disease.

Keywords: Hippo pathway, YAP1/TAZ

ES03 BAP-1 AND OTHER NOVEL MOLECULAR AND METABOLIC TARGETS IN MESOTHELIOMA
SUNDAY, SEPTEMBER 8 10:30–12:00

ES03.04 PEGARGIMINASE TO TREAT MESOTHELIOMA

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Treatments based on targeting metabolism remain central to the management of malignant mesothelioma, an intractable malignancy with a median overall survival (OS) of ~12 months. The standard of care since 2003 is an antifolate drug (pemetrexed or raltitrexed) paired with a platinum salt which provides a 2-3 month median survival benefit. Arginine metabolism is dysregulated in mesothelioma with deficiency of the rate limiting enzyme argininosuccinate synthetase 1 (ASS1) three-fold higher in sarcomatoid and biphasic compared to epithelioid tumours. ASS1 inactivation via promoter methylation diverts the precursor aspartate for enhanced pyrimidine synthesis via carbamoyl-phosphate synthetase 2 (CAD), accounting in part for increased tumorigenesis. However, loss of ASS1 generates a collateral dependence on exogenous arginine for growth (auxotrophy) that may be exploited with arginine-degrading enzymes, such as arginine deiminase and arginase. A randomised phase 2 trial of pegargiminase (ADI-PEG20, pegylated arginine deiminase) monotherapy delivered as a weekly intramuscular (IM) injection (36mg/m2) in patients with ASS1-deficient mesothelioma (ADAM study; NCT01279967) revealed a 1.2 month progression-free survival benefit over best-supportive care (BSC) only (3.2 versus 2.0 months; hazard ratio of 0.56; and p=0.03). The restricted mean survival for OS, calculated due to early survival curve cross-over, was 15.7 months for the pegargiminase group versus 12.1 months for the BSC group, for a difference of 3.6 months (p=0.13). Pegargiminase was well-tolerated with a 13.6% grade 3-4 allergic rate, including anaphylactoid reactions and serum sickness, which were readily reversible and a low frequency of grade 1-2 reactions, mostly local skin irritation and discomfort due to the IM therapy. Pharmacodynamically, pegargiminase suppressed arginine plasma levels (measured on the day of and prior to drug dosing) for 4 weeks before a return to baseline with a reciprocal change in the degradation product, citrulline, a consequence of the production of drug-neutralising antibodies. Partial metabolic responses were documented by FDG-PET in almost 50% of patients by the third week of pegargiminase administration. Thus, while the PFS primary endpoint was modest, the ADAM trial is the first proof of principle study to show a survival benefit using an ASS1 biomarker-directed strategy. More recent efforts in the arginine deprivation field have focused on rational drug combinations. Preclinically, pegargiminase reduces intracellular thymidine pools via inhibition of enzymes involved in de novo synthesis, specifically thymidylate synthetase and dihydrofolate reductase, and pyrimidine salvage via thymidine kinase 1, collectively enhancing pemetrexed cytotoxicity in arginine-auxotrophic tumour cell lines, including mesothelioma. This was tested in the phase 1 TRAP study (NCT02029690) combining pegargiminase with pemetrexed and cisplatin (ADIPemCis) in patients with ASS1-deficient mesothelioma (n=5) and non-squamous non-small cell lung cancer (NSCLC, n=4). The dose-escalation portion of the study revealed ADIPemCis was safe with a 78% (n=7/9) partial response rate and an overall 100% disease control rate. Moreover, partial responses were seen in biphasic and sarcomatoid mesothelioma considered to be largely chemorefractory. The overall PFS and OS in this small study was 7.5 and 13.9 months, respectively. A dose expansion cohort in mesothelioma at the maximum tolerated dose confirmed a similarly high disease control rate of 93.5% (29/31) and, with two-thirds of patients with non-epithelioid mesothelioma (10 biphasic and 10 sarcomatoid), an overall median PFS of 5.6 and OS of 10.1 months was observed. Although, a small series there was a 3 fold-higher survival at 12 months for patients with sarcomatoid mesothelioma compared with historical controls (30% versus 10% survival). These data supported the opening of a randomised double-blind phase 2/3 trial called ATOMIC-meso and the first to focus on the most aggressive subtypes of mesothelioma that is expected to report initial results by 2020 (NCT02709512). Mesothelioma therapeutics are at a crossroads with increasing evidence for a key role of immunotherapy in a subset of patients. Objective responses of 10-30% have been reported in several phase 1-2 studies of PD1/PD-L1 antagonists with or without CTLA4 blockade in patients with mesothelioma. Pegargiminase increases PD-L1 expression on mesothelioma cells and leads to an influx of T cells in immunocompetent murine tumour models. Furthermore, urea cycle dysregulated cancers with increased aspartate flux and pyrimidine synthesis are hypothesized to generate genomic signatures more amenable to immune checkpoint blockade. Preliminary results of a phase 1 study of pegargiminase and pembrolizumab reveal activity in arginine auxotrophic cancers with good safety and tolerability (NCT03254732). Similarly, a first-in-man trial of platinum, pemetrexed combined with pegargiminase and atezolizumab (iTRAP study) is planned to start in 2019 focusing on patients with ASS1-deficient non-squamous NSCLC (NCT03498222). Pending these early data, and further ASS1 and PD-L1 biomarker analyses, additional studies are planned in patients with mesothelioma. Recent preclinical work in our laboratory has revealed that arginine deprivation has a key role in remodulating the tumour microenvironment with an increase in macrophages involved in resistance to pegargiminase. Mesothelioma cells co-cultured with macrophages released several proinflammatory cytokines including IL-1alpha and the CXCR-2 dependent chemokines IL-8, CXCL2 and CXCL8 with a co-ordinate increase in ASS1 and ASL in macrophages and tumour cells, respectively bypassing sensitivity to pegargiminase. Moreover, analysis of blood from the ADAM study revealed an increase in argininosuccinate in the plasma of early metabolic progressors and paired biopsies from the TRAP mesothelioma expansion cohort revealed an influx of macrophages consistent with the preclinical work. Thus, re-education of macrophages with chemokine or "don't' eat me" inhibitors may be a viable strategy in mitigating stromal resistance to pegargiminase. Further optimisation of pegargiminase for the treatment of mesothelioma may come from manipulation of additional resistance pathways. Thus, antimalarial agents such as chloroquine inhibit autophagy, a common escape mechanism to nutrient deprivation, and have enhanced the effect of arginine depletion in various ASS1 negative tumour cell lines including mesothelioma. Lastly, synthetic lethal approaches targeting polyamine metabolism in ASS1-negative mesothelioma cells, also merit clinical investigation in combination with pegargiminase and may lead to deeper and more durable metabolic responses. In summary, bench-to-bedside studies of pegargiminase have progressed to a phase 2/3 trial in mesothelioma. Combinations of pegargiminase with immune checkpoint blockade and modulators of resistance pathways appear promising areas for further development.

Keywords: pegargiminase, arginine, mesothelioma systemic therapy

ES03 BAP-1 AND OTHER NOVEL MOLECULAR AND METABOLIC TARGETS IN MESOTHELIOMA
SUNDAY, SEPTEMBER 8 10:30–12:00

ES03.05 INHERITED PREDISPOSITION TO MESOTHELIOMA, BIOLOGICAL AND CLINICAL DIFFERENCES WITH SPORADIC MESOTHELIOMA

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Why less than 5% of those exposed to asbestos develop malignant mesothelioma, [1] has long fueled the hypothesis that inherited genetic factors may contribute to risk. Studies in erionite exposed households in Turkey suggested that inherited genetic factors cooperate with shared exposures in mesothelioma development.[2] In 2011, the discovery of inherited mutations in the gene *BAP1* in families clustering multiple cases of mesothelioma[3] and demonstration of further proof of causation in a mouse model, showing that mice

with one abnormal copy of *Bap1* develop mesothelioma more quickly, with lower asbestos doses, and at a higher proportion than wild-type mice[4, 5] solidified the role of inherited genetics in mesothelioma risk. Failure to detect inherited *BAP1* mutations in a substantial subset of cancer-prone and sporadic mesothelioma cases suggested, however, that *BAP1* was not the only gene involved. A strong family history of many types of cancer has also been observed, suggesting that other broad cancer susceptibility genes were involved.[6, 7] Recently, our group as well as groups at the NCI and in Italy all published results of targeted panel-based genomic sequencing of three unselected series of mesothelioma cases (Table 1).[8-10] We all found a similar overall germline mutation frequency of 10-12%, placing mesothelioma among a growing number of solid tumors, such as metastatic prostate cancer, with mutation frequencies in this range. Clinical predictors of a germline mutation from all three series include: peritoneal compared with pleural disease, younger age, those with a personal history of other cancers, female gender, and lower level of prior asbestos exposure. By gene, *BAP1* accounted for the most mutations, but overall more than half of those carrying a germline mutation carried a mutation in a gene other than *BAP1*. Biologically, most of these genes function predominantly in DNA repair pathways, especially the homologous recombination pathway involved in double strand break repair. These data may explain prior observations of complex cytogenetics and other features of genomic instability in mesothelioma tumors[9-11] and could explain platinum sensitivity, a chemotherapy drug known to have increased efficacy in solid tumors, such as ovarian cancer, in those with germline mutations in genes in the same pathway. To investigate this possibility, we combined our data with data from the NCI series and together, our groups found that a germline mutation in any DNA repair gene was associated with improved OS after platinum based chemotherapy and that this effect was independent of age at diagnosis and gender, two key known prognostic factors.[9] Interestingly, this effect was only present in those with pleural disease, in whom mutation carriers had a median OS of 7.9 vs 2.4 years in non-mutation carriers (p=0.0012). Further, among germline mutation carriers, OS for those with pleural or peritoneal disease was similar suggesting a similar biology is a more important predictor of OS than site in those cases. These data support the investigation of other DNA repair based therapies, such as PARP inhibitors, in patients with mesothelioma, especially among those with a relevant germline mutation. Further investigation of the full spectrum of inherited risk factors in mesothelioma, their interaction with response to various therapies, as well as how patterns of acquired mutations in mesothelioma tumors differ by germline mutation status and whether those without a germline mutation but whose tumors acquire similar gene mutations respond to similar therapies are all yet to be determined.

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Table 1. Summary of multigene panel-based germline genetic testing studies in unselected series of malignant mesothelioma

Paper	Sequencing method	Site of origin (n)	Patient selection criteria	Overall proportion with P or LP germline mutation	Genes mutated (n)	Clinical factors associated with mutation frequency
Betti et al 2017	Targeted capture and NGS of 94 genes	Pleural (93)	none	10% (9 of 93)	*ATM* (1) *BRCA1* (1) *BRCA2* (1) *FANCC* (1)** *FANCF* (1)** *PALB2* (1) *PMS1* (1)** *SLX4* (1)** *XPC* (1)**	Lower mean lifetime quantitative asbestos exposure index in carriers of a pathogenic variant vs those without (3.8 vs 24.9 p=0.0015)
Panou et al 2018	Targeted capture and NGS of 85 genes	Pleural (148) Peritoneal (44) Both (3) TV (3)	none	12% (13 of 198)	*ATM* (2) *BAP1* (6) *BRCA1* (1) *BRCA2* (3) *CDKN2A* (2) *CHEK2* (3) *MRE11A* (1)** *MSH6* (1) *SDHA* (1) *TMEM127* (1) *TP53* (1) *VHL* (1) *WT1* (1)	Pleural (OR 0.23; 0.1 to 0.58) Asbestos exposure (OR 0.28; 0.1 to 0.72) Age (OR 0.96; 0.92 to 0.99)
Hassan et al 2019	Targeted capture and NGS + CNV analysis of 73 genes	Pleural (140) Peritoneal (92) Pericardial (2) TV (7)	none	12% (28 of 239)	*BAP1* (16) *BRCA2* (1) *CHEK2* (5) *MLH1* (1) *MRE11A* (1)** *PALB2* (2) *POT1* (1)** *TP53* (1)	Female gender (p=0.02) Age <60 (p=0.03)

**Association of a single truncating variant in this gene with moderate to high penetrance cancer risk is controversial or not yet definitively established.

Keywords: inherited genetics, Mesothelioma, Germline

ES04.01 UPDATE IN SYSTEMIC TREATMENT OF SCLC

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Chemotherapy combination of cisplatin plus etoposide is the standard option for extensive stage Small Cell Lung Cancer (SCLC); though the response rate was very high, however most cases of the extensive stage recurred within one year and there was no good regimen for second line. Several chemotherapeutic agents such as topotecan, irinotecan, amrubicin or combination of cyclophosphamide, doxorubicin and vincristine (CAV) had been used as second line treatment with minimal benefit. Within the past couple years there're the new way of treating lung cancer especially the use of immunotherapy, which several agents had their roles in the treatment of Non-Small Cell Lung Cancer (NSCLC). The study of immunotherapy in SCLC was very slow. The use of T cell immune-checkpoint inhibitors (anti-PD1: nivolumab, pembrolizumab; anti-PD-L1: atezolizumab, durvalumab; anti-CTLA-4: ipilimumab, tremelimumab) have shown promising antitumor activity with the potential to prolong survival in SCLC patients. Nivolumab was the first immunotherapy agent that had approved by The US Food and Drug Administration (FDA) 2018 to be the third line drug according to the outcome in CheckMate-032, which's a multicenter, open-label trial in patients with metastatic solid tumors. This subgroup comprised 109 patients with metastatic SCLC, with disease progression after platinum-based therapy and at least one other prior line of therapy, regardless of tumor PD-L1 status. All patients received nivolumab at3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. The ORR was 12% (95% CI: 6.5, 19.5). Responses were durable for 6 months or longer in 77%, 12 months or longer in 62%, and 18 months or longer in 39% of the 13 responding patients. PD-L1 tumor status did not appear to be predictive of response. Pembrolizumab has been granted a priority review designation by the FDA for the treatment of patients with advanced small cell lung cancer (SCLC) whose disease has progressed following ≥2 prior lines of therapy. Data from the phase II KEYNOTE-158 and phase Ib KEYNOTE-028 studies, pembrolizumab at 200 mg intravenously (IV) every 3 weeks for 2 years or until disease progression, unacceptable toxicity, or study withdrawal elicited 19% and 33% overall response rates (ORRs) in patients with extensive-stage SCLC, respectively. Atezolizumab plus carboplatin and etoposide, was approved by FDA for the first-line treatment of adult patients with extensive-stage small cell lung cancer based on the data from IMpower133 which is a randomized treatment using atezolizumab 1200 mg and carboplatin AUC 5 mg/mL/min on day 1 and etoposide 100 mg/m2 intravenously on days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by atezolizumab 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or placebo and carboplatin AUC 5 mg/mL/min on day 1 and etoposide 100 mg/m2 intravenously on days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles, followed by placebo once every 3 weeks until disease progression or unacceptable toxicity. Overall survival (OS) was 12.3 months for patients receiving atezolizumab with chemotherapy and 10.3 months for those receiving placebo with chemotherapy (hazard ratio 0.70; 95% CI: 0.54, 0.91; p=0.0069). Median PFS was 5.2 months (4.4, 5.6) compared with 4.3 months (4.2, 4.5) in the atezolizumab and placebo arms, respectively (HR 0.77; 0.62, 0.96; p=0.0170). In conclusion, there are several new ways and also new agents that target the immune cell and should be able to improve the outcome and survival of SCLC.

Keywords: small cell lung cancer, immunotherapy

ES04 MULTIMODALITY MANAGEMENT OF SMALL CELL AND NEUROENDOCRINE CANCERS
SUNDAY, SEPTEMBER 8 10:30–12:00

ES04.02 PATHOLOGY OVERVIEW FOR CARCINOID AND NE SPECTRUM

E. Brambilla

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The spectrum of neuroendocrine (NE) tumors ranges from low grade typical carcinoid (TC) to intermediate grade Atypical carcinoids to high grade small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) Although very different from high grade tumors in their molecular genetics and expression profiling, carcinoid are included in the spectrum of NE tumors since WHO 2015 (1) on the basis of their common NE epithelial differentiation.Carcinoids display many clinical differences with high grade NE tumors being not strongly associated with smoking (only 20-40% smokers), their specific association with Multiple Endocrine Neoplasia type 1 (MEN1) not seen in High grade tumors and their occurrence on the background of NE cell hyperplasia and tumorlets in 60% of TC and AC, very rare in high grade tumors. Whereas carcinoid are never combined with conventional lung cancer, 20 to 25% of SCLC and LCNEC are combined. Since the NE markers are common in the full spectrum, morphology, mitoses and KI 67 (proliferations markers) are useful to differentiate carcinoids from SCLC and LCNEC. The accurate diagnosis of each is critical in view of their eminently different therapeutic management. Small cell lung carcinoma (SCLC SCLC is the most frequent NE lung tumor (15-20% of lung cancer) and has the worse prognosis in the spectrum. Most are proximal, 70% perihilar forming peribronchial growth involving lymph nodes .Less than 5% are solitary primary nodules stage I. SCLC is a high grade malignant epithelial NE tumor with characteristic cytopathologic features recognizable in routine microscopy without use of immunohistochemistry (IHC) in optimal cell preservation. IHC may be used in suboptimal condition (crush artifact) to confirm the diagnosis. SCLC is made of sheets of small cells ,round/oval or spindle shaped forming whorls, with little cytoplasm, nuclei with unconspicuous nucleoli, finely granular dispersed chromatin, and nuclear molding. Mitotic rate is very high more than 50 reaching 100 for 2mm^2 and KI67 exceeds 50% (50-100%).Extensive necrosis is frequent .Most SCLC express NE markers Chromogranine A, Synaptophysin and CD56. 75% express TTF1 (recommended clone 8G7G3 1). Less than 10% remain negative for all 3 NE markers and TTF1. In these cases a P40 staining is mandatory to eliminate a basaloid carcinoma (P40 Positive) with which it may be confused in suboptimal preparations. SCLC can present as pure or combined. Any association of small cells with another NSCLC (Adenocarcinoma, Squamous cell carcinoma, large cell or large cell NE carcinoma, sarcomatoid giant and spindle cells) is diagnosed as combined SCLC (20%). Several studies of their molecular characteristics were recently published and compared with other tumors of the NE spectrum. Theses are specific, closer from a part of LCNEC but distinct from theses of carcinoids (Georges 2016, Georges 2018). Small cell carcinoma in non-smokers should be looked for EGFR mutation (acquired after TKI therapy of an Adenocarcinoma or spontaneous). Large cell neuro endocrine carcinoma (LCNEC) LCNEC is a high grade NE lung tumor accounting for 3% of lung cancers .The diagnosis is based on the necessary association of NE morphology (organoid nesting ,rosettes ,palisading) and expression of NE markers (at least one):chromogranine A, synaptophysin and CD56. Seventy-nine % develop in the lung periphery, 5% show endobronchial growth .They form circonscribed nodular mass intensely necrotic .They lack typical cytology in contrast with SCLC .The mitotic rate is more than 10 per 2mm^{2}to distinguish them from atypical carcinoid (2 -10/2mm ^{2}) ,ranging from 20 to 80-100 with KI67 very high exceeding 50% usually 80-100%. They are composed of large cells with low nuclear to cytoplasmic ratio, a conspicuous nucleoli and vesicular chromatin .A spectrum of morphologies range from SCLC (small cell –like) to non small cell-like or to a few atypical carcinoids-like, showing the need for an accurate diagnosis using objective criteria (proliferation). A constellation of multiple criteria should be used to distinguish them fro SCLC or AC .Combined LCNEC is the association of any LCNEC component with a conventional component (25%). Due to spatial heterogeneity of NE morphology and NE expression the diagnostic may be difficult on small biopsies .However a NSCLC without NE morphology but 1 or 2 NE markers is diagnosed as a NSCLC (with unclear phenotype) since 15 % of NSCLC also express 1 or 2 NE markers.TTF1 is expressed in 41 % of LCNEC specially when combined with adenocarcinoma.Molecular genomics and expression profiling

classify in 2 categories one simiilar to SCLC with biallelic inactivation of P53 and RB genes and another with KEAP 1 or LKB1 mutations looking like NSCLC .LCNEC are very different from Carcinoids (Georges 2018) Carcinoids tumors:Typical and Atypical Carcinoids Carcinoids account for 1-2 % of lung tumors of which 10% are Atypical carcinoid .Typical (low grade) and atypical carcinoids(intermediate grade) are distinquished on objective criteria (mitoses index (table I) and necrosis, but KI67 has no defined cut- off to separate them. They develop centrally as endobronchial growth or in the lung periphery (16-40 %) Cytology allows accurate recognition. NE morphology is well achieved with organoid patterns(glandular, follicular ,trabecular, angiomatoid...) most often multiple .Spindle cell pattern is more frequent in the peripheral carcinoids. All express the 3 NE markers and TTF1 is usually negative (except in a few peripheral carcinoids) References Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO classification of tumours of the lung, pleura, thymus and heart, 4th ed. Lyon: IARC; 2015. Travis WD ,Nicholson AG ,Geisinger KR, Brambilla E.Tumors of the lower respiratory tract AFIP Atlas of Tumor pathology series 4 ed. AFIP Press Bethesda 2019

ES04 MULTIMODALITY MANAGEMENT OF SMALL CELL AND NEUROENDOCRINE CANCERS
SUNDAY, SEPTEMBER 8 10:30–12:00

ES04.04 ROLE OF STEREOTACTIC BODY RADIATION IN EARLY AND ADVANCED SCLC

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Stereotactic Body Radiotherapy (SBRT) has been rapidly adopted as the standard of care for patients with early-stage Non-Small Cell Lung Cancer (NSCLC) who are medically inoperable, and more recently for selected patients with oligometastatic cancer. The utilization of SBRT in patients with Small Cell Lung Cancer (SCLC) is markedly lower, reflecting both the lower incidence and the lack of clinical data, but it has been increasing over the past several years. Given the aggressive nature and high metastatic potential of SCLC, the optimal integration of SBRT into the multimodality treatment of early-stage SCLC patients is critical, so that we don't delay or otherwise compromise systemic therapy. In patients with advanced or recurrent SCLC, SBRT offers a valuable treatment option for well selected patients, a group that may be increasing as new therapeutic options emerge. Small Cell Lung Cancer (SCLC) represents less than 20% of all new lung cancer diagnoses. Compared to NSCLC, SCLC is less likely to present with localized disease, carries a higher risk of metastatic failure, and stage for stage is associated with worse overall survival. The majority of limited stage SCLC patients have locally advanced tumors, and the standard of care remains concurrent chemotherapy with fractionated thoracic radiation. Stage I SCLC is diagnosed in less than 5% of incident cases. Given the propensity for nodal metastasis, invasive staging of the mediastinum is indicated in all of these patients. For those who are node negative, there is a limited amount of data to guide decisions about optimal management. Surgery has emerged as a standard of care for operable patients, based on favorable outcomes in population-based studies. Following surgery, adjuvant chemotherapy is recommended regardless of tumor size, based on the high risk of subsequent metastatic failure. For those patients who won't tolerate lobectomy, consensus guidelines now recognize that Stereotactic Body Radiotherapy (SBRT) is a treatment option, and a reasonable alternative to conventional chemoradiotherapy. This is largely justified by the observed increased efficacy of SBRT compared to fractionated radiation in stage I NSCLC, an observation which is now supported by a randomized trial. The published data to date suggests that the utilization of SBRT in stage I SCLC has been increasing. Single- and multi-institutional case series suggest, unsurprisingly, that this approach appears to be safe, and the efficacy in terms of local control appears to be similar to that seen in NSCLC patients. In the US, the use of SBRT in SCLC appears to be more common in elderly patients, and the utilization seems to be driven by large institutions. Chemotherapy is an essential part of multimodality care of SCLC in all stages of disease. The addition of adjuvant chemotherapy sequentially after SBRT in early stage patients is associated with improved survival in retrospective studies, similar to the better outcomes seen with surgery and chemotherapy in operable SCLC patients. Recent and ongoing prospective efforts are evaluating concurrent chemotherapy with SBRT, including both traditional short-course and more extended hypo-fractionated radiation schedules. Trends in stereotactic body radiation therapy for stage I small cell lung cancer. Stahl JM, Corso CD, Verma V, Park HS, Nath SK, Husain ZA, Simone CB 2nd, Kim AW, Decker RH. Lung Cancer. 2017 Jan;103:11-16. Multi-Institutional Experience of Stereotactic Ablative Radiation Therapy for Stage I Small Cell Lung Cancer. Verma V, Simone CB 2nd, Allen PK, Gajjar SR, Shah C, Zhen W, Harkenrider MM, Hallemeier CL, Jabbour SK, Matthiesen CL, Braunstein SE, Lee P, Dilling TJ, Allen BG, Nichols EM, Attia A, Zeng J, Biswas T, Paximadis P, Wang F, Walker JM, Stahl JM, Daly ME, Decker RH, Hales RK, Willers H, Videtic GM, Mehta MP, Lin SH. Int J Radiat Oncol Biol Phys. 2017 Feb 1;97(2):362-371. Clinical Outcomes of Stereotactic Body Radiotherapy for Patients With Stage I Small-Cell Lung Cancer: Analysis of a Subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database. Shioyama Y, Onishi H, Takayama K, Matsuo Y, Takeda A, Yamashita H, Miyakawa A, Murakami N, Aoki M, Matsushita H, Matsumoto Y, Shibamoto Y; Japanese Radiological Society Multi-Institutional SBRT Study Group (JRS-SBRTSG). Technol Cancer Res Treat. 2018 Jan 1;17:1533033818783904. Stereotactic body radiotherapy with concurrent chemotherapy extends survival of patients with limited stage small cell lung cancer: a single-center prospective phase II study. Li C, Xiong Y, Zhou Z, Peng Y, Huang H, Xu M, Kang H, Peng B, Wang D, Yang X. Med Oncol. 2014 Dec;31(12):369. Outcomes of Stereotactic Body Radiotherapy for T1-T2N0 Small Cell Carcinoma According to Addition of Chemotherapy and Prophylactic Cranial Irradiation: A Multicenter Analysis. Verma V, Simone CB 2nd, Allen PK, Lin SH. Clin Lung Cancer. 2017 Nov;18(6):675-681.e1.

Keywords: SBRT, small cell lung cancer

ES04 MULTIMODALITY MANAGEMENT OF SMALL CELL AND NEUROENDOCRINE CANCERS
SUNDAY, SEPTEMBER 8 10:30–12:00

ES04.05 ADVANCES IN RADIONUCLIDE TREATMENT FOR NEUROENDOCRINE TUMOURS

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Lung carcinoids (LC) are rare tumours, however incidence is increasing due to improvement in diagnostic techniques. They account for approximately 2% of all lung malignancies and around 20-30% of all neuroendocrine tumours (NETs). They characteristically have an indolent clinical behaviour with longer survival intervals compared to poorly differentiated lung neuroendocrine malignancies. LC are divided into typical or atypical carcinoid tumours according to pathological characteristics, such as amount of mitosis and necrosis. A significant proportion of LC expresses somatostatin receptors by immunohistochemistry. Nuclear medicine imaging, such as somatostatin receptor scintigraphy, has been employed for staging of LC for years. Development of new nuclear medicine imaging techniques, including Positron Emission Tomography (PET) combined with CT has improved diagnosis, staging and treatment of patients diagnosed with LC. 68-Gallium(^{68}Ga)-radiolabelled PET (^{68}Ga-DOTA-PET) tracers for functional NET imaging have emerged as potentially useful tools for diagnosis and staging. For localised stages of LCs, surgery is the treatment of choice, performed with curative intent. Locally advanced inoperable or metastatic tumours are treated with palliative approaches based on somatostatin analogues (SSAs), temozolomide-based chemotherapy combination and targeted therapies (everolimus). Recently, the use of Peptide Receptor Radionuclide Therapy (PRRT) has revolutionised the treatment of extra-pulmonary neuroendocrine tumours. Based on the results of the NETTER-1 study, PRRT has been approved for the management of small bowel and pancreatic NETs and it is considered a standard of care after progression to SSA for patients with uptake in ^{68}Ga-DOTA-PET (theranostic approach). This lecture will summarise the state of the art of LC with a focus behind the rationale of PRRT and its potential role in the management of LCs.

Keywords: Neuroendocrine, PRRT, carcinoid

ES04.06 SYSTEMIC TREATMENT OF LARGE CELL NEUROENDOCRINE CANCER

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Large cell neuroendocrine cancer (LCNEC) is a rare, aggressive cancer that accounts for approximately 3% of all lung cancer. It is characterised by high-grade features (>10 mitoses/2mm2) and the presence of neuroendocrine morphology and markers (1). The diagnosis of LCNEC is distinct from both non-small cell lung cancer (NSCLC) and other pulmonary neuroendocrine tumours such as carcinoids and small cell lung cancer (SCLC). Survival is poor with only 5% of patients alive at 5 years from diagnosis regardless of stage at presentation. Conventionally treatment has mirrored that of SCLC despite limited evidence for this approach. The recommended standard of care is a combination of platinum with etoposide based on the results of one single arm phase 2 study in which there were only 29 evaluable patients (2). The median progression free survival (PFS) and overall survival (OS) rates were 5 months and 8 months respectively. Of note the observed objective response rate was 34%, lower than reported ORRs in SCLC of ~70%. Similar worse outcomes in the LCNEC population are observed for treatment with irinotecan and cisplatin (3). The explanation for this disparity is provided by emerging evidence that LCNEC can be subcategorised into two major and clinically relevant subsets according to genomic characteristics (4). A 'SCLC-like' genomic profile is estimated to account for about 40% of LCNEC, characterised by RB1 and TP53 that hallmark SCLC and 'SCLC-like' LCNEC has clinical behaviour consistent with SCLC. The other subset is 'NSCLC-like' with wild-type RB1 as the main distinction alongside mutations that also occur recurrently, at various frequencies, in NSCLC such as STK11, KRAS, KEAP1 and NFE2L2. The latter were hypothesised to be relatively more sensitive to chemotherapy approved for NSCLC. Consistent with this, in a carefully conducted retrospective analysis patients with NSCLC-like LCNEC (RB1 wild type) who received platinum with gemcitabine or a taxane had a median OS of 9.6 months whereas those who received platinum and etoposide had a significantly shorter median OS of 5.8 months (p=0.026) (5). These results question the current standard of care for LCNEC and highlight the need for prospective examination of molecular subtyping to direct treatment decision making. The molecular heterogeneity underpinning LCNEC may also have implications for selection of immune checkpoint inhibitors (6) and other precision medicines targeting actionable mutations (7). The advent of specific KRAS inhibitors that appear promising in early phase development (8) generates further impetus to redesign our therapeutic algorithms for LCNEC according to genomic context if we are to improve outcomes for patients with this orphan disease. References 1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors. Journal of Thoracic Oncology.10(9):1243-60. 2. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. Le Treut J et al. Ann Oncol. 2013: 24(6):1548-52. 3. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicentre phase II study. Niho et al. J Thoracic Oncol 2013: 8:980-4 4. Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma–like and Non–Small Cell Carcinoma–like Subsets. Rekhtman N et al. Clinical Cancer Research. 2016;22(14):3618. 5. Molecular Subtypes of Pulmonary Large-cell Neuroendocrine Carcinoma Predict Chemotherapy Treatment Outcome. Derks JL et al. Clinical Cancer Research. 2018;24(1):33. 6. Genomic Alterations (GA) and Tumor Mutational Burden (TMB) in Large Cell Neuroendocrine Carcinoma of Lung (L-LCNEC) as Compared to Small Cell Lung Carcinoma (SCLC) as Assessed Via Comprehensive Genomic Profiling (CGP). Chae et al. J Clin Oncol 2017; 35:15 suppl, 851 7. Comparison of genomic landscapes of large cell neuroendocrine carcinoma, small cell lung carcinoma, and large cell carcinoma. Zhou Z et al. Thorac Cancer 2019 10(4):839-847 8. Direct Ras G12C Inhibitors:Crossing the Rubicon. Lindsay C and Blackhall F. BJC. 2019 In press

Keywords: LCNEC, RB1, Chemotherapy

ES05.01 LUNG CANCER SURVIVAL: PROGRESS AND CHALLENGES

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Background Between 1970s and 2011, many tumour 10-year survival rates increased significantly (eg prostate cancer from 25% to 84%) yet lung cancer lags behind with 5-year survival below 20%.1, 2 Most countries have no lung cancer screening programme and >80% of patients are diagnosed with advanced disease. A significant challenge for the United States lung cancer screening programme is poor uptake by low income but high risk candidates.3 To optimise results from potential curative radical radiotherapy and surgery, accurate staging of patients is vital; modern staging can improve patient selection for radical treatment, with stage 1 lung cancer 4-year overall survival (OS) increased in one study by 14.3% between 2001 and 2010, and postoperative survival improved from 51.5% to 66.5%.4 Over 80% of patients diagnosed with lung cancer are active or past cigarette smokers, and the need to maximise prevention remains. Government implemented smoking bans and funding of smoking cessation programmes are important, despite sketchy evidence for the latter being of benefit to lung cancer patients.5 Radiotherapy progress Improved techniques allow accurate targeting with stereotactic ablative radiotherapy (SABR) for patients with a small tumour who are unfit for surgery. In stage III NSCLC, CT simulation results in a smaller tumour target, better dose delivery and fewer side-effects. The immune stimulating effect of radiotherapy may increase effectiveness of immunotherapy (IO) on which further research continues. Radiotherapy ablation of oligometastatic tumours is also under investigation in ongoing attempts to improve survival in advanced disease. Systemic therapies improving survival There has been little improvement in small cell lung cancer (SCLC) outcomes the since 1980s, but progress for the 85% of patients with non-small cell lung cancer (NSCLC) is impressive, resulting from improved understanding of tumour molecular biology. Chemotherapy combinations seemed equivalent in NSCLC until groundbreaking results showed better survival in non-squamous NSCLC who received platinum with pemetrexed over gemcitabine.6 Maintenance pemetrexed improved survival still further in patients with NSCLC stable or responsive to induction chemotherapy. Controversy over patient selection for targeted therapy with tyrosine kinase inhibitors was resolved by the IPASS study which confirmed that testing for a sensitising EGFR mutation status was mandatory to ensure benefit.7 Patients inevitably develop resistance to EGFR TKIs and tumour rebiopsy is encouraged to determine the new molecular profile to optimise subsequent treatment. The new generation TKI osimertinib gave superior survival as first line therapy compared with erlotinib or gefitinib. In patients with ALK translocated NSCLC (approximately 5% of tumours), crizotinib was better than chemotherapy. More recently alectinib or brigatinib superceded as survival improved through their enhanced effectiveness in the CNS.8 Drugs are available to treat lung cancers with less common genetic drivers like ROS1 and BRAF but the commonest NSCLC mutation KRAS - in up to 30% cases - is not yet amenable to specific therapy, although several drugs are in development. Reflex testing by pathologists of non-squamous NSCLC is recommended with squamous tumours tested only in never smokers or mixed adenosquamous lung cancer.9 Identification of EGFR or ALK oncogene addicted lung cancers is vital to ensure delivery first line of appropriate targeted therapy since this increases patients' survival. NSCLC response to IO drugs targeting PD-1 and PD-L1 has revolutionised systemic therapy. Nivolumab was effective in relapsed squamous NSCLC, then first line pembrolizumab superceded chemotherapy in patients with >50% PD-L1 expressing non-squamous tumours. Atezolizumab (second line) and pembrolizumab-chemo (first line) efficacy are independent of PD-L1 expression. In stage III NSCLC, patients with no tumour progression following combination chemoradiotherapy have better OS with maintenance durvalumab.10 An important feature is the durable response to IO seen in some patients, with toxicity usually manageable and less than many chemotherapies. Studies with IO as adjuvant and neoadjuvant treatments are ongoing. Since IO treatment may continue every 2-3 weeks by intravenous infusion for up to two years, there is a significant impact on pharmacy, hospital time for patients and healthcare costs. More research is ongoing to mitigate these burdens. Conclusion Improving survival in lung cancer patients remains a challenge dependent on prevention, screening,

optimal surgery, modern radiotherapy and improved systemic therapies targeted through understanding the molecular biology of these heterogenous tumours. Despite clear progress to date, there is much need for improvement, offering ample opportunity for future research. References 1 Quaresma M, Coleman MP, Rachet B (2015) 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales 1971-2011: a population-based study. Lancet 385:1206-1218 2 Allemani C, Weir HK, Carreira H et al (2018) Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391:1023-1075 3 Schutte S, Dietrich D, Montet X and Flahault A (2018) Particiation in lung cancer screening programs: are there gender and social differences? A systematic review. Public Health Reviews 39: 23-35 4 Boyer MJ, Williams CD, Harpole DH et al (2017) Improved survival of Stage I Non-Small Cell Lung Cancer: A VA Central Cancer Registry Analysis. J Thorac Oncol 12:1814-1823 5 Zeng L, Yu X, Xiao J, Huang Y (2019) Interventions for smoking cessation in people diagnosed with lung cancer. CochraneSystematic Review https://doi.org/10.1002/14651858. CD011751.pub3 6 Scagliotti G, Hanna N, Fossella F et al (2009) The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist 14:253-263 7 Mok TS, Yi-Long W, Thongprasert S, Chih-Hsin Y (2009) Gefitiib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957 8 Peters S, Camidge DR, Shaw AT et ak (2017) Alectinib versus crizotinib in untreated ALK-positive nono-small cell lung cancer. N Engl J Med 377:829-838 9 Planchard D, Popat S, Kerr K et al (2018) Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29 (suppl4):iv192 - iv236 10 Antonia SJ, Villegas A, Daniel D et al (2018) Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 379:2342-2350

Keywords: progress, Lung cancer, Survival

ES05 JOINT SESSION GLCC/IASLC: HOT TOPICS FOR LUNG CANCER ADVOCATES
SUNDAY, SEPTEMBER 8 10:30–12:00

ES05.02 FROM LIVING LONGER TO ALSO LIVING BETTER – THE ROLE OF COMMUNICATION AND INTERPROFESSIONAL COLLABORATION IN METASTATIC LUNG CANCER

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Despite ongoing progress in diagnostics and treatment, many patients with metastatic lung cancer still harbor a limited prognosis that may lead to existential uncertainty. These patients and their caregivers are confronted with a complex situation as burden comprises physical, psychosocial and spiritual needs [1]. During the illness trajectory they are exposed to different multiprofessional healthcare settings and providers that challenge the continuity and coordination of care. Therefore, the care of these patients and their relatives is often characterized by discontinuity, lack of coordination and insufficient communication [2]. Additionally, shared decision-making between active cancer treatment and end-of-life care constitutes a continuous and challenging balancing act for all who are involved in the process. Several studies have shown that early integration of palliative care (EPC) and adequate advance care planning (ACP) improve quality of life and satisfaction with care. Two studies evaluating EPC have even shown positive results in survival [3,4]. In the recommendation of the American Society of Clinical Oncology concerning the integration of palliative care into standard oncology care, the following were defined as essential components: "rapport and relationship building with patients and family caregivers; symptom, distress, and functional status management; exploration of understanding and education about illness and prognosis; clarification of treatment goals; assessment and support of coping needs; assistance with medical decision making; coordination with other care providers" [5]. This underlines the importance of communication in this setting and defines it as a central element for the effective provision of early palliative care. Another central element is interprofessional collaboration. Studies incorporating interprofessional involvement (notably physicians and nurses) showed more consistent results regarding the positive effects of EPC [6]. Through the different perspectives of the involved professions towards care needs, healthcare delivery may be enriched and become more holistic. Additionally, nurse navigation supports orientation in the healthcare system and provides continuity and coordination of care. For this strategy communication skills of healthcare providers and interprofessional collaboration should be strengthened. Joint communication training may play an important role to overcome interprofessional barriers and sharpen communication skills. Advanced communication techniques are essential for early integration of palliative care, facilitation of prognostic awareness, and by this means introduction or adaptation of advance care planning [7]. An interprofessional, longitudinally structured communication approach should improve the experience and outcomes of patients with advanced lung cancer and their caregivers [8]. Further research should address the feasibility of institutional strategies for implementing this approach. References: 1 Baile WF, Palmer JL, Bruera E, Parker P: Assessment of palliative care cancer patients' most important concerns. Support Care Cancer 2011;19:475-481. 2 Gagliardi AR, Dobrow MJ, Wright FC: How can we improve cancer care? A review of interprofessional collaboration models and their use in clinical management. Surg Oncol 2011; 20:146–54. 3 Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, Dionne-Odom JN, Frost J, Dragnev KH, Hegel MT, Azuero A, Ahles TA: Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. J Clin Oncol 2015;33:1438-1445. 4 Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ: Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2010;363:733-42. 5 Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, Firn JI, Paice JA, Peppercorn JM, Phillips T, Stovall EL, Zimmermann C, Smith T: Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:96-112. 6 Hui D, Bruera E: Integrating palliative care into the trajectory of cancer care. Nature Reviews Clinical Oncology 2016;13:159-71. 7 Jackson VA, Jacobsen J, Greer JA, Pirl WF, Temel JS, Black AL: The cultivation of prognostic awareness through the provision of early palliative care in the ambulatory setting: a communication guide. Journal of Palliative Medicine 2013;16:894-900. 8 Villalobos M, Siegle A, Hagelskamp L, Jung C, Thomas M. Communication along milestones in lung cancer patients with advanced disease. Oncology Research and Treatment 2019;42:41-46.

Keywords: Communication, interprofessional collaboration, metastatic lung cancer

ES05 JOINT SESSION GLCC/IASLC: HOT TOPICS FOR LUNG CANCER ADVOCATES
SUNDAY, SEPTEMBER 8 10:30–12:00

ES05.03 FROM LIVING LONGER TO ALSO LIVING BETTER; MANAGING LUNG CANCER AS A CHRONIC DISEASE - THE PRINCIPLE OF SURVIVORSHIP

M. Rigney

GO2 Foundation for Lung Cancer, Washington/United States of America

With exciting advances in lung cancer screening, diagnosis, and treatment, those diagnosed are living longer than ever before. Around the globe, more and more people are balancing the great hope and vast uncertainty of living with advanced lung cancer as a chronic disease. A chronic disease is one that lasts three months or longer, doesn't disappear, and is not preventable by vaccines nor curable by medicine. (US National Center for Health Statistics). Uncontrolled, any chronic disease can be life threatening. The 2008 IOM report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,* outlined the physical, emotional, social challenges, and financial stressors that result from living with a chronic disease. Cancer as a chronic disease increases anxiety, adds fear of recurrence, causes difficulties in making life plans, affects interpersonal relationships and prompts existential questioning. People diagnosed with lung cancer may additionally experience a myriad of distinct stigma-related challenges, including guilt, shame and increased isolation. Over ten years after the IOM report, cancer as a chronic disease remains a relatively unexamined area of study and, as Dr. Ross Camidge has said, "The rulebook hasn't been written." This presentation seeks to help us, the loved ones, advocates, clinicians, organizations and researchers begin to understand the unique needs of this population as we consider lung cancer as a chronic disease through: -- The lens of the ecological concept of the

ecotone -- Recognizing the effects of months or years of continuous or intermittent treatment on the individual -- A commonly accepted model of chronic disease management and coping -- The lived experiences of those effected, gathered through focus groups and one-to-one conversations

Keywords: Survivorship, Chronic disease

ES05 JOINT SESSION GLCC/IASLC: HOT TOPICS FOR LUNG CANCER ADVOCATES
SUNDAY, SEPTEMBER 8 10:30–12:00

ES05.04 SOCIAL MEDIA AND LUNG CANCER - A GLOBAL PICTURE

C. Sit[1], J. Fox[2], S. Malia[1]

[1]*Lung Cancer Canada, Toronto/Canada,* [2]*Roy Castle Lung Cancer Foundation, Liverpool/United Kingdom*

Social media has transformed the health communication landscape. It is evident in the rise of social media groups that social media is an important communications and connection tool for the community impacted by lung cancer. Individuals across the cancer continuum use social media for a myriad of purposes and there are differences between user profiles. For example, physicians and academics use social media to announce new innovative treatment options, for debate, and to highlight the successes and failures of lung cancer research. The general population utilizes social media to fundraise, garner support, and share their personal experiences with cancer. Social media may now be one of the most common communications vehicles for global campaigns concerning lung cancer, impacting education, fundraising and advocacy. In order to more optimally use social media to further objectives for patient organizations, it is integral to understand global trends in social media usage and what users are saying online. This global research project aims to answer these questions, as possessing more information on user trends will better inform those that are trying to reach and engage with these individuals. This global research project will also provide an opportunity for lung cancer professionals and organizations to refine their social media communications strategies. The research will identify best practices for organizations in engaging their lung cancer communities, as well as content strategies to boost reach, engagement and community size. *Purpose:*The objective of this research project is to evaluate the use of social media platforms, including Twitter, Facebook, and blogs, to understand *how*and *why*individuals are using each platform and *what*is being said. *Methodology:*Through the social listening tool *Brandwatch*this study will analyze social media usage between November 2018 to May 2019 in eleven (11) countries: Canada, United States, United Kingdom, Russia, Brazil, China, India, Israel, Australia, South Africa and Poland. This study utilizes topic analysis to understand the qualitative themes that are currently happening in the online conversation. These eleven (11) countries have been chosen due to high incidents of lung cancer, confidence in government data on lung cancer statistics, and frequency of social media use. In each jurisdiction, *Brandwatch*monitors the use and flux of specific key terms relating to lung cancer. In analyzing the data that *Brandwatch* generates, the team can effectively monitor the conversations (frequency, subject, emotion, and corresponding debate) that happen at a grassroots level. In a parallel research method, the project will gather data from over forty (40) lung cancer organizations' social media accounts across all major platforms including Facebook, Twitter, LinkedIn, Pinterest and YouTube. This data will be analyzed quantitatively and qualitatively to identify which social media strategies work best to engage members of the online lung cancer communities globally. *Analysis:*Preliminary findings indicate that the conversations occurring on social media across jurisdictions are both profoundly different yet have underlying similarities. Data will be extracted from initial findings to target populations with campaigns on issues that matter distinctly to them. As technology continues to drive decision-makers, organizations must adapt to foster the best results. In understanding who and how to target populations, it is expected that global lung cancer campaigns—for awareness, public policy changes or research funding—will reach, and hopefully exceed, their targets.

Keywords: social media, patient community, patient reported outcomes

ES05 JOINT SESSION GLCC/IASLC: HOT TOPICS FOR LUNG CANCER ADVOCATES
SUNDAY, SEPTEMBER 8 10:30–12:00

ES05.05 STILL STRUGGLING FOR TRACTION - FROM PROVING LUNG CANCER SCREENING WORKS TO GLOBAL PRACTICAL IMPLEMENTATION, INCLUDING ENGAGEMENT OF THE TARGET POPULATION

J. Mulshine

Rush University, Chicago/United States of America

Still Struggling for Traction-from Proving Lung Cancer Screening Works to Global Practical Implementation, Including Engagement of the Target Population

James L. Mulshine, Rush University, Chicago, IL 60612 Based on the results of the National Lung Screening Trial, United States Preventive Services Task Force (USPSTF) reviewed and recommended low-dose CT screening for lung cancer. Next the Centers for Medicaid and Medicare reviewed this service and after February 5, 2015 issued a National Coverage Decisions to add coverage under Medicare Part B to allow low-dose CT screening in high-risk populations began (1, 2). A few years on, articles are frequently reporting that screening uptake in the United States is anemic. In a setting where enthusiasm differs about the prospects for lung cancer screening, issues of cost and bandwidth loom large (3, 4). Realistically, cancer screening whether cervical cancer, breast cancer or colon cancer all took extended periods of time to become established and problems of compliance with all three measures still exist. However, the results of the National Lung Screening Trial are now buttressed with the results of Dutch/Belgian trial (NELSON), as well as the 10 year follow up of the Milan randomized cohort experience (MILD) (4-5). Consequently, we are now seeing national screening not only being implemented in the United States but and with similar activity moving forward in Canada, Poland, the United Kingdom, South Korea as well as other nations. It is heartening to see evidence of careful planning to define the optimal screening programs for national implementation ongoing in a number of countries such as the United Kingdom, Canada and Poland. Cautious optimism that lung cancer screening may have turned a corner seems justified. These early adaptor national screening programs will provide an opportunity to evaluate national statistics for the annual distribution of stage frequencies. As it is a critical measure of public health progress to have falling national smoking rates, now we can also look for national level stage shifts to determine if the detection rates of Stage I cases rise along with corresponding drops in Stage III/IV frequencies. Furthermore, critical information about actual experience in these large national settings can inform the discussion about the realities of harms experienced in the screening process and this information would be useful in advancing lung cancer screening participation. Communication disseminated by venues like IASLC and GLCC will be essential to encourage efforts to enhance the process of screening to sustain the brisk pace of research focusing on screening management optimization. The efforts of the American College of Radiology in adapting breast cancer screening process for managing the lung cancer screening process has been important as it creates a much more familiar transition for institutions attempting to launch lung cancer screening services (6). This ACR process, called LungRADS leverages a management approach that is already well established in the radiology community and makes for a smooth transition in defining a systematic screening management approach for lung cancer. This recent development has addressed a major concern relative to the rate of false positive screening cases that was dampening screening enthusiasm for some healthcare professionals. Fortunately, there are even more advanced developments in the offing for more effective and workflow friendly software tools. If best-practice nodule management of I-ELCAP, NELSON, and UKLS using software-driven direct measurement of lung cancer volume become more generally available, these tools can further reduce the rate of false-positive diagnosis and improve the efficiency of the case finding process (7-11). Fortunately, in collaboration with I-ELCAP and the Veterans Administration in the US, activities are underway to address this complex issue. Annual lung cancer screening has also provided an opportunity to re-consider how to best encourage more effective smoking cessation. The National Cancer institute in the United States launched a number of studies to experiment with more intensive approaches to smoking cessation specifically in the setting of screening. These studies will be completed over the next few years and these new approaches can be applied to help more people overcome this dangerous but deeply additive behavior and in a

complementary fashion improve the prospects for more favorable health outcomes. Quietly over the last decade, we have witnesses continuous refinements in the surgical approach to resecting early lung cancer (12). We would expect further evidence to accrue informing the most favorable approach to curative resection. Within this time window, we expect to also start seeing more experimental approaches to managing small, favorably located lung cancers with inter-luminal approaches. In the wake of recent cardiology guidelines revisions to include low-dose thoracic CT as a biomarker for managing coronary calcium deposition, we would expect to see greater awareness of other routine tobacco-related findings seen in the course of a thoracic CT screening (13). Together lung cancer, coronary artery disease and COPD constitute the three most lethal diseases across the world. The pathogenesis of all three of these diseases is greatly accelerated by tobacco-combustion product deposition in the lungs. As the prevalence of lung cancer screening evolves, considerably more cases of coronary artery disease and COPD cases will come to clinical attention than lung cancer, so collaboration across relevant disciplines will increase to provide thoughtfully integrated management of CT screen identified consequences of prolong tobacco exposure (13). The bulk of the preventive managements of these three most lethal diseases detected in high risk but asymptomatic individuals will include more concerted tobacco cessation support, advice to enhance levels of physical activity and to improve the quality of dietary consumption. Through time, CT-informed lung cancer screening will create an annual opportunity for a health check to improve the health of tobacco-exposed individuals. This possibility could great enhance the support of low-dose CT evaluation of thorax in smokers across many communities. In parallel, targeted drug development guided by information derived from systematically examining resected screen-detected cancer looking for signatures of aggressive behaving cancers that will need adjuvant interventions beyond surgery to ensure curative outcomes. In this strategy, lung cancer care may follow breast cancer care and we will see the emergence of neoadjuvant and adjuvant early lung cancer therapies as a critical part of ensuring favorable individual outcomes. In closing, screening is a complex process with many moving parts. Establishing this process with careful attention to quality and then testing to see how to optimize the delivery as outlined in a recent I-ELCAP report, takes time (14). Participation in lung cancer screening is low. Given the recent strong screening results from multiple international sites especially with the NELSON trial as well as contributions such as LungRADS, and process research such as with I-ELCAP, there is a basis for optimism that significantly greater uptake will be occurring in large measure due to mutually beneficial collaborations. References: National Lung Screening Trial Research Team, Aberle DR, Berg CD, Black WC et al. The National Lung Screening Trial: overview and study design. Radiology. 2011 Jan;258(1):243-53. doi: 10.1148/radiol.10091808. Epub 2010 Nov 2. National Coverage Decision, low-dose CT screening for lung cancer, https://www.medicare.gov/coverage/lung-cancer-screenings Bach PB. Perilous potential: the chance to save lives, or lose them, through low dose computed tomography screening for lung cancer. J Surg Oncol. 2013 Oct;108(5):287-8. doi: 10.1002/jso.23389. Epub 2013 Aug 27. PMID: 23983184, DOI: 10.1002/jso.23389 Mulshine JL, D'Amico TA. 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Keywords: lung cancer, lung cancer screening, low dose CT detection

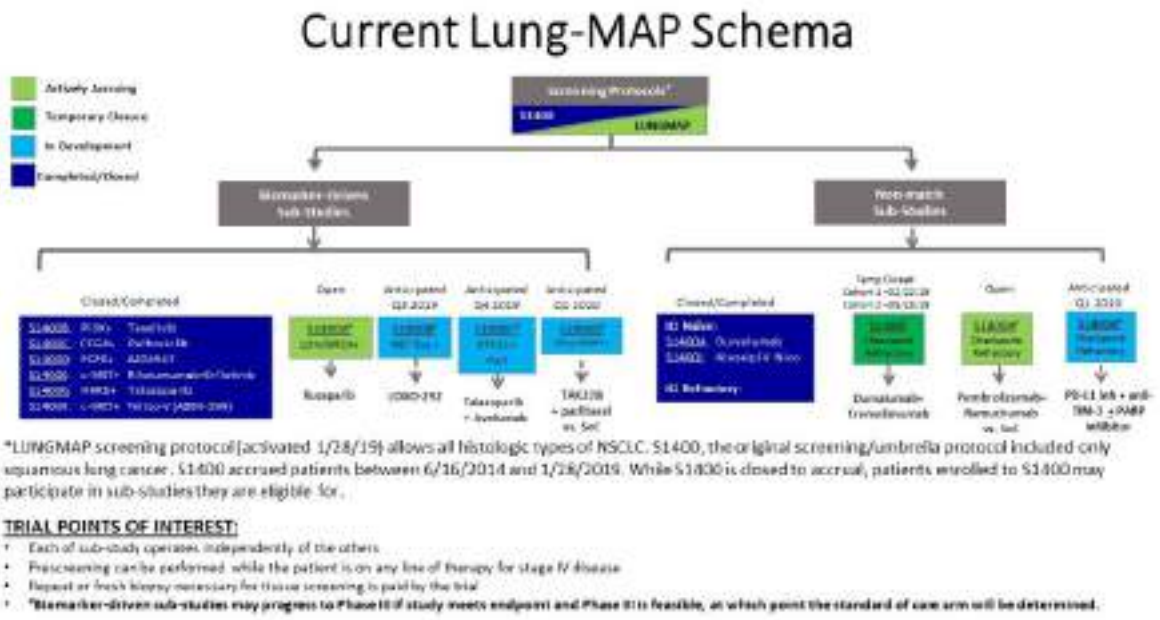
ES06 NEW APPROACHES IN SECOND LINE TREATMENT IN NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES06.01 RECENT ADVANCES IN SECOND LINE TREATMENT

R. Herbst

Yale University School of Medicine, New Haven/United States of America

Despite advances in the treatment of cancer and reductions in smoking rates, lung cancer continues to be one of the leading causes of cancer death worldwide. Over the past decade, a handful of immune-checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab) have been shown to improve survival and changes have been made to the standard of care for first-line treatment of patients with non-small cell lung cancer (NSCLC). However, only a minority of patients respond to these treatments and even these patients acquire resistance to the therapy. Continued investigation and research for second-line therapy options are vital to provide treatment options to patients who progress. Master protocols, like LUNGMAP, are efficient trial designs used to quickly and safely investigate new therapies or combinations. LUNGMAP is the first major trial, supported by the National Cancer Institute (U.S.) to simultaneously test multiple treatments under an umbrella design. LUNGMAP was launched in 2014 to investigate new therapies for squamous cell lung cancer, enrolling over 2000 patients. In 2018, the trial underwent a major expansion to include all non-small cell lung cancer patients. Treatments being tested include immunotherapy combinations and targeted therapies that are associated with specific genomic alterations. This allows for the identification of potential biomarkers which can help identify the treatments that would most likely benefit a patient. LUNGMAP is an unprecedented public-private partnership that is more flexible and efficient and will help to speed-up the development process for new lung cancer drugs. References: RS Herbst et al. Clin Cancer Res. 2015 Apr 1;21(7):1514-24 doi: 10.1158/1078-0432.CCR-13-3473. Epub 2015 Feb 13.



ES06 NEW APPROACHES IN SECOND LINE TREATMENT IN NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES06.02 WHAT IS THE BEST STRATEGY IN PROGRESSIVE DISEASE AFTER CONSOLIDATION WITH DURVALUMANB, OR RAPID PROGRESSORS TO FIRST LINE?

F. Barlesi

Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille/France

Immune Check Points Inhibitors (ICIs) have dramatically changed the management of locally advanced and advanced NSCLC patients. While the survival improvement compared to previous standard of care is undoubtable, several patients still progress on or relapse after ICIs. How should these patients be managed? To better understand how to manage these patients, we should probably try to better understand the underlying mechanism(s) of resistance to ICIs. Schematically, we can propose three main categories, with primary resistances, occurring early after ICIs initiation, secondary resistances, occurring after a previous response or disease stabilization on ICIs, and follow-up resistances, occurring after stopping ICIs, either per protocol or severe adverse event(s). Management of primary resistances to ICIs. Although no validated definition is available, primary resistances might include hyperprogressors and progressors within the first 12- (to 18) weeks of treatment with ICIs. It represents approximately 20 to 30% of stage III NSCLC patients receiving durvalumab after concomitant chemo-radiation, 30% of stage IV patients PD-L1 50% or more NSCLC patients treated with pembrolizumab and 20 to 30% of stage IV patients NSCLC patients treated with a combination of chemotherapy and ICIs. Few data are available on the underlying biological mechanisms to explain these primary resistances. Considering clinical data of the PACIFIC trial, 41% of patients in the durvalumab arm (without precise characterization of the time or progression) received a subsequent therapy. For the patients who already received durvalumab as a consolidation treatment, 20 patients received a subsequent ICI. The response rate in this case was 0%. With a longer follow, different patients' profiles will certainly be reported in this setting, with possibly responses to ICIs alone or in combination for patients relapsing a long time after stopping Durvalumab. Considering clinical data for stage IV NSCLC patients treated in the first line setting in monotherapy, a recent long term analysis of the Keynote 024 trial. The management of patients with an early progression on Pembrolizumab was not specifically detailed. Globally, 56 out of 154 patients received a subsequent oncologic treatment, mainly chemotherapy. Considering clinical data for stage IV NSCLC patients treated in the first line setting with combination of chemotherapy and ICIs, few results are available to date on the management of early progressors. Finally, all trials assessing the efficacy of new IO agents or new ICI-based combinations as a rescue treatment after failure of a previous line of ICIs are globally disappointing. A summary of ongoing trials will be presented at the meeting. In summary, the best strategy to date for early progressors on ICIs, alone or in combination, unfortunately remains a standard chemotherapy; a participation in a clinical trials should be also discussed giving the efficacy of rescue treatments in this situation.

Keywords: durvalumab, Rescue immunotherapy, Early progressors

ES06 NEW APPROACHES IN SECOND LINE TREATMENT IN NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES06.03 FUTURE STRATEGIES IN SECOND LINE TREATMENT

G. Riely

Memorial Sloan Kettering Cancer Center, New York/United States of America

With the continued refinement of molecularly targeted therapy and the dramatic changes in initial therapy for patients with newly diagnosed NSCLC without a molecular target, the concept of "second line" therapy has largely become outdated. For the more than one-third of patients who have a targetable oncogenic driver (with aberrations in genes such as EGFR [exon 19 deletion, exon 21 point mutation, or exon 20 insertion], ALK, ROS1, BRAF, RET, MET exon 14, or TRK), multiple lines of targeted therapy are possible prior to receiving a platinum-based combination chemotherapy combination (sometimes with the addition of an anti-PD-1/PD-L1 antibody). In such patients, "second line treatment" could actually be the fifth treatment regimen. Similarly, for patients with PD-L1 that is 50% or greater, the second-line treatment is typically platinum-based doublet chemotherapy. Practically, "second line treatment" is that given after a regimen that contains platinum-based chemotherapy. Despite the difficulties in defining second line treatment, it is an area with critical need for development of new treatments. Some new approaches to development of second line therapies are dependent upon a molecular evaluation of the patient's tumor, typically selecting for targets that are not oncogenic drivers but rather other, non-driver, vulnerabilities found in a patient's tumor. This approach is best exemplified by the Lung MAP (Lung Cancer Master Protocol). This NCI-sponsored trial that began by enrolling only patients with squamous cell lung cancer but now enrolls patients with any NSCLC,

uses the results of a comprehensive genomic profiling platform that looks at over 200 cancer-related genes for genomic alterations to assign patients to a genetically matched sub-study or randomize patients to an immunotherapy treatment. Cohorts have included patients with PI3KCA mutations receiving GDC-0032, patients with FGFR amplifications receiving AZD4547, patients with homologous repair deficiency receiving PARP inhibitors, and patients with STK11 alterations receiving talazoparib + avelumab. Critically, this trial uses staged evaluation of an arm to minimize the number of patients treated with relatively ineffective therapies. There is a great deal of interest in identifying new immunologic approaches for patients with NSCLC who have progressed after initial treatment with anti-PD-1/PD-L1 therapy. These approaches include the exploration of antibodies against such targets as the T-cell inhibitory receptor Tim-3 (T-cell immunoglobulin and mucin-domain containing-3) or small molecule inhibitors of indoleamine 2,3-dioxygenase 1 (IDO1), a principle enzyme in tryptophan catabolism alone or in combination with anti-PD-1 or PD-L1 antibodies. Beyond this, there are attempts to improve the efficacy of single-agent anti-PD-1 antibodies by adding MEK inhibitors. Building off great successes in hematologic malignancies, there are new effort that seek to use cell-based therapies in patients with solid tumors. These include clinical trials of autologous T-cells that have been transduced with vectors expressing T-cell receptors against such targets as NY-ESO-1 and LAGE-1a for patients with NSCLC as well as trials exploring ex vivo expansion of tumor infiltrating lymphocytes. Treatment of patients who have progressed on available targeted therapies as well as platinum-based chemotherapies remains a notable challenge, with current treatments having limited activity. While none have yet proven effective, there are a broad array of treatments under study, whether using targeted therapies, chemotherapy combinations, or immunologic approaches.

Keywords: second line, Chemotherapy, platinum-based

ES06 NEW APPROACHES IN SECOND LINE TREATMENT IN NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES06.04 THE BEST TREATMENT SEQUENCE FOR ADVANCED NSCLC EGFR/ALK/ROS/BRAF WT

J. Wolf[1,2]

[1]*University Hospital of Cologne, Cologne/Germany,* [2]*Center for Integrated Oncology, Cologne/Germany*

Most current guidelines recommend molecular testing of activating alterations in EGFR, ALK, ROS1 and BRAF before first line treatment decision in advanced NSCLC. These recommendations mostly are based on the approval status of the respective targeted therapies. For the remaining patients combinations of immunecheckpoint inhibitor (ICI) therapy and platinum-based chemotherapy (CT) has become standard for patients with a PD-L1 tumor proportion score (TPS) of below 50% and may also be used for patients with a higher score in case of aggressive tumor growth and good performance score (PS). Patients with a TPS of 50% and more may be treated with ICI alone. Tumor mutational burden (TMB) is currently evaluated as new predictive marker for either ICI mono- or combination therapy, the definitive value of this approach in first or second line so far, however, is still unclear. If these (EGFR-, ALK-, ROS1-, BRAF wildtype) patients relapse after ICI monotherapy, platinum-based CT, eventually with the addition of bevacizumab, widely is considered standard treatment. By comparison, for patients with relapse after ICI/CT combination systemic treatment options are quite unsatisfying. Docetaxel monotherapy has only marginal efficacy which may be modestly increased by the addition of antiangiogenic agents. Numerous immunotherapeutic approaches are evaluated In this situation (next generation ICIs and other immunomodulatory drugs), preferably in combinations. However, so far, no convincing results have been reported from these clinical trials. It is therefore particularly important to identify from these patients the subgroup with a possible benefit from driver-mutation directed treatments – either within a clinical trial or a compassionate use program or as off-label treatment. Numerous such approaches are in clinical evaluation. Examples are kinase inhibitors against RET-fusions, TRK-fusions, MET exon 14 skipping mutations, MET amplification, HER2 mutations, EGFR-/HER2 exon 20 mutations, NRG-1 fusions. High response rates and clinical significant duration of responses have already been reported for many of these personalized treatment options, some of them are already in accelerated approval procedures. Many of them will forge ahead towards first line treatment in particulary, since ICI therapy partly seems not to work well here. Until the approval of these new treatment options it is of particular importance to test patients at the latest upon failure of ICI with or without chemotherapy on the presence of driver mutations in their tumors and to try hard to bring them into a clinical trial or to enable off-label treatment. Given the dynamics in the field, this treatment algorithm will change in the near future not only by the approval of several of these new driver-mutation directed treatments, but also by the development of more effective and more tailored immunotherapies as well as by the availability of potent KRAS inhibitors.

Keywords: rare driver mutations, immune checkpoint inhibitor failure, predictive biomarkers

ES07 THORACIC ULTRASONOGRAPHY: DIAGNOSIS AND STAGING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES07.01 TRANSTHORACIC ULTRASONOGRAPHY

N. Rahman

University of Oxford, Oxford/United Kingdom

This presentation will review data on the utility of thoracic ultrasound in diagnosis, staging and subsequent management of malignant thoracic and pleural disease.

ES07 THORACIC ULTRASONOGRAPHY: DIAGNOSIS AND STAGING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES07.03 RADIAL ENDOSONOGRAPHY

L. Crombag

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Flexible bronchoscopy, with its attendant procedures, is a valuable tool for diagnosis and staging of patients with suspected lung cancer. The development of endobronchial ultrasound (EBUS) has extended the view of the bronchoscopist beyond the bronchial wall. Two types of EBUS exist. The curved linear (convex) probe EBUS and the radial probe EBUS. The convex ultrasound transducer is located at the tip of a flexible bronchoscope (linear scanning EBUS) and allows real-time sampling. This technique is mainly used for mediastinal nodal staging and assessment of centrally located lung tumours when lung cancer is known or suspected. The radial EBUS probe houses a rotating ultrasound transducer at the distal end which produces a high-resolution radial (360˚) ultrasound image of the airway wall and surrounding structures. This probe is inserted through the biopsy channel of a standard bronchoscope. In a lung cancer setting, this technique is used for evaluation of the depth of tumour invasion in the central airways enabling differentiation between early and invasive lung cancer and detection of peripheral pulmonary lesions (PPLs). Radial EBUS does not permit sampling in real-time such that sequential sampling with separate equipment is necessary. The current focus of this abstract is the role of radial EBUS for PPLs. With the increased use of chest CT-scans, the frequency of incidentally found PPLs has increased as well. Guidelines advise to evaluate and manage individuals with pulmonary nodules by estimating the probability of malignancy. The goal is to diagnose a malignancy promptly for timely treatment and to avoid invasive procedures and surgery in patients with benign lesions. Approaches to establish a tissue diagnosis include imaging-guided transthoracic and bronchoscopic sampling techniques. The sensitivity of traditional flexible bronchoscopy - with or without fluoroscopic guidance – for peripheral lesions in patients suspected of having lung cancer is suboptimal and is affected most by the size of the lesion (<2cm 34%; >2cm 63%).[(1)] For PPLs, the sensitivity of transthoracic needle aspiration (TTNA) is greater than that of bronchoscopy. In this setting, TTNA has an approximately 90% chance of providing confirmation of a diagnosis. However, CT-guided percutaneous TTNA has a considerable risk of pneumothorax.[(1)] This has led to the development of new modalities as radial EBUS, virtual bronchoscopy, electromagnetic navigation bronchoscopy and ultrathin bronchoscopes. In 2002, radial EBUS was first used to guide transbronchial lung biopsy (TBLB).[(2)] Numerous papers has been published since, reporting varying diagnostic performances of radial EBUS. Three systematic reviews and meta-analyses report

a sensitivity of radial EBUS for diagnosis of peripheral lesions of 70% to 73%. Although there is considerable heterogeneity in lesion size, prevalence of malignancy, variable use of additional image guiding technology and reference standard in included studies.[3-5] The diagnostic yield of radial EBUS is significantly higher for lesion > 2 cm in size, malignant in nature and those associated with a bronchus sign on CT scan.[3-5] The diagnostic yield is also higher when the radial EBUS probe is in the center of the lesion opposed to being adjacent to it.[3] The diagnostic yield of radial EBUS does not exceed CT-guided percutaneous needle biopsy / aspiration. The major advantage of radial EBUS over a transthoracic approach is its safety profile (overall pneumothorax rate of just 1.0%)[4] and the ability to combine with staging procedures. In conclusion, to diagnose PPLs (not visible by bronchoscopy) radial EBUS is a safe and has a reasonably high diagnostic yield. Main limitations of the technique include operator dependence and the need for sequential sampling as radial EBUS does not allow real-time sampling. 1. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e65S. 2. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. The European respiratory journal. 2002;20(4):972- 3. Ali MS, Trick W, Mba BI, Mohananey D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis. Respirology (Carlton, Vic). 2017;22(3):443-53. 4. Steinfort DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. The European respiratory journal. 2011;37(4):902-10. 5. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012;142(2):385-93.

Keywords: Radial endosonography, diagnosis, lung cancer

ES07 THORACIC ULTRASONOGRAPHY: DIAGNOSIS AND STAGING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES07.04 PREDICTIVE MOLECULAR TESTING ON SMALL BIOPSY SAMPLES

C. Dooms

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According to international guidelines for molecular testing as updated in 2018, any lung cancer sample (tissue biopsy or cytology) with adenocarcinoma or not-otherwise specified (NOS) histology and adequate tumor cellularity should be tested for routinely treatable mutations with a turnaround time of no more than 10 working days.1,2 Single gene testing or restricted hotspot testing methods were developed to screen for EGFR p.Leu858Arg mutations or deletions with the exon 19 in advanced stage non-small cell lung cancer. Next-generation sequencing (NGS) platforms have facilitated multigene mutational profiling using small amounts of nanograms (ng) of DNA, making the NGS technology attractive for and applicable to small biopsy and cytology specimens. NGS and especially targeted NGS panels were rapidly validated for small biopsy samples and implemented in diagnostic laboratories as they focus on hotspot regions and frequently altered genes with direct and known consequence on therapy.3,4 Compared to sequential single-gene testing, targeted NGS is considerably faster and more cost-effective.5 There are however several barriers to universal broad biomarker testing. Despite most tests can be run on only small biopsy and cytology specimen, in real world testing rates are far from 100% (even for EGFR, ALK and ROS1 testing) and up to 25% of samples lack sufficient tumor material in small biopsies. Molecular testing accuracy depends on multiple factors that include overall tumor cellularity, method of fixation, tumor fraction of the sample, and the analytical sensitivity of the molecular testing platform used for the analysis. Pre-analytical strategies to improve testing success are: (1) work with dedicated interventionalists (e.g. radiology, pulmonology) to get sufficient tissue as one single pass is not enough, (2) work with dedicated pathologists to enhance quality control and reflex testing, and (3) consider ROSE. In a reference center with dedicated interventionalists, a dropout rate of 3.4% was observed either due to quantitatively insufficient tumor material or inadequate nucleic acid quality based on a series of 3,000 consecutive lung cancer cases that were sequenced.6 In a randomized trial comparing two different needle sizes and a turn-around team (interventional pulmonologist, pathologist, molecular biologist) using standard operating procedures, several conclusions could be drawn given a successful NGS testing rate for all clinically relevant genes in 96% of samples.7 Four needle passes were needed to obtain adequate material for molecular analysis. A tissue core was reported present in almost 70% of specimens for both needle types. Less than 3% of samples had tumor cellularity of <10%, and there was no significant difference in tumor cellularity between 19G and 22G needles. Both the tumor surface area measured and the amount of DNA extracted from the selected cell block were larger for the 19G compared to the 22G specimen, with a median tumor surface area of 4.91 mm2 vs 2.35 mm2 and median DNA extracted of 1150 ng vs 818 ng, respectively. There is a paucity of articles outlining best practice guidelines for immunocytochemistry. With proper optimization and rigorous quality control, high-quality staining can be achieved on cellblock and non-cellblock preparations.8 Cytology preparations that are non-formalin-fixed provide the best alternative source of well-preserved DNA. Cytology specimens allow for rapid on-site adequacy assessment (ROSE), which can ensure the collection of adequate and sufficient material for ancillary studies including immunohistochemistry and molecular testing. Although there are no universally accepted criteria for EBUS-TBNA lymph node adequacy, structured semi-quantitative scoring schemes for ROSE and diagnostic category assignments have been proposed. The decision of whether or not to provide ROSE for EBUS-TBNA procedures is largely institution dependent. Validation studies are essential with correct implementation of these pre-analytical factors for any molecular testing in cytologic samples. In conclusion, a single NGS panel test covering all clinical relevant markers is most tissue and cost efficient. Strategies to obtain a higher rate of successful testing, even on only small biopsy and cytology specimens should be considered whenever needed: reflex testing, dedicated interventionalists, and strong communication with all team members. References. 1. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Mol Diagn. 2018 Mar;20(2):129-159. 2. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology. 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Keywords: Pre-analytical strategies, Molecular Testing, Small endoscopic samples

ES08 CRITICAL CONCERNS IN SCREENING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES08.01 PARTICIPATION OF THE TARGET POPULATION IN LUNG CANCER SCREENING

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Participation of the Target Population in Lung Cancer Screening Robin Cornelissen, MD, PhD. Erasmus MC cancer institute Rotterdam, The Netherlands The two largest randomized controlled trials performed, The National Lung Screening Trial (NLST) and the Nederlands-Leuvens Longkanker ScreeningsONderzoek (NELSON) [1,2], proved that lung cancer screening using low dose CT scan, resulted in a significant reduction in lung cancer mortality. Following the results of the NLST trial, lung cancer screening was initiated in the United States and Canada. However, the uptake of lung cancer screening is poor, with only 3% to 4% of all eligible persons participating in the implemented screening program [3]. Given more recent positive results of the NELSON study that were presented at the World Conference on Lung Cancer last year in Toronto, lung cancer screening is now considered in many countries across the globe. This low uptake of lung cancer screening is however a cause of concern. The reasons for the low participation rate are multi-factorial. The novelty of the lung cancer screening program is such a factor, resulting in lower uptake and might be the easiest one to address. The identification of the target population is more challenging due to the fact that the population to be screened is more defined than just age and sex. In addition, the lower socioeconomic status, which presents a significant portion of the to be screened population, and those who face barriers to care present a major challenge for implementing a successful screening program with a satisfactory uptake rate. Several strategies have been proposed to improve lung cancer screening uptake. In the socioeconomically deprived and heavy smoking communities, lung cancer is perceived as an uncontrollable disease [4], while cure rates in yearly screening programs lead to a cure in the majority of patients when lung cancer is detected [5,6]. Therefore, public awareness of the curability of lung cancer when screening programs are implemented could boost the participation rate. Mobile lung cancer testing in supermarket car parks proved to be a successful pilot [7]. This strategy avoids difficulties relating to the distance of travel, lack of public transport available, and the cost of either the journey itself or hospital parking. This strategy is currently explored in a larger cohort. One potential intervention that is being evaluated in clinical trials to improve the uptake and implementation of lung cancer screening is a patient navigator. A navigator can be a layperson, a medical assistant, or a nurse who will directly contact potential candidates for lung cancer screening for enrollment [3]. The Accelerate, Coordinate, Evaluate (ACE) Programme, initiated in the United Kingdom, is an early diagnosis of cancer initiative focused on testing innovations that either identify individuals at high risk of cancer earlier [8]. This program consists of several individual programs in different regions of the UK, of which The Liverpool Healthy Lung Programme is a participant. Among other goals, this initiative tries to improve uptake in the hard to reach cohort. They used general practitioners' records to invite participants meeting the criteria to a 'Lung Health Check'. This 'Lung Health Check' is a novel approach that may overcome or minimize the emotional barriers associate with the term "lung cancer screening". This method resulted in an uptake level up to 40% [9]. This initiative is an example that a higher uptake rate is indeed possible, even in the hard to reach population. At the IASLC World Conference on Lung Cancer in Barcelona, the issues regarding participation of the target population in lung cancer screening will be addressed and possible strategies will be discussed to overcome these challenges. As lung cancer screening is yet to be implemented in the majority of countries worldwide, we now have a unique opportunity to test and apply these strategies to successfully implement lung cancer screening in order to reduce lung cancer mortality. References 1. The National Lung Screening Trial Research Team. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. *N Engl J Med*. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873 2. Koning HD, Aalst CVD, Haaf KT, Oudkerk M. PL02.05 Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. *J Thorac Oncol*. 2018;13(10):S185. doi:10.1016/j.jtho.2018.08.012 3. Triplette M, Thayer JH, Pipavath SN, Crothers K. Poor Uptake of Lung Cancer Screening: Opportunities for Improvement. *J Am Coll Radiol JACR*. 2019;16(4 Pt A):446-450. doi:10.1016/j.jacr.2018.12.018 4. Quaife SL, Marlow LAV, McEwen A, Janes SM, Wardle J. 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ES08 CRITICAL CONCERNS IN SCREENING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES08.02 NODULE GROWTH ASSESSMENT

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In the past 15 years several lung cancer screening trials have been performed in Europe[1]. Experts involved in these trials recently published a position paper in the Lancet Oncology[2]. Several conclusions and recommendations were drawn to enable a smooth and timely implementation of lung cancer screening in Europe. The experts made a strong and conditional argument on the methodology of lung cancer screening by low-dose computed tomography (CT). Quality control by regular CT phantom testing enabling standardization of CT data acquisition as well as benchmarking of CT software post processing and data analysis are mandatory. It is promoted to execute the CT screening Q/A control through national reference centers similar to the organizational structure of breast screening programs. In this manner the CT screening programs can be implemented in a responsible way avoiding the detrimental side effects of too high false positive CT outcome rates on the one hand and keeping up the most effective lung cancer early detection rate on the other hand. Apart from the acquisition protocol, the CT lung nodule analysis methodology is a critical factor for successful implementation of CT lung cancer screening [3]. The diameter based NLST protocol used a 4 mm threshold (~ 30 mm^3) as significant suspicion for malignancy. This approach yielded a positive rate of approximately 27% in the baseline round with a very low positive predictive value for lung cancer of 3.8%[4]. The NELSON study introduced a nodule volume analysis and a volume doubling time methodology with 2 CT measurements with a 3-month interval to calculate the volume doubling time as a biomarker for growth rate in indeterminate nodules. This approach resulted in a 2.6% positive rate in the baseline round with a high positive predictive value for lung cancer of approximately 36%, which is within the criteria needed for lung cancer screening implementation[3]. In the meantime, a ten times higher threshold of 8 mm (~300 mm^3) was recommended to correct the high false positive rate of the NLST diameter methodology by several international societies[5]. After the publications of the NELSON data on increased lung cancer probability in baseline nodules at a threshold of 100 $mm^3$the US guideline recommendations shifted from 300 $mm^3$to 100 mm^3(~ 6mm)[6]. A direct comparison of diameter and volume protocols cannot be performed through the assumption that all nodules are spherical. While this approach was chosen in a recent publication of the IELCAP investigators[7], even the slightest correction for the assumption of sphericity reveals the substantial inferiority of diameter protocols. At follow-up CT examination at annual incident screen new nodules represent a high lung cancer probability at lower volumes than at baseline screen[8,9]. The upper threshold is at 200 mm^3as indication for further clinical workup while new nodule at incident screen between the 30-200 $mm^3$are classified as indeterminate and need a repeat scan at 3 months to calculate the volume doubling time. Lung cancer screening should be integrated in a defined national program and therefore opportunistic screening is not recommended. Calcium scoring as a *screening method*is not yet established as a validated tool for early detection of coronary

artery disease and the outcomes of the ROBINSCA study (risk or benefit in screening for cardiovascular disease www.robinsca.nl) are being awaited. Thus, so far, it is not indicated as a combined clinical routine screening methodology since ECG triggering is mandatory[10]. Non-triggered CT coronary artery calcium scoring will result in high false negative percentages. A lower CT radiation exposure threshold at a DLP of 50 mGy or 0.6 mSv is defined to assure the calibration of the quantitative imaging biomarkers for lung nodule detection. Lower radiation doses will induce false negative and unreliable growth rate results. References 1 An update on the European Lung Cancer Screening Trials and Comparison of the Lung Cancer Screening Recommendations in Europe. *Han et alJournal of Thoracic Imaging 2019; 34(1): 65–71.* 2 European position statement on lung cancer screening *Oudkerk M Devaraj ALancet Oncology 2017 Dec;18(12):e754-e766.* 3 Management of lung nodules detected by volume CT scanning *van Klaveren R Oudkerk M et al N Engl J Med. 2009 Dec 3;361(23):2221-9.* 4 Reduced lung-cancer mortality with low-dose computed tomographic screening *Aberle DR et al N Engl J Med 2011 Aug 4;365(5):395-409.* 5 CT screening for lung cancer: alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases *Yip R Henschke CI Radiology 2014 Nov;273(2):591-6.* 6 Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017 *Mac Mahon H Radiology: Volume 284: Number 1—July 2017* 7 CT screening for lung cancer: comparison of three baseline screening protocol *Henschke CI et al Eur Rad 2018 Dec 3* 8 Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial *Walter JE Heuvelmans MA et al Lancet Oncology 2016 Jul;17(7):907-916.* 9.Persisting new nodules in incidence rounds of the NELSON CT lungcancer screening study *Walter JE Heuvelmnans MA Thorax. 2018 Dec 27* 10 Can nontriggered thoracic CT be used for coronary artery calcium scoring? A phantom study *Xueqian Xie et al Medical Physics, Vol. 40, No. 8, August 2013*

Keywords: lungcancer screening, lungnodule growth, lungnodule volumetry

ES08 CRITICAL CONCERNS IN SCREENING
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ES08.03 THE MAGNITUDE OF THE BENEFIT

D. Yankelevitz

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Why do people get screened? The obvious answer is so that cancer can be detected early with a view towards a higher chance of cure with early treatment. Therefore the critical questions that must be addressed relate to the risk of cancer over time and then, how likely cure will be when screen-detected versus clinically detected. Current approaches to evaluate screening have relied on randomized controlled trials with a view towards demonstrating that a benefit actually exists but are not designed to quantify the magnitude of the benefit. Current trial designs have limited rounds of screening and long-term follow up after screening has stopped. When these parameters change, the results of the trial will also change. Several approaches currently exist to estimate that critical parameter regarding the curability of screen detected lung cancer. This includes modeling approaches which can use data extracted from a variety of sources, they can also be measured directly as was done in the I-ELCAP study which measures directly the reduction in case fatality rate by using long term survival as a measure of cure, and an additional approach would be to screen continuously in the context of a clinical trial and measure the reduction in mortality after several years of screening where the benefit of screening reaches its maximum and becomes equivalent to the reduction in case fatality rate. When applied to lung cancer it can be shown that this benefit is far greater than the 20% so commonly reported and instead is in the 60=80% range for cure. Were this to be fully understood the entire rationale behind requiring shared decision making would be called into question as it was thought that the balance between benefits and harms was so tenuous that shared decision making was necessary. When considering whether a particular type of screening is to be considered beneficial there is also a tendency to compare different types of screening and seeing how many screens are necessary to save a life. Here to, this approach suffers from the same mistake. Each of those screening exams estimates this number based on their own randomized trial and each of these differ in terms of the design parameters, therefore the comparisons are essentially meaningless.

Keywords: benefit, lung cancer screening

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ES08.04 MANAGEMENT ALGORITHMS

C. Henschke[1], R. Yip[1], T. Ma[2], S. Aguayo[3], J. Zulueta[4], D. Yankelevitz[1]

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Introduction Clinical management decisions arising from the first, baseline round of screening for lung cancer are most challenging, as nodules that are seen for the first time may have accumulated over a lifetime and almost all of them are of no clinical concern [1]. In contrast, new or changing findings on subsequent annual repeat low-dose CT scans (LDCTs) have much greater clinical significance. Efficiency is particularly important in the baseline round in order to minimize unnecessary harms caused by work-up within the 12 months after the baseline LDCT. Potential workup includes surgery, biopsies, and diagnostic tests requiring intravenous injection (e.g., PET scans, contrast CT). Biopsies and surgery have greater risks than LDCT, and thus the management protocols should aim to minimize these higher risk procedures as much as possible [2]. It is also important not to discourage participants undergoing the baseline round from future participation in annual rounds as these provide the real benefit of annual LDCT screening. Methods We compared the efficiency of three published baseline LDCT screening protocols [2], the International Early Lung Cancer Action Program (I-ELCAP) [3], American College of Radiology (ACR)-LungRADS [4], and the European Consortium protocols [5] for participants 50 years of age or older with at least 20 pack-years of smoking. The three protocols provide recommendations for immediate workup, 3-month and 6-month LDCT as shown in Table 1 [1]. The three protocols use the diameter of the entire solid and nonsolid non-calcified nodule (NCN), but differ for part-solid NCNs. For part-solid NCNs, I-ELCAP uses the diameter of the solid component [6], while ACR-LungRADS uses both the entire diameter of the part-solid NCN as well as the diameter of its solid component. The European Consortium protocol determines the volume of a solid NCN using their software [5], but also specifies the equivalent diameter values for the entire part-solid and nonsolid NCNs as volumetric measurements for these are problematic as was recognized [5]. Measurement error and rounding of measurements are also an important consideration [7,8]. Efficiency was defined as an efficiency ratio (ER): the number of participants recommended for a particular workup divided by the resulting number of participants diagnosed with lung cancer [2]. An ER of 1 would mean that each recommended workup resulted in a diagnosis of lung cancer. An optimum ER has not been established for lung cancer, but it has been suggested that for lung surgery, a rate of 10% for non-malignant resections is desirable (9), this would be an ER of 1.1. In breast cancer biopsies which have a much lower risk than lung biopsies, it is recommended that 40% of biopsies should be negative to ensure sufficient workup to diagnose breast cancers early enough this would represent an ER of 1.4 Results Table 1 provides the frequency of following the recommendations, the number of cancers diagnosed and the ER for each protocol. In summary, I-ELCAP recommendations had the lowest ER values for overall, immediate and delayed workup, and for potential biopsies. Discussion All three protocols used LDCT to guide evaluation of NCNs, particularly for the smaller NCNs. LDCT is a very low risk test as it requires no injection of contrast, the radiation dose is deemed “small” and “hypothetical” by the American Association of Physicists in Medicine [10], and the charge for a LDCT is 10-20 times lower than for a PET scan. This underscores the recognition that LDCT is a very useful tool for identifying growth at a malignant rate prior to further invasive testing. The main point is that the definition of a “positive result” needs to be continually reevaluated and updated in light of emerging technology and evidence from ongoing screening programs with the goal of reducing unnecessary invasive procedures for non-malignant pulmonary NCNs, which will markedly reduce the concerns about potential harms and increase the benefit by early diagnosis and treatment of small, early *curable* lung cancers. References 1. Henschke CI, Salvatore M, Cham M, Powell CA,

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Table 1. For each baseline protocol, the ER values for overall protocol and for the recommendations for a) immediate, b) 3-month follow-up LDCT, c) 6-month follow-up LDCT are given. The potential biopsy recommendations are also provided.

Summary of all workups	I-ELCAP	ACR-Scenario 1	ACR-Scenario 2	European
Total # of workups (sum a-c)	2557	3431	3431	6052
Total # Lung Ca dx	184	188	188	190
ER (#all workups/Ca Dx)	**13.9**	**18.3**	**18.3**	**31.9**
a. Immediate workup (% participants)	1.4%	5.9%	2.1%	3.1%
# participants	352	1507	543	794
# Lung Ca Dx	123	176	138	140
ER (#participants/Ca Dx)	2.9	8.6	3.9	5.6
b. 3-month LDCT (% participants)	8.6%	0.5%	4.4%	20.6%
# participants	2205	153	1117	5258
# Lung Ca Dx	61	2	40	47
ER (#participants/Ca Dx)	36.1	76.5	27.9	111.9
c. 6-month LDCT (% participants)		6.9%	6.9%	
# participants		1771	1771	
# Lung Ca Dx		10	10	
ER (#participants/Ca Dx)		177.1	177.1	
Potential biopsies (%)	1.6%	6.0%	2.3%	3.3%
# biopsies	413	1519	593	841
# Lung Ca Dx	184	188	188	190
ER (# biopsies/Ca Dx)	**2.2**	**8.1**	**3.2**	**4.4**

Keywords: protocol, efficiency, Screening

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ES08.05 ADVANCES IN ARTIFICIAL INTELLIGENCE - HOW LUNG CANCER CT SCREENING WILL PROGRESS?

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Predictive models for personalized medicine (also known as radiomics) is a recent discipline that uses sophisticated image analysis and artificial intelligence (AI) methods to obtain quantitative image-based features that correlate to final diagnosis and treatment outcome [1]. The application of radiomics in lung cancer screening can represent a critical shift in this field. Some recent studies, like [2-3], show that radiomic features (including tumor shape descriptors and texture analysis) extracted from CT scans have significantly better predictive value than volumetry alone (AUC= 0.9 vs 0.74). Texture analysis reflects tumour heterogeneity and has recently introduced in PET images. In fact, PET texture analysis has demonstrated its value in establishing survival [4], predicting distant metastasis [5], detecting mutations and establishing radiotherapy doses [6]. However, and despite the promising results, there are some limitations like the low reliability of heterogeneity parameters in tumours with small volume, the low repeatability and reproducibility of textural features in the clinical setting and the limitation of the analytic methods. A multi-radiomic model that could integrate morphological features from the CT together with biological characteristics from the PET and clinical risk factors (age, smoking history, contact with asbestos or family cancer background), would become a highly accurate diagnostic and prognostic method and, thus, make lung cancer screening programs cost-effective. However, in order that radiomics become the cornerstone for clinical decision-making, new machine learning and statistical strategies adapted to the specific requirements of clinical applications should be formulated. A main pitfall in current state of the art AI methods is the use of generic machine learning and statistical tools borrowed from other fields of application which fall short under clinical conditions [7]. Predictive radiomic models for personalized medicine should address several specific challenges different from the ones common to other application areas of artificial intelligence. First, models should collect and integrate diverse multimodal data sources in a quantitative manner that delivers unambiguous clinical predictions. Second, models should also be easily interpreted from a clinical point of view to allow the analysis of the clinical factors that have an impact on the clinical decision. Third, predictions should be robust concerning data uncertainties due to the impact of collection conditions (like acquisition parameters or variability in manual annotations) and the presence of rare and/or outlying cases, which become highly influential for minority classes lead to overfitting. This work reviews state-of-the-art AI methods for radiomics, the specific

challenges that they must face in medical imaging applications and the latest advances for reliable personalized early diagnosis of lung cancer. References [1] P Lambin, et al, Radiomics: the bridge between medical imaging and personalized medicine, Nature Reviews, 12, 749-53, 2017. [2] Hawkins et al. Prediction of pathological nodal involvement by CT-based Radiomic features of the primary tumor in patients with clinically node-negative peripheral lung adenocarcinomas, Med. Phys. 45 (6), 2018. [3] Peikert T et al. Novel high-resolution computed tomography-based radiomic classifier for screen-identified pulmonary nodules in the National Lung Screening Trial, PLOS ONE 13(10), 2018. [4] Ohri N, Duan F, Snyder BS, Wei B, Machtay M, Alavi A, et al. Pretreatment 18F-FDG PET textural features in locally Advanced non-small cell lung cancer: secondary analysis of ACRIN 6668/RTOG 0235. J Nucl Med.57:842–8, 2016. [5] Wu J,Aguilera, et al. Early-stage non-small cell lung cancer: quantitative imaging characteristics of (18)F fluorodeoxyglucose PET/CT allow prediction of distant metastasis. Radiology, 281:270–8, 2016. [6] Yip SS, et al. Associations between somatic mutations and metabolic imaging phenotypes in non-small cell lung cancer. J Nucl Med. 58:569–76, 2017. [7] JP. Cohen et al, Distribution matching losses can hallucinate features in medical image translation, MICCAI 2018.

Keywords: lung cancer screening, radiomic predictive models, personalized early diagnosis

ES08 CRITICAL CONCERNS IN SCREENING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES08.06 COST EFFECTIVENESS OF COMPREHENSIVE SCREENING AND SMOKING CESSATION PROGRAMMES

B. Pyenson

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There is broad consensus that lung cancer screening with low-dose CT is cost-effective. However, there has been slow take-up in the US where it is covered by commercial insurance and by the federal Medicare program. One way to optimize LC screening is to consider screening as part of an integrated program that specializes in population health for the cluster of smoking-related illness. There are four components of this, LC screening centers can provide high-quality screening and systematic follow-up and appropriate referrals Imaging for LC screening can quantify cardiac calcification, COPD, and osteoporosis, all of which may be associated with smoking LC screening centers can operate as a center for smoking cessation, exercise counseling, and adherence support For the 1.5 million annual indeterminant pulmonary nodules in the US, LC screening centers can provide appropriate follow-up. The vast majority of such cases receive no follow-up. There are both economic and financial consequences for integrated screening. The economic consequences are measured in cost-effectiveness. The financial consequences are attracting high-utilizing people away from lower-quality providers, which can offset the loss of income from treating late stage lung cancers.

Keywords: screening cost-effectiveness financial

ES08 CRITICAL CONCERNS IN SCREENING
SUNDAY, SEPTEMBER 8 13:30–15:00

ES08.07 SYSTEM APPROACH TO SCREENING MANAGEMENT

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Screening seeks to identify a specific disease or set of diseases at an early stage where therapy can be most effective. It involves application of a medical test or tests to a group of asymptomatic individuals at-risk for the disease. Only a very small fraction of the tested population will be expected to have the target disease. Thus, a system for managing the screening process focuses on a single complex protocol and differs significantly from the more traditional medical practice that has a focus on symptomatic diseases and medical conditions. Very high compliance with the protocol and timeliness in follow up actions are critical to extract the maximum benefit of the screening process and avoid unnecessary actions on the majority of the participants that do not have the disease. System requirements for Lung Cancer Screening Screening involves detection of early stage asymptomatic disease and timely follow-up to provide the maximum therapeutic benefit of early stage detection. This requires a system to track participants throughout the screening process, from initial contact to documentation of screening results to follow-up. To maintain the highest degree of quality and timeliness, the screening management system should be comprehensive for all the digital data in the screening program and incorporate the screening protocol in its design. For lung cancer screening (LCS), the web-based I-ELCAP management system was implemented in 2000 [1] with integration of all screening functions into a single system, including: scheduling, data collection, follow-up, patient reports and QA reports. This system includes structured reports for all patient interactions and medical events. The screening protocol is built in to the system; hence, there are real-time checks on adherence to the screening protocol. Any deviations from the protocol, such as a missing report or appointment schedule are flagged for attention. In addition, the management system includes all acquired digital images linked to the patient records; physicians may review images from within the system. Finally, the system includes computer image analysis methods for automated pulmonary nodule detection and for nodule growth rate assessment. Additional findings and Computer Aided Diagnosis Since that early system implementation in 2000, the importance of additional findings for other organs visible in the chest CT scans have become apparent. The radiological structured reporting requirements have been increased to include findings of the heart, and the lungs (emphysema, COPD) which, with lung cancer, covers the three main causes of death for the high-risk screening population. The detailed reporting of the CT scan reading, especially once the initial baseline scan has been read, places an increased burden on the radiologist. To improve the program quality and to address the reading issues a number of additional automated computer analysis functions have been integrated into the system, Reeves et. al. (2017) [2]. These include measures for: coronary calcium, heart size, the aorta, pulmonary hypertension, emphysema, major airways, bone mineral density from thoracic vertebra, breast density, and liver density. In addition, an automated quality assessment of the CT scan itself is reported. The role for AI in screening management Recent advances in AI technology, including deep learning with convolutional neural networks, have increased the capabilities of computer aided diagnostics. A landmark paper by Gulshan et. al. (2016) [3] showed that an automated end-to-end review of eye fundus images for diabetic retinopathy to determine if a follow-up action was indicated could be effectively accomplished without requiring a human read of the images. Following this work a commercial product for this task is now available. A recent paper by Ardila et. al. (2019) [4] showed that, for LCS CT scans, a similar approach with a more complex system could be used for predicting cancer events in a manner similar to LungRADS. A challenge with this LCS study, compared to Gulshan diabetic retinopathy study, is the cost and reporting complexity of the former for training data. While the Gulshan study was prospective and trained on over 120,000 cases, the Ardila study was retrospective with a subset of the NLST data of around 10,000 cases and only considered lung cancer. These methods employ the natural advantage of computer analysis with respect to human readers in attention to detail and lack of fatigue. Further, modern AI methods when appropriately designed, can assimilate data from millions of cases, far beyond human capacity. Efficient large-scale documentation methods have been developed to address the data issue for LCS [2] in which over 25,000 cases have been documented for multiple diseases. These studies move us closer to the point where the majority of the CT image report for LCS could be automatically completed and the role of the physician focused to reviewing a small number of the most significant findings. References 1. Reeves, A. P., Kostis, W. J., Yankelevitz, D. F., and Henschke, C. I. A web-based database system for multi-institutional research studies on lung cancer. RSNA 87th Scientific Meeting 221 (Nov. 2001), 372 2. Reeves, A. P., Xie, Y., and Liu, S. Large-scale image region documentation for fully automated image biomarker algorithm development and evaluation. Journal of Medical Imaging 4, 2 (2017), 024505. 3. Gulshan, V., Peng, L., Coram, M., Stumpe, M. C., Wu, D., Narayanaswamy, A., .. & Kim, R. (2016). 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Keywords: data management, lung cancer screening, AI image analysis

ES09 HOW I DO IT - REAL WORLD ISSUES IN THE DIAGNOSIS AND TREATMENT OF METASTATIC NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES09.01 HOW I OPTIMIZE TISSUE SPECIMEN PROCESSING FOR HISTOPATHOLOGICAL AND MOLECULAR PROFILING

A. Bal

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Lung cancer is the most common cancer in males worldwide, and the most common cause of cancer related mortality in both sexes. There have been significant advances in the treatment of non-small cell lung cancer (NSCLC) in the last several years, which require careful biopsy sample acquisition and processing. Approximately 70% lung cancer patients present in advanced stage, thus most diagnosis of lung cancer are offered on cytology specimens and small biopsies. Specimens for diagnosing lung cancer For diagnosis of lung cancer, the specimens received in pathology laboratory includes; Effusions and FNAC samples from which cell blocks can be prepared, endobronchial biopsies, transbronchial lung biopsies, CT/PET guided core biopsies and biopsies from metastatic sites like lymph nodes, bone etc. Since tissue is an issue in diagnosis and management of lung cancer, thus strategies to manage limited tissues have been developed: The pre-analytical steps involved in handling, fixing and processing these precious tissue samples are critically controlled to obtain accurate and meaningful biomarker tests. For molecular testing two block setting is used: One block for diagnostic immunostains and second block is reserved for molecular workup. Pathological analysis of NSCLC on small biopsies: *Histological Sub-typing of NSCLC:*The subtyping of NSCLC on small biopsies has poor inter-observer agreement. WHO 2015 classification recommends use of ancillary techniques like mucin histochemsitry and immunohistochemistry for cases that cannot be classified based on light microscopy and minimize the use of term NSCLC-NOS.[1]To refine separation of squamous from adenocarcinoma; use of one adenocarcinoma marker and one squamous marker is suggested to preserve tissue for further molecular testing.For adenocarcinoma, TTF-1, Keratin 7 and napsin and for squamous, P40, p63 and keratin5/6 are used. Cocktails of nuclear and cytoplasmic antibodies like, TTF1/CK5/6 and napsin/p63 are also available. For neuroendocrine tumours, the specific markers include; neuron-specific enolase, chromogranin, synaptophysin, and CD56. With the use of immunohistochemistry the NSCLC-NOS category has been reduced from 10% to 5% in our setup.[2] *Morphological Patterns of Adenocarcinoma:*The histologic patterns of adenocarcinoma described in WHO 2015 classification include; lepidic predominant, acinar predominant, papillary predominant, solid predominant and micropapillary predominant pattern. These histological patterns though described for resection specimens, should be reported on small biopsies as they provide prognostic information; Lepidic pattern is associated with favorable prognosis, acinar and papillary with intermediate prognosis whereas the solid and micropapillary patterns have poor prognosis.[3] Genetics for personalized medicine in lung cancer *Epidermal Growth Factor Receptor gene (EGFR) mutation:*Most common mutations in young Asian females and/or never smokers and involves exons 18-21 of EGFR gene, the encoding a portion of the tyrosine kinase domain. Ninety percent of EGFR mutations are exon 19 deletions or missense point mutation in L858P in exon 21. Additional mutations in EGFR (T790M in exon 20) as well as mutations in other genes such as MET have been responsible for resistance to EGFR inhibitors. *Anaplastic Lymphoma Kinase (ALK) rearrangement:*EML4-ALK translocation of the transcription activation domain of ALK and the dimerization domain of EML4, leads to interstitial inversion in the short arm of chromosome 2. EML4-ALK translocation is seen in 5-8% of adenocarcinomas and is detected by break apart FISH or by IHC (D5F3 clone on Ventana system). *Overall incidence of EGFR mutations in our set up is 22.3% and for ALK re-arrangement is 9.5%.*[3,4] *ROS1 re-arrangement:* Similar to ALK mutations, ROS1 re-arranged tumours respond to tyrosine kinase inhibitor therapyandaccounts for 1-2% of pulmonary adenocarcinomas. ROS1 expression is screened by immunohistochemistry (D4D6 clone from Cell signaling) and break-apart FISH confirms the positive cases. *Rare genetic changes:*Other rare mutations reported in lung cancer includes; HER2 mutations (1%); BRAF mutations (2%); RET and NTRK rearrangements reported in 1.9% and 0.9%, respectively Immunotherapy In addition to targetable mutations, immune checkpoint inhibitors have revolutionized the treatment of lung cancer. The programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) have monoclonal antibodies directed towards them, which have shown promise with regards to overall survival in advanced NSCLC. PD-L1 expression status as assessed by immunohistochemistry is important in predicting response to PD-1/PD-L1 inhibitors. However, there are challenges in PD-L1 testing that includes; four different IHC clones on different staining platforms, due to limited tissue all assays cannot be performed, heterogeneity of staining and the need for standardization of interpretation and scoring criteria. Recent advances Since tissue is an issue in molecular testing of lung cancer, targeted next generation sequencing panels are available for testing all relevant molecular changes in one go. Oncomine Dx is one such panel for lung cancer that has got FDA approval. In absence of available tissue especially in setting of relapse, cell free DNA is an alternative for detecting molecular alterations. Conclusions The exact histological subtyping of NSCLC, thus reducing the 'NOS' rate, analysis of genetic alterations for targeted therapy and evaluation of targets for immune checkpoint inhibitors has significantly impacted the treatment and prognosis of lung cancer patients. Thus procurement of adequate tissue and its judicious use is of utmost importance. As the number of clinically significant targetable mutations and chromosomal rearrangements continues to grow, the next generation sequencing becomes the need of the day. References Travis WD, Brambilla E, Nicholson AG et al. The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification.J Thorac Oncol 2015;10(9):1243 60. Kaur H, Sehgal IS, Bal A et al. Evolving epidemiology of lung cancer in India: Reducing non-small cell lung cancer-not otherwise specified and quantifying tobacco smoke exposure are the key. Indian J Cancer 2017;54:285-90. Maturu VN, Singh N, Bal A, et al. 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Keywords: NSCLC, Pathology, Molecular profiling

ES09 HOW I DO IT - REAL WORLD ISSUES IN THE DIAGNOSIS AND TREATMENT OF METASTATIC NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES09.02 HOW I REPORT IMAGING FOR ASSESSMENT OF RESPONSES TO TARGETED THERAPIES VS. IMMUNE CHECKPOINT INHIBITORS VS. CHEMOTHERAPY

R. Gill

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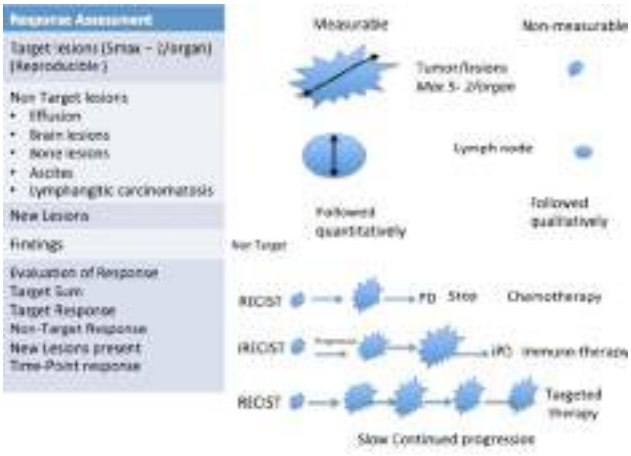
Response assessment is an integral part of radiological reporting in tumor imaging. Our daily workflow includes diagnostic evalaution, determining resectability and response assessment. The radiology template and format is determined by the indication of the exam, and the clinical report may not include detail of all the lesions, but is a synopsis of the findings and an overview of the disease state and longitudinal change on the current therapy. In general our clinical reports do not have details related to detailed response categories and criteria. Response assessment is reported through a separate portal, which is generally overseen by the clinical trials office. Response to therapy is the primary endpoint in most Phase I and II clinical trials. The response criteria to be used and primary and secondary endpoints are detailed in the study protocols based on the type of drug being used. In the era of precision medicine, the traditional response criteria have been evaluated and modified to assess response in targeted and immune therapies. The immune response criteria were developed to follow delayed healing and pseudoprogression. This presentation will discuss details on how I assess response in the context of chemotherapy, targeted therapy and immunotherapy. Assessment of response to chemotherapy was performed using RECIST initially published in 2000 and revised in 2009(1,2). In the current practice RECIST 1.1 is used unless specified by the study protocol. The study protocol will detail the modality technique, duration and reporting criteria. In general the detailed protocol will prove information on the modality of choice. In traditional chemotherapy, the effect of cytotoxic drugs results in gross rumor reduction in most cases. Most trials require more than I independent reviewers, and may have an onsite review and a central review for confirmation of response. Targeted therapies require matching the right gene mutation to the right pharmaceutical

agent, which improves the efficacy and the effectiveness of therapy. Response assessment is on similar lines as chemotherapy. However, response beyond RECIST progression may be allowed on investigator discretion, if the tumor is progressing very slowly and the subject is asymptomatic. In patients with EGFR-mutant NSCLC treated with EGFRTKI, continued EGFR-TKI therapy may be indicated in those patients with progressive disease as these tumors grow slowly over many months and some tumor cells may remain sensitive to EGFR-TKI (3). Erlotinib and crizotinib are commonly continued beyond RECIST progression, because of an initial dramatic response followed by slow progression over many months in relatively asymptomatic patients. Immunotherapy trials are assessed using immune response criteria (iRECIST), the main difference between iRECIST and RECIST, is that the patients are allowed to continue on therapy once disease progresses (PD) for another cycle is continued PD, to ensure it is not pseudoprogression(4). Response assessment in immune therapy trials, allows an extra cycle at 4 to 5 weeks after progression is documented before a decision is made to change therapy. Progression is confirmed at the following cycle or with pathology confirmation. Additional criteria from PETCT and MRI and CT using volumetric assessment is used in the research arena, but not yet used universally for clinical trials. Modified RECIST(5) is more appropriate for pleural tumors as it improves reproducibility of measurements across reviewers and time points. Volumetric assessment is thought to more representative of the morphological changes but definite cut offs as surrogate of the response need validation(6). MRI can assess both size and cellularity and function and hence MR based response assessment derived from apparent diffusion coefficient and pharmacokinetic parameters such as area under the curve, permeability coefficient and elimination coefficient can provide anatomical and functional response to therapy(7,8). It is vital to make a note of any atypical findings and also to recognize adverse events related to the drug and help with timely management. The presentation will detail how I assess response in the real world with case specific examples and illustration of some atypical responses and lesions that can mimic progression.



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Keywords: Response criteria, RECIST, Volumetric, CT

ES09 HOW I DO IT - REAL WORLD ISSUES IN THE DIAGNOSIS AND TREATMENT OF METASTATIC NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES09.03 HOW I DECIDE 1ST LINE TREATMENT OPTIONS FOR METASTATIC NSCLC WITHOUT DRIVER MUTATIONS - BALANCING EFFICACY, TOXICITY AND COST

M. Frueh

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Chemotherapy alone has been the accepted standard treatment for patients with stage IV non-small cell lung cancer (NSCLC) for more than two decades based on trials demonstrating a survival benefit and improved quality of life. In the first line setting, the addition of the anti-VEGF antibody (AB) bevacizumab and anti-EGFR ABs cetuximab and necitumumab resulted in modest improvement of survival. Recently, immune-checkpoint inhibitors (ICI) have revolutionized systemic treatment approaches of patients with EGFR/ALK wild type NSCLC in the first and further line setting, mainly due to their ability to achieve long-term tumor control in a subset of patients. Although a considerable proportion of patients doesn`t respond to ICI, immunotherapy is now widely used in combination with chemotherapy as first line treatment in an increasing number of patients as a result of the absence of a reliable predictive biomarker. This situation leaves physicians in the dilemma of balancing the benefit of potential long term disease control in a limited number of patients with the harms which include not only toxicities but also costs. The implementation of novel ICI treatment options in the first line treatment of metastatic NSCLC into current clinical practise will be discussed.

ES09 HOW I DO IT - REAL WORLD ISSUES IN THE DIAGNOSIS AND TREATMENT OF METASTATIC NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES09.04 HOW I DECIDE 2ND LINE TREATMENT OPTIONS FOR RELAPSED/REFRACTORY METASTATIC NSCLC

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Management of advanced and metastatic non-small cell lung cancer (NSCLC) has been revolutionized in the past decade with the advent of testing for 'druggable' molecular driver alterations and availability of therapies for the same. More recently, immunotherapy (in particular PD-1/PD-L1 immune check point inhibitors) have opened up a fifth frontier for the treatment of this disease. However, barring exceptions, patients with advanced/metastatic NSCLC relapse irrespective of whether they received a targeted therapy or chemotherapy (with/without immunotherapy) or immuno(mono) therapy in the front line setting. This is understandable as cures are uncommon in metastatic disease although sustained and durable responses to immunotherapy and targeted therapies are well known. Treatment of relapsed disease presents a greater challenge as performance status, ability to bear cost of treatment and finally wishes of patients and caregivers often change as opposed to the treatment naïve state. Additional factors also come into play in low and middle income group countries (LMICs) and resource constrained settings. Practicing precision medicine remains the goal even for the relapsed setting. However, finding additional targets or drugs for identified secondary targets mandates rebiopsy which may be limited by ease of access to the desired site for rebiopsy as well as patients' willingness to undergo the same. Liquid biopsy (typically blood and less commonly other body fluids) appears to be an increasingly promising alternative to conventional tissue biopsy with the availability of highly sensitive testing platforms (especially NGS) and the ability of the former to provide 'global' assessment of biomarker status as opposed to the latter. Tissue heterogeneity is more pronounced in the setting of relapsed disease as compared to treatment naïve settings. In case of EGFR mutated NSCLC,

the advent of T790M inhibitors (osimertinib) was the preferred treatment approach for patients progressing on 1st/2nd generation EGFR TKIs and with a demonstrable exon 20 T790M mutation on either tissue or liquid biopsy (AURA trial). However, the FLAURA trial led to osimertinib moving to the frontline setting and therefore relapses on osimertinib is typically followed by chemotherapy unless specific mechanisms of resistance can be demonstrated which can be further targeted by available drugs. It is likely that 4th generation TKIs will be available for patients in the coming few years thus providing an opportunity to use another TKI following progression on osimertinib. For ALK rearranged NSCLC, there is a similar story. 2nd generation ALK inhibitors (alectinib, ceritinib and brigatinib) were developed and initially approved for patients intolerant to or having progressed on the 1st generation ALK inhibitor crizotinib. The ALEX/J-ALEX trials (for alectinib) and ASCEND-4 trial (for ceritinib) meant that these drugs moved to the front-line setting. In particular data from ASCEND-8 trial showed that 450 mg of ceritinib with a low-fat meal was as effective and better tolerated than the conventional 750 mg taken empty stomach. For resource constrained settings, this has an additional implication of lower cost of treatment. Lorlatinib, a 3rd generation ALK inhibitor, approved for use following progression on the 1st/2nd generation ALK inhibitors described above is also attempting to move to the frontline setting pending results of ongoing trials for this purpose. For both EGFR and ALK, the debate on using the best and most effective drug first vs. sequencing lower followed by higher generation drugs continues to be hotly debated as treatment options for progressors on 3rd generation TKIs given upfront are mostly limited to chemotherapy or experimental therapies as part of ongoing clinical trials. Platinum based doublet chemotherapy (pemetrexed based for non-squamous histology and gemcitabine/paclitaxel/nab-paclitaxel for squamous histology) was the cornerstone of treatment for patients without a targetable genetic alteration. Docetaxel single agent was the standard 2nd line treatment option and attempts were made to enhance its efficacy by combining it with VEGF inhibitors like ramucirumab (REVEL trial) or nintedanib (non-squamous only; LUME LUNG-1). Simultaneous time period saw the results of PD-1 inhibitors (nivolumab; CheckMate 017 and 057 and pembrolizumab; KEYNOTE 001 & 010) as well as PD-L1 inhibitor (atezolizumab; OAK) and thus these drugs become the preferred and standard 2nd line treatment. However, a similar story as for EGFR and ALK happened herein as well with the KEYNOTE 024 trial (pembrolizumab monotherapy for PD-L1 expression of 50% or higher) and KEYNOTE 189 and 407 trials (pembrolizumab combined with chemotherapy irrespective of PD-L1 expression) leading this drug to be part of front line treatment. Atezolizumab as part of a 4 drug regiment (paclitaxel-carboplatin-bevacizumab-atezolizumab) also appeared to provide similar efficacy in the front line setting (IMPOWER 150) for non-squamous NSCLC although concerns about toxicity remain. The effect of immunotherapy coming to the front line treatment setting (alone or in combination with chemotherapy) also implies that these drugs have no proven role in relapse as there is no data currently that patients treated initially with immune check point inhibitors benefit from the same class of drugs on relapse. Patients in LMICs and resource constrained settings tend to get treatment in more conventional ways than listed above as newer drugs and regimens are either not available or are not approved as fast as in the US/Europe or are very expensive. Hence it is fairly common for EGFR mutated patients to receive 1st generation EGFR TKIs, for ALK rearranged patients to receive crizotinib and for those without any driver mutations/rearrangements to receive only platinum doublet chemotherapy in the first line setting. This sort of represents a time lag compared to what is applicable in the US/Europe. The need to provide affordable yet effective treatment remains the primary aim of clinical oncologists in LMICs and precision medicine is therefore informally and practically adapted to the available resources. Navneet Singh MD DM Email: *navneetchd@hotmail.com; singh.navneet@pgimer.edu.in* [*The author is a thoracic medical oncologist and pulmonologist currently working as an Additional Professor of Pulmonary Medicine at PGIMER, Chandigarh, India. He is a member of IASLC's Staging & Prognostic Factors Committee; Publications and its Regent for South Asia. Additionally, he is Chair of American Society of Clinical Oncology's(ASCO) International-Development-and-Education-Award(IDEA) Working Group and Thoracic-Cancer Guideline Advisory Group. His detailed profile is accessible at http://www.linkedin.com/in/navneet-singh-160012.*]

Keywords: NSCLC, Resource constraint, Relapse

ES09 HOW I DO IT - REAL WORLD ISSUES IN THE DIAGNOSIS AND TREATMENT OF METASTATIC NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

ES09.05 LIMITATIONS IN THE AVAILABILITY OF RADIOTHERAPY

J. Khader

King Hussein Cancer Center, Amman/Jordan

Limitations in the Availability of Radiotherapy Abstract The annual global incidence of cancer, according to Globocan 2018 report is 18 million new cancer cases, and the number is projected to rise in 2035 to 25 million cases (13 million deaths), with 70% occurring in low- and middle -income countries (LMICs), where there is a severe shortfall in the availability of radiotherapy (1). Radiotherapy is an essential component of overall curative and palliative cancer care. It is estimated that about half of cancer patients would benefit from radiotherapy for treatment of localized disease, local control, and palliation (2). Yet, this crucial component of the response to cancer has been largely absent from global health discourse, and has received limited domestic and international funding. As a result, there is a worldwide shortfall of radiotherapy services; with more than 90% of the population in low-income countries, lacking access to radiotherapy(2). The growing burden of cancer will place increased demand on the already-scarce radiotherapy services worldwide. A 2015 report by the Global Task Force on Radiotherapy for Cancer Control estimated that by 2035 at least 5000 additional megavolt treatment machines would be needed to meet LMIC demands, together with about 30 000 radiation oncologists, 22 000 medical physicists and 80 000 radiation therapy technologists(3). Many of the challenges in delivering radiotherapy in LMICs that were identified including: (a) a shortage of good-quality radiotherapy equipment capable of both simple and more complex radiotherapy treatment delivery, (b) the challenge of servicing the linacs, both for preventative maintenance and upon equipment breakdown and (c) the chronic shortage of adequately trained personnel(3). In LMICs, the costs of equipment, building and salaries are 81, 9 and 10% of the total cost of the facility, respectively, compared with 30, 6 and 64% in high-income countries. Some of the challenges facing LMICs are also related radiofrequency power systems, linac beam production and control, durable and sustainable power supplies, computer applications in radiation therapy & linac safety and operability(4). Investment in radiotherapy is crucial and an imperative in low-income and middle-income countries, if unnecessary cancer deaths and suffering are to be avoided. Investment in radiotherapy is timely for many reasons, including evidence from The Lancet Commission on Investing in Health (5) showing the benefits of investing in health to achieve convergence in health outcomes between low-income countries and upper-middle-income countries, the momentum for investing in low-income and middle-income countries to expand surgery,(6) and the UN resolution on sustainable development, which recognises that "universal health coverage is a key instrument to enhancing health, social cohesion and sustainable human and economic development".(7) Conclusion It is a call for action to enhance population-based cancer control plans, expansion of access to radiotherapy, human resources for radiotherapy, sustainable financing to expand access to radiotherapy and align radiotherapy access with universal health coverage. References 1.Freddie B et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA CANCER J CLIN 2018;68:394–424 2.Barton MB et al. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiother Oncol 2014; 112: 140–44. 3.Atun R, et al. Expanding global access to radiotherapy. Lancet Oncol 2015;16(10):1153e1186 4. Dosanjh M et al. Developing Innovative, Robust and Affordable Medical Linear Accelerators for Challenging Environments, Clin Oncol, 2019 Jun; 31(6):352-355 5.Jamison DT et al. Global health 2035: A world converging within a generation. Lancet 2013; 382: 1898–955. 6. Meara JG et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet 2015; 386: 569–624. 7. UN. Sustainable development, the Future We Want, UN General Assembly Resolution, A/66/L.56, para 138–141. http://www.uncsd2012.org/content/documents/ (accessed July 5, 2015).

Keywords: Radiotherapy,low and middle income countries.

ES10 ONCOLOGY DRUG APPROVAL: CHALLENGES AND OPPORTUNITIES
SUNDAY, SEPTEMBER 8 13:30–15:00

ES10.01 US FOOD AND DRUG ADMINISTRATION

G. Blumenthal

FDA, Silver Spring/United States of America

Dr Blumenthal will provide the US FDA Oncology Center of Excellence perspective on Oncology Drug Approval: Challenges and Opportunity. With the recent influx of novel targeted therapies, immunotherapy and chemotherapy to treat patients with lung cancers, there are increased challenges to ensuring that safe and effective therapies are available to patients as efficiently as possible while ensuring that the evidence generated is robust and reliable. This talk will discuss FDA's perspective on global drug development.

Keywords: regulation, development, access

ES10 ONCOLOGY DRUG APPROVAL: CHALLENGES AND OPPORTUNITIES
SUNDAY, SEPTEMBER 8 13:30–15:00

ES10.02 JAPAN PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

S. Nagai

The University of Tokyo Hospital, Tokyo/Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labour and Welfare (MHLW) are responsible for reviewing applications and approving the marketing authorization of drugs, medical devices, and regenerative medicines in Japan. All applications for marketing authorization in Japan are submitted to the PMDA. The PMDA conducts scientific review. Review reports prepared by the PMDA are then submitted to MHLW. The MHLW approves the marketing authorization. Japanese regulation has two categories of regulatory review: standard review and priority review. Priority review is applied to orphan drugs and products designated by the MHLW. Other than orphan drugs, the MHLW designates medical products as priority review products based on the following criteria described: 1. Seriousness of the target disease and 2. Clinical usefulness of the drug: no standard therapy exists, and clinical usefulness is superior to the existing products in terms of efficacy, safety, or the patient's quality of life. The target total review time for standard review products and priority review products is 12 months and 9 months, respectively. The conditional and term-limited approval system has been first introduced for regenerative medical products since November, 2014. Regenerative medical products may be granted conditional and term-limited approval if their efficacy can be assumed and safety is confirmed in early-phase (phase I and/or II) registration trials. In the approval system, sponsors of the products must confirm their efficacy and safety after marketing authorization in postmarketing clinical studies etc and by resubmitting applications for regular approval within a predetermined period (not more than 7 years). The conditional and term-limited approval for regenerative medical products is similar to the accelerated approval in the US. In addition, the conditional approval system for drugs has been newly instituted since October, 2017 in Japan. This may be granted if all of the following requirements are met: 1. seriousness of the target disease, 2. clinical usefulness of the drug: no standard therapy exists, and clinical usefulness is superior to the existing products in terms of efficacy, safety, or quality of life, 3. it is difficult or it takes too long time to conduct a confirmatory study, 4. exploratory clinical studies can show efficacy and safety, and 5. surveillance or clinical studies must be conducted as post-marketing requirement. Because these requirements include the requirements for priority review (seriousness of the target disease and clinical usefulness of the drug), drugs granted conditional approval can automatically enjoy priority review. Moreover, the requirement for conditional approval "it is difficult or it takes too long time to conduct a confirmatory study" in Japan is totally different from accelerated approval based on surrogate endpoint in the US. The requirement is similar to the requirement for marketing authorization under exceptional circumstances "companies cannot provide comprehensive clinical data because of the rarity of the disease" in the EU. Although the requirements for conditional approval for drugs in Japan include "surveillance or clinical studies must be conducted as post-marketing requirement", the term of validity for conditional approval of drugs in Japan is not established, which is different from the conditional and term-limited approval for regenerative medical products in Japan. As of May 31, 2019, only lorlatinib for ALK fusion-positive non-small cell lung cancer and pembrolizumab for MSI-high solid cancer have been granted conditional approval for drugs in Japan. Conducting confirmatory comparative studies is not included in postmarketing requirements for the both drugs. The MHLW instituted in 2015 the SAKIGAKE (meaning pioneer or forerunner in Japanese) designation system for medical products for diseases in urgent medical need of innovative therapy and that may satisfying the following two conditions: 1. The medical product has been first developed in Japan, and a sponsor is planning to submit a marketing authorization application; and 2. Prominent effectiveness can be expected based on data from the mechanism of action, non-clinical studies, and early-phase clinical studies. Advantages of sponsors who have medical products granted SAKIGAKE designation are as follows: prioritized consultation (reduced waiting time), substantial pre-application consultation, prioritized review (target total review time of 6 months only for drugs, devices, and IVDs), assigning a PMDA manager as a concierge, and an extension of the reexamination period. Total review time for SAKIGAKE-designated regenerative medical products is not established. Although the SAKIGAKE designation is similar to a breakthrough therapy designation in the US and PRIME in the EU, the requirement "the medical product has been first developed in Japan" and the advantage of specific shortened total review time are unique to the SAKIGAKE. Companion diagnostics (CDx) are important for oncology drug development. Current regulatory considerations regarding CDx and tumor profiling test in Japan are similar to those in the US. As of May 31, 2019, three next generation sequencing-based oncology panel tests have been approved as CDx and/or tumor profiling test in Japan. However, more flexible regulations regarding CDx are necessary for efficient clinical practice and drug development. I will give an overview of regulatory frameworks and challenges regarding oncology drugs and companion diagnostics in Japan. References: •Nagai S, Ozawa K. 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Keywords: MHLW, PMDA, conditional approval

ES10 ONCOLOGY DRUG APPROVAL: CHALLENGES AND OPPORTUNITIES
SUNDAY, SEPTEMBER 8 13:30–15:00

ES10.04 EUROPEAN MEDICINES AGENCY

J. Camarero

Spanish Medicines Agency, Madrid/Spain

Oncology Drugs Approval: Challenges and Opportunities In recent years, the development of new drugs in the oncology field has notably increased. This growth in oncology clinical trials appears to be mainly associated with the increasing knowledge in pathophysiology and molecular medicine in oncology. Targeted therapies have been approved, overall, on the basis of its ability to prolong progression free survival and/or life expectancy of patients. In addition, immunotherapy has arisen as a turning point in the treatment of cancer, opening a new era and setting up a milestone in the current armamentarium. However, the regulatory decision making process behind some of the approvals for these products have proven difficult and lead to important uncertainties still to be addressed. Such unanswered questions relate, among others, to the target population, subgroups of patients partially covered by authorized indications and limitations on important aspects such as duration and combination of treatments. Likewise, this increase in new molecules development poses a remarkable pressure on regulators, clinicians and payers, who albeit from different perspectives, face the very same problem of how to ensure (timely) access to patients of new authorized products. From a regulatory perspective, randomized clinical trials remain the gold standard for

adequate assessment of both efficacy and safety. Nevertheless, conducting single arm studies is becoming a commonly approach for companies to speed up regulatory approval in those situations where there is an unmet medical need. The latter cast important doubts on when, where and how this strategy can be accepted. Last but not least, new clinical trials designs and the proposal of using Real Word Evidence/Real World Data to complement non-compelling clinical development, are creating a new parading when it comes to making a decision upon the benefit-risk balance

Keywords: Randomised clinical trials, single arm trials, regulatory process

ES10 ONCOLOGY DRUG APPROVAL: CHALLENGES AND OPPORTUNITIES
SUNDAY, SEPTEMBER 8 13:30–15:00

ES10.05 BRAZILIAN HEALTH REGULATORY AGENCY - AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

C.G. Ferreira

Oncoclinicas Institute For Research and Education, Rio Janeiro/Brazil

Brazil, the largest country in South America, has become the second largest pharmaceutical market in the emerging world. The Brazilian Health Surveillance Agency (Agencia Nacional de Vigilancia Sanitaria - ANVISA) was created in 1999 with the primary goal to protect and promote public health surveillance over products and services in Brazil. Its hallmarks are administrative independence, financial autonomy, and the stability of its directors. Within the federal public regulatory structure, the agency is linked to the Ministry of Health [1]. Despite major advances in the regulatory process in Brazil, it is important to highlight that a major delay in cancer drugs approval over the last decade has had a negative impact on patient access to novel medications in Brazil. According to Barrios et al., [2] well-established and adequately functional drug approval legislation is indispensable to guarantee a country's population health. Any malfunctions or delay in such a crucial process have serious consequences. As an example, the drug Crizotinib (Xalcori®Pfizer, NY, USA), which had its approval denied by ANVISA in June 2014 may be seen as a landmark. Assuming different premises, Barrios et al. [2] calculated 1.367 years of life lost over 34 months due to lack of access to Crizotinib between August 2011 (FDA approval) to June 2014 (refusal by ANVISA). Of note, Crizotinib was not approved in Brazil until Feb 2016, what may have added additional 804 years of life lost to final numbers due to this delay. Other example of unexplained delay in drug approval in lenalidomide. The gap between the drug approval in the US and Brazil was 12 years. Regarding drugs that do require a companion diagnostic, the situation may become more complicated since, unlike the US Food and Drug Administration, no clear mechanism is in place with ANVISA for the simultaneous linking of most companion diagnostic tests with their respective targeted therapeutic drug [3]. In trying to understand the reasons behind this delayed drug approval process, methodological, cultural, political and ideologic reasons may account. At odds with other regulatory agencies such the FDA that allow conditioned approval based on non randomized data for drugs addressing unmet medical needs. For many years ANVISA authorities mandated randomized phase 3 data for a definitive approval, since no conditioned approval was allowed. In this context, having a specific oncology area or committee, such as the FDA Oncology Drug Advisory Committee [4], may be crucial. Fast track approval, breakthrough designation, companion diagnostics, different surrogate endpoints, integration of real world evidence (RWE) into the regulatory process are very specific topics from the oncology field and do require to be analyzed under the perspective of cancer specialists. From a political, cultural and ideologic perspective, althoughit is notorious that Brazil has invested substantially in expanding access to health care for all of its citizens, the country has, essentially, two clear distinct and dissimilar health systems [3]. The public system allows drugs to become commercially available through processes that are different from those in place in the private health-care system. Although difficult to measure those disparities and difficulties to reimburse expensive drugs in the public system, may have influenced the delayed process during the last decade. Over the last decade, delays at ANVISA's approval process have been considered the only reason for the inequitable access to oncology care between the USA and Brazil. Yet, this may be a biased conclusion and a more comprehensive analysis in needed. By analyzinga basket of twenty-three oncology products approved by ANVISA after 2002 Bustamante et al. [5] identified that on average there was a difference of 8.6 months (449 X 186 days). However on average, a delay in the manufacturers' submission for regulatory approval of 1.1 years (393 days between Brazil and the USA) was also identified. More recently, a trend toward improvements in the drug approval process has been identified (ex. Osimertinib and Durvalumab). Osimertinib was firstly approved by ANVISA in 2017 as a second line treatment in patients who did not respond well to the initial drug. With the new determination, in 2018 ANVISA approved its use as a first therapy to treat locally advanced non-small cell lung cancer. Durvalumab was approved by ANVISA in 2017. Nevertheless there is clear room for a continuous improvement. Increase in the number of ANVISA technicians, continuous training and collaboration with academic institutions and other regulatory agencies elsewhere are mandatory. Close scientific collaboration and open and transparent dialogue between ANVISA and pharmaceutical companies are required. In sum, if we are to have a continuous improvement in the oncology drug approval process, all the stakeholders (ANVISA, drug manufactures, patient advocacy, players at the private and public health systems) must act together. References 1. Ba KH andSassi AB. ANVISA: an introduction to a new regulatory agency with many challenges. AAPS Open2018; 12 Dec 2018; 4:9. 2. Barrios PM, Debiasi M, Lopes G, Barrios CH. P1.51: Impact of Regulatory Delays in Drug Approval: Mortality and Morbidity Due to With Lack of Access to Crizotinib in Brazil: Track: Supportive Care and Others. 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Keywords: Drug registration, Regulatory agency, delay

ES11 LUNG CANCER PLASTICITY AND DRUG RESISTANCE
SUNDAY, SEPTEMBER 8 15:15–16:45

ES11.01 LUNG ADENOCARCINOMA TO SQUAMOUS CELL CARCINOMA TRANSDIFFERENTIATION AND DRUG RESISTANCE

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Lung cancer is notorious for high heterogeneity and strong plasticity, which might contribute to the development of drug resistance. Lineage transition from lung adenocarcinoma (ADC) to squamous cell carcinoma (SCC), as implicated by clinical observation of mixed ADC and SCC pathologies in adenosquamous cell carcinoma (Ad-SCC), reflects strong cancer plasticity and potentially links to drug resistance. Using Genetically Engineered Murine Model (GEMM), we have provided *in vivo* evidence in supporting the ADC to SCC transdifferentiation (AST): *Lkb1*-deficient mouse lung ADC transdifferentiates into SCC progressively via pathologically mixed Ad-SCC. Mechanistically, we find that down-regulation of reactive oxygen species (ROS) level through N-acetyl cysteine (NAC) treatment or NRF2 expression inhibits this transition, highlighting the functional importance of ROS in regulating cancer plasticity. Pentose phosphate pathway deregulation and impaired fatty acid oxidation collectively contribute to the redox imbalance and functionally affect the AST process. Importantly, similar tumor and redox heterogeneity are also found in human LKB1-inactivated lung cancer. In preclinical trials toward metabolic stress, Lkb1-inactivated ADC can develop drug resistance through squamous transdifferentiation. Recent observations in clinic further suggest that such pathological transition might be responsible for resistance to tyrosine kinase inhibitor (TKI) therapy and chemotherapy in relapsed EGFR-mutant lung ADC patients. These findings demonstrate that lung cancer plasticity potentially affects therapeutic response and precision medicine through histological transition.

ES11.02 SCLC LINEAGE TRANSFORMATION IN LUNG ADENOCARCINOMA AND RESISTANCE TO TARGETED THERAPIES

W. Lockwood, Y. Inoue

British Columbia Cancer Research Centre, Vancouver/Canada

Lung cancers are typically divided into two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all cases and lung adenocarcinoma (LUAD) is the most frequent subtype. Current treatments of LUAD aim to inhibit driver oncogene alterations and have shown unprecedented success. Among the oncogenic alterations in LUAD, EGFR kinase domain mutations are found in ~40-50% of patients in east-Asian countries and 20% of patients in western countries1. EGFR tyrosine kinase inhibitor (TKIs) are highly effective for tumors with EGFR mutations and resistance mechanisms to these compounds have been well documented: the most frequent being the acquisition of a secondary mutation in EGFR (T790M)2, followed by amplification of the hepatocyte growth factor receptor (MET) gene3 and mutations in BRAF and PIK3CA genes4,5. Histological transformation from LUAD to SCLC occurs in up to 15% of cases with acquired resistance to first and second generation EGFR TKIs5. Histological plasticity as a mechanism of resistance is becoming increasingly prominent as other resistant mechanisms can now be successfully targeted: MET-inhibitors are employed for MET-amplified tumours and 3rd generation EGFR TKIs are used to overcome resistance driven by the EGFR T790M muation6. Importantly, the 3rd generation EGFR TKI osimertinib was approved by the FDA in 2018 and thus, cases of treatment-induced SCLC transformation may increase in prominence as other mechanisms are targeted. Currently, conventional platinum doublet chemotherapy is the standard of care for patients with treatment-induced SCLC as well as de novo SCLC. Unfortunately, this treatment often produces an incomplete and non-durable response followed by inevitable relapse within months, leading to poor patient outcomes7. Thus, this mechanism of resistance will represent a major barrier towards the success of 3rd generation TKIs and new strategies to prevent this lineage shift or to treat SCLC transformed tumors are urgently needed. Despite the increasing clinical importance of LUAD to SCLC transformation, the biological pathways regulating this process are poorly understood. Since the first description in 20068, numerous studies have aimed to characterize the molecular changes that drive transformation in the context of drug resistance. Assessment of clinical samples has revealed that EGFR-mutant tumors universally lose EGFR protein expression upon SCLC transformation, despite still harboring EGFR mutations that confirms their clonal origin9. Furthermore, the mutation spectrum of these transformed cases often resemble de novo SCLC, containing inactivation of the tumor suppressors RB and p53 in nearly all cases9. This mirrors neuroendocrine transformation that occurs in prostate adenocarcinoma, where loss of RB/p53 are known to upregulate the reprogramming transcription factor SOX2, driving lineage plasticity and resistance upon anti-androgen therapy10. Furthermore, loss of RB and inactivation of p53 are required to reprogram a normal cell of epithelial lineage to a neuroendocrine lineage, and when combined with expression of myristoylated AKT1 and overexpression of MYC and BCL2, leads to the development of lethal SCLC in vivo11. Inactivation of p53 and RB also leads to the development of SCLC in transgenic mouse models, even when targeted in specifically to type-II airway epithelial cells, the putative cell of origin for EGFR-mutant LUAD12. Together, these studies highlight the essential role for these tumor suppressor genes in reprograming transcriptional profiles and chromatin accessibility in facilitating neuroendocrine lineage transformation. However, accumulating experimental evidence has demonstrated that while necessary, dual inactivation of RB and p53 is not sufficient to cause SCLC lineage transformation in EGFR-mutated LUAD, suggesting that additional factors are required9. MYC amplification and PIK3CA mutation have been proposed to potentially cooperate with RB/p53 loss to facilitate transformation13, and specific epigenetic regulators may also provide the appropriate context for lineage reprograming to occur. Despite this, no *in vitro* or in vivo models of SCLC transformation in EGFR TKI resistance have been developed, making it difficult to comprehensively explore the molecular events driving this lineage shift. Interestingly, there are clear differences between LUAD and SCLC regarding EGFR expression and gene alterations in MAPK pathway including EGFR/KRAS mutations: EGFR is usually not expressed14 and EGFR/KRAS mutations are extremely rare in SCLC15; in contrast, EGFR/KRAS play crucial roles in LUAD biology, including regulating differentiation in addition to prolferation16. To date, however, no clear explanation has been given for these differences. We have recently shown that activation of MAPK signaling in SCLC leads to suppression of the neuroendocrine phenotype - including downregulation of the transcription factors NEUROD1, INSM1, BRN2 and ASCL1 - and transformation to a NSCLC-like state17. Using this model system, we have begun to elucidate the key transcription factors and epigenetic changes that drive SCLC to NSCLC transformation in the hope that the same processes will also be involved in the clinically relevant scenario: SCLC transformation from EGFR mutant LUAD during TKI resistance. We suggest that only EGFR-mutant LUADs that do not reactivate MAPK signaling through secondary EGFR mutations or alterations in parallel kinase pathways (ie. MET) during development of TKI resistance will be able to undergo SCLC lineage transformation, and that RB/p53 loss and epigenetic plasticity provide the permissive context for which this transformation can occur. Greater understanding of lineage transformation in LUAD will provide important insights in terms of managing outcomes of patients undergoing targeted therapy and offer new avenues towards treatment of TKI resistant tumors. References: 1. Dearden S et al. Ann Oncol 2013;24:2371-6. 2. Kobayashi S et al. NEJM 2005;352:786-92. 3. Bean J et al. PNAS 2007;104:20932-7. 4. Ohashi K et al. PNAS 2012;109:E2127-33. 5. Sequist LV et al. Sci Transl Med 2011;3:75ra26. 6. Mok TS et al. NEJM 2017;376:629-40. 7. Roca E et al. Cancer Treat Rev 2017;59:117-22. 8. Zakowski MF et al. NEJM 2006;355:213-5. 9. Niederst MJ et al. Nat Commun 2015;6:6377. 10. Mu P et al. Science 2017;355: 84-8. 11. Park et al. Science. 2018;362:91-95. 12. Sutherland KD et al. Cancer Cell 2011;19:754-64 13. Lee JK et al. J Clin Oncol. 2017;35:3065-3074. 14. Gamou S et al. Cancer Res 1987;47:2668-73. 15. Cristea S et al. J Thorac Oncol 2016;11:1233-41. 16. Byers LA et al. Cancer Discov 2012;2:798-811. 17. Y. Inoue and W. Lockwood. J Thorac Oncol 2018;13:S433–S434.

Keywords: SCLC, lineage transformaton, EGFR

ES11.03 IMMUNOTHERAPY AND ENDOGENOUS RETROVIRUSES IN SMALL-CELL LUNG CANCER

I. Canadas

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Introduction: Tumor cell heterogeneity is a key determinant of cancer progression and drug resistance, which is often mediated by mesenchymal cell subpopulations. While these subclones can secrete growth factors, chemokines and cytokines, the immune signaling networks that fuel this pro-tumorigenic state remain incompletely defined. Elucidating what underlies this state would provide insights into tumor biology and inform clinical strategies to improve anti-cancer therapies. Methods: Because of their well-defined nature, we used the phenotypically distinct H69M and H69AR Small Cell Lung Cancer (SCLC) mesenchymal subclones to uncover a novel mechanism of dysregulated innate immune signaling as compared with parental neuroendocrine H69 cells. Analysis of gene signatures across TCGA and CCLE databases, functional studies in additional cell lines, and ex vivo testing of patient-derived organotypic tumor spheroids (PDOTS) were conducted to determine the broader relevance across human cancers. Results: We discovered a novel epigenetically regulated subclass of endogenous retroviruses (ERVs) that engages innate immune signaling in mesenchymal cancer subpopulations. Stimulated 3 Prime Antisense Retroviral Coding Sequences (SPARCS) are oriented inversely in 3'UTRs of certain interferon-inducible genes and silenced by EZH2. De-repression of these loci resulted in dsRNA generation following IFNγ exposure due to bi-directional transcription from the STAT1-activated gene promoter and the 5' LTR of the antisense ERV. We found that dsRNA sensing preferentially by MAVS fuels activation of TBK1, IRF3, and STAT1 signaling, sustaining a positive feedback loop. SPARCS induction across specific human tumors and cell lines is tightly associated with downregulation of chromatin modifying enzymes, including EZH2, a mesenchymal AXL positive cell state, and B2M and MHC class 1 antigen expression. SPARCS high tumors were marked by immune infiltration, but also exhibited multiple features of tumor immune suppression. IFNγ treatment of PDOTS with de-repressed SPARCS markedly enhanced CXCL10 production and sensitized them to PD-1 blockade. Conclusions: Together, these data unveil a novel

subclass of ERVs whose de-repression triggers pathologic innate immune signaling in cancer, with potentially important implications for cancer immunotherapy.

Keywords: Endogenous Retroviruses, Tumor Immunity, small-cell lung cancer

ES11 LUNG CANCER PLASTICITY AND DRUG RESISTANCE
SUNDAY, SEPTEMBER 8 15:15–16:45

ES11.04 MECHANISMS FOR RESISTANCE TO TKI AND ICI

K. Politi

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Targeted therapies and immunotherapies have transformed the treatment landscape for lung cancer over the past 15 years. These therapies are effective in subsets of patients, however, acquired resistance is an impediment to cures. In the case of targeted therapies, acquired resistance occurs in all cases although new generations of targeted therapies delay inevitable relapse. Upon treatment with immune checkpoint inhibitors, data suggest that acquired resistance occurs in ~50% of cases following an initial response to the therapies. However, studies of acquired resistance to these immunotherapies are limited and the exact frequency remains to be determined. Therefore understanding the mechanisms of acquired resistance to targeted therapies and immunotherapies is of critical importance to developing new therapeutic strategies to overcome and prevent the emergence of drug resistance. EGFR mutant lung cancer is a paradigm for the use of targeted therapies in this disease. Tyrosine kinase inhibitors (TKIs) are the first line of treatment for EGFR mutant lung cancer and are effective in 70-80% of cases. Acquired resistance to first and second generation inhibitors, like erlotinib, gefitinib and afatinib, most frequently is the result of a secondary mutation in EGFR, EGFR T790M. Third generation TKIs that can inhibit the activity of EGFR T790M-containing mutants were recently developed and one of these, osimertinib, is now approved for the first- and second-line treatment of EGFR mutant lung cancer and is increasingly used in the clinic. Even with osimertinib, acquired resistance occurs and there is a need to understand the mechanisms of resistance to this TKI. We will review current knowledge of acquired resistance to osimertinib and discuss new findings from studies in genetically engineered mouse models, patient-derived xenografts, patient specimens and cell line models. In contrast to the extensive knowledge of the mechanisms of acquired resistance to TKIs, very little is known about acquired resistance to immune checkpoint inhibitors. In melanoma, lung cancer and colon cancer, defects in antigen processing and presentation have emerged as a mechanism of acquired resistance to these agents. Defects in this pathway can occur in different ways including loss of specific neoantigens and genetic loss or downregulation of essential components of the pathway like b2-microglobulin. In the presentation, we will discuss known mechanisms of acquired resistance to immune checkpoint inhibitors and new approaches and models that we and others are developing to study this problem.

ES11 LUNG CANCER PLASTICITY AND DRUG RESISTANCE
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ES11.05 MSK-IMPACT, A HOSPITAL BASED GENETIC SCREENING USING FDA-APPROVED NGS SYSTEM

A. Drilon

Memorial Sloan Kettering Cancer Center, New York/United States of America

A variety of actionable genomic signatures are found across different cancer types. These signatures have been associated with clinical benefit from a variety of therapeutics, including targeted therapy and immunotherapy. MSK-IMPACT is a broad, hybrid capture-based next-genereation sequencing platform that is capable of detecting sequence mutations, small insertions and deletions, copy number alterations, and select structural rearrangements. The assay has been validated and approved for clinical use by the New York State Department of Health Clinical Laboratory Evaluation Program. Furthermore, the assay has received authorization by the United States Food and Drug Authority. Comprehensive profiling of various cancers with assays such as MSK-IMPACT has advanced genomic medicine by increasing the identification of patients for whom matched therapies may be appropriate, elucidating putative resistance mechanisms, and identifying novel, potentiallly actionable signatures.

Keywords: MSK-IMPACT, Next-generation sequencing

ES11 LUNG CANCER PLASTICITY AND DRUG RESISTANCE
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ES11.06 TOXICOLOGY OF TOBACCO AND METABOLITES, AND IMPACT ON CANCER

M. Goniewicz

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Tobacco smoke is a significant source of exposure to toxic compounds among active smokers and those exposed to secondhand smoke (SHS). Over 7000 chemicals have been identified in tobacco smoke, including 69 known carcinogens. Characterizing human exposure to tobacco smoke constituents is important for public health efforts aimed at reducing exposure to these chemicals. Tobacco smoke exposure can be assessed through biomonitoring, i.e., by measuring the concentration of a toxicant or its metabolites in human physiological fluids. Biomarkers, ideally unique to a toxic mixture such as tobacco smoke, are useful for exposure assessment and for source apportionment. Nicotine, its metabolites, and the tobacco-specific nitrosamine (TSNA) metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are the most specific of the commonly used biomarkers for tobacco smoke exposure. Carbon monoxide, metabolites of volatile organic compounds (VOCs), and polycyclic aromatic hydrocarbons (PAHs) metabolites, are also useful biomarkers, but they have sources other than tobacco smoke. Levels of these biomarkers are generally elevated in smokers as compared to nonsmokers, but specificity may be inadequate to measure SHS exposure. In general, biomarker studies can demonstrate internal exposure to toxic constituents due to tobacco product use and can be used to assess relative harm of modified-risk tobacco products. Epidemiologic studies directly support a link between exposure to tobacco-specific toxicants and subsequent risk for cancer in smokers of conventional cigarettes as well as lifelong never-smokers. Nicotine metabolites and total nicotine equivalents (sum of nicotine, cotinine, 3'-hydroxycotinine, and their glucuronides), which can be measured in urine, blood or saliva, represent approximately 73%–96% of the nicotine dose and provide a superb indicator of nicotine uptake. Although nicotine was one of the first biomarkers to be used for assessing exposure to cigarette smoke, its short half-life ($t_{1/2}$=~2 h) and variable rate of metabolism led to the use of cotinine and other nicotine metabolites as biomarkers of nicotine exposure. Cotinine is the major metabolite of nicotine, and its longer elimination half-time ($t_{1/2}$=16–18 h) makes it a good biomarker for nicotine uptake in various biological fluids and tissues. The nicotine metabolite ratio (ratio of 3'-hydroxycotinine to cotinine) in plasma is an excellent phenotypic indicator of hepatic CYP2A6 activity in smokers and can be used as a measure of individual risk for addiction. Tobacco-specific nitrosamines (TSNAs) include the potent lung carcinogen NNK and the oral cavity and esophageal carcinogen N'-nitrosonornicotine (NNN) and are—as indicated by their common name—regarded as completely specific to tobacco. Consequently, these compounds and their metabolites are among the most important biomarkers for monitoring tobacco exposure and evaluating cancer risk in tobacco users. NNAL is a metabolite of NNK and itself is a carcinogen. A key benefit of NNAL assays is the compound's elimination half-time ($t_{1/2}$ of 10–18 days), which is longer than other tobacco biomarkers. The main disadvantage is that the urinary concentration of NNAL is many times lower than that of cotinine, so the assay is more technically challenging and expensive to perform. Measurements of NNAL typically require extensive sample preparation and fewer laboratories can reliably measure NNAL than cotinine or nicotine. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants formed from incomplete combustion of organic matter and use of combustible tobacco products results in substantial exposure to those chemicals. Over 500 PAHs and their alkyl derivatives have been identified in tobacco smoke. Some PAHs induce tumors in animals and are carcinogenic to humans. For example, benzo[a]pyrene induces malignant lesions in animal studies. Urinary concentrations of PAH metabolites, specifically monohydroxylated PAHs, have been used as biomarkers of human exposure to PAHs including naphthalene, fluorene, phenanthrene and pyrene. The PAH exposure profiles for tobacco smoke may differ from other sources, and it may be possible to identify PAH

biomarkers that are more selective for tobacco smoke than others. Volatile organic compounds (VOCs) are a diverse group of chemicals that are abundant in tobacco product emissions and in the polluted atmosphere. Many VOCs are formed by incomplete combustion of organic materials, and tobacco is not the only source of exposure. Although VOCs are also present in foods and beverages, the levels of many VOCs and VOC metabolites are elevated in smokers' urine compared with nonsmokers. Several VOCs in tobacco smoke, including acrolein, benzene, and 1,3-butadiene, can cause cardiovascular and lung damage. 1,3-butadiene is also a human carcinogen and benzene is a human carcinogen known to cause leukemia. A number of harmful VOCs and their metabolites can be measured in human blood, urine, and breath and those biomarkers serve as a surrogate measure for tobacco smoke exposure. While tobacco-specific biomarkers are useful for interim assessments of exposure, there are several sources of variation to consider when interpreting such data. These include frequency and intensity of tobacco use product type, inter- and intra-individual variability, biomarker/chemical half-life, and variability in lab methods. Differences in carcinogen exposure from different cigarette products could contribute to differences in smoking-associated cancer incidence. Due to the introduction of new tobacco-derived products and the development of novel ways to modify and use conventional tobacco products, biomarker studies can be used to assess relative harm of modified-risk tobacco products. For example, short-term observational studies have shown reduction in biomarker levels for VOCs, TSNAs, and PAHs in cigarette smokers who switched to e-cigarettes, smokeless or heated tobacco products. This suite of biomarkers has the potential to provide objective data on levels of nicotine as well as selected important carcinogens and toxicants that may be associated with use of novel tobacco products.

Selected Biomarkers of Exposure to Tobacco Products			
Toxicant Group	**Tobacco Constituents**	**Biomarkers**	**Clinical Relevance**
Nicotine Metabolites	Nicotine	Cotinine	Addictive chemical
Tobacco Specific Nitrosamines (TSNAs)	4-methyl-nitrosamino)-4-(3-pyridyl)-1-butanon (NNK)	4-methylnitrosamino-l)-4-(3-pyridyl)-1-butanol (NNAL)	Carcinogen
Polycyclic Aromatic Hydrocarbons (PAHs)	Naphthalene and Pyrene	2-Napthol and 1-Hydroxypyrene	Possible human carcinogens
Volatile Organic Compounds (VOCs)	Acrylonitrile, acrolein, acrylamide	CYMA, CEMA, AAMA	Probable human carcinogens

Keywords: cancer risk, Tobacco, biomarkers

ES12 LUNG CANCER PATHOLOGY IN THE AGE OF GENOMICS
SUNDAY, SEPTEMBER 8 15:15–16:45

ES12.01 MULTIPLE LUNG NODULES

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Advanced imaging techniques resulted in increased detection of multiple tumors of the lung. Distinguishing synchronous primary lung cancers from intrapulmonary metastases (separate nodules) is important because treatments are very different. In addition, patients with independent primary tumors are expected to have better prognosis. Staging of such tumors as independent primary tumors or intrapulmonary metastases is often challenging, particularly in squamous cell carcinomas. Martini and Melamed modified criteria were used as the main approach for many decades with the idea that morphology of metastases should match the primary tumor, while different morphology supports classification of tumors as unrelated separate primaries. The 8th edition of the AJCC staging of the lung cancer pretty much has replaced this classification by establishing a multidisciplinary approach to these tumors as a standard of care and by promoting the tools such as comprehensive histologic assessment, imaging studies and molecular characterization either by CGH or biomarker testing. Comprehensive histologic assessment is based on the 2015 WHO classification of lung cancers and includes determination of the main histologic tumor type, quantitative subtyping particularly of lung adenocarcinomas, and assessment of cytologic and stromal characteristics. This approach can be relatively easily applied in lung adenocarcinomas, while squamous cell carcinoma remains a great challenge. A recent study conducted by the IASLC Pathology committee showed a good agreement (κ score 0.60) among thoracic pathologists in the histologic assessment of independent primary tumors from intrapulmonary metastasis. Despite a good agreement, there were cases with split opinions supporting a need for ancillary studies. Over the past decade many studies reported different molecular approaches to analysis of multiple lung tumor nodules including DNA microsatellite analysis, CGH/aCHG and most recently next generation sequencing. The data from published reports indicate a highly variable percentage of multifocal tumors identified as clonally related (up to 70%). Discrepancy between clinical and molecular classification of originally presumed cases of multiple primary lung cancers ranged in different series from 18% to 30%. Recent recommendations for routine molecular profiling of lung adenocarcinoma resulted in a widespread use of targeted mutational profiling for oncogenic mutations (i.e. EGFR, KRAS, BRAF etc) and gene rearrangements (i.e.ALK, ROS1) which results can be used in staging of multiple lung cancers. A different mutation profile in oncogenic mutations strongly indicates two separate primary tumors. However, the presence of a common driver mutation does not necessarily indicate tumors of similar origin. Therefore, limited molecular panels may not be sufficient in some cases. The detection of shared identical breakpoints by whole genome sequencing has been recently proposed as potentially more accurate and specific for lineage determination than the analysis of driver mutations alone. Also whole exome and whole genome sequencing approaches have been reported, but these assays may be technically challenging and turnaround time may not be suitable for routine clinical use.
References: Girard N, Deshpande C, Lau C, Finley D, Rusch V, Pao W, et al. Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. Am J Surg Pathol. 2009;33(12):1752-64. Detterbeck FC, Franklin WA, Nicholson AG, Girard N, Arenberg DA, Travis WD, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(5):651-65 Nicholson AG, Torkko K, Viola P, Duhig E, Geisinger K, Borczuk AC, et al. Interobserver Variation among Pathologists ts and Refinement of Criteria in Distinguishing Separate Primary Tumors from Intrapulmonary Metastases in Lung. J Thorac Oncol. 2018;13(2):205-17. Murphy SJ, Aubry MC, Harris FR, Halling GC, Johnson SH, Terra S, et al. Identification of independent primary tumors and intrapulmonary metastases using DNA rearrangements in non-small-cell lung cancer. J Clin Oncol. 2014;32(36):4050-8. Liu Y, Zhang J, Li L et al. Genomic heterogeneity of multiple synchronous lung cancer. Nat Commun 2016 Oct 21;7:13200.

Keywords: multiple nodules- histology-molecular

ES12 LUNG CANCER PATHOLOGY IN THE AGE OF GENOMICS
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ES12.02 INVASIVE MUCINOUS ADENOCARCINOMA

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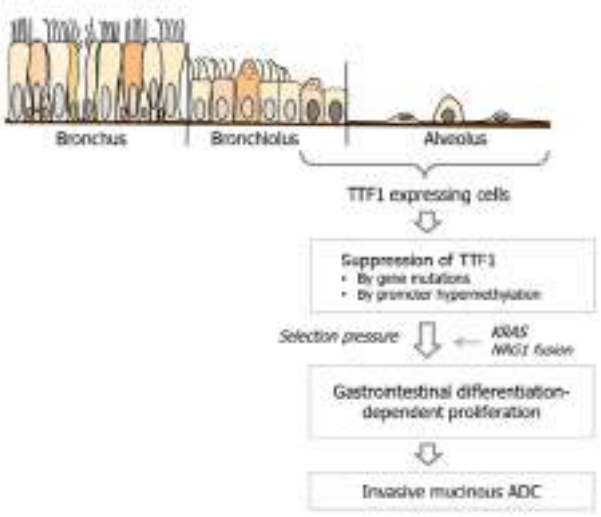
Invasive mucinous adenocarcinoma (IMA) is a variant of adenocarcinoma defined by the current WHO classification of lung tumors.[1] Although IMA used to be categorized into mucinous bronchioloalveolar carcinoma in most cases with the previous classification scheme,[2] separation of this variant was based on unique clinical, radiological, pathological, and genetic characteristics as shown in the following table. Morphologically, IMAs consist of goblet and/or columnar tumor cells, which resemble normal intestinal and/or primitive gut epithelium. This subtype adenocarcinoma develops not only in the lung but also in every organ system, such as the ovary, pancreas, colorectum, and stomach, which are associated with the primitive gut tube in development. Interesting, all mucinous carcinomas have frequent KRAS mutations and quite similar immunohistochemical phenotype, including expression of CK20,

CDX2, HNF4a, and villin. The strong correlation between KRAS mutations and heavy smokers is known, but IMA is not such a case. Indeed, TP53 mutations, which is also associated more with smokers, are quite rare in IMAs. IMA commonly develops in the peripheral lung parenchyma, but there are no normal counterpart cells. Recently, inactivating mutations of TTF1/NKX2.1 have been reported in IMA.[3,4] This alteration can repress TTF1 function, resulting in gastrointestinal differentiation. TTF1-depletion using KRASG12D-transgenic mice induced mucinous tumors, which shared a morphological and phenotypical resemblance to IMA, including columnar tumor cells with goblet cell features and HNF4a expression.[5,6] Because the other mechanisms of TTF1 impairment, the molecular pathway of IMA could be summarized in figure 1. However, it remains unclear why KRAS is selectively mutated in this subtype, and what induce TTF1 mutations. References 1. Travis WD, Brambilla E, Burke A, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer; 2015. 2. Travis WD, Brambilla E, Noguchi M, et al. International Association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-285. 3. Matsubara D, Soda M, Yoshimoto T, et al. Inactivating mutations and hypermethylation of the NKX2-1/TTF-1 gene in non-terminal respiratory unit-type lung adenocarcinomas. Cancer science 2017;108:1888-1896. 4. Hwang DH, Sholl LM, Rojas-Rudilla V, et al. KRAS and NKX2-1 Mutations in Invasive Mucinous Adenocarcinoma of the Lung. J Thorac Oncol 2016;11:496-503. 5. Maeda Y, Tsuchiya T, Hao H, et al. Kras(G12D) and Nkx2-1 haploinsufficiency induce mucinous adenocarcinoma of the lung. J Clin Invest 2012;122:4388-4400. 6. Snyder EL, Watanabe H, Magendantz M, et al. Nkx2-1 represses a latent gastric differentiation program in lung adenocarcinoma. Mol Cell 2013;50:185-199. Table 1 Difference between IMA and AIS/MIA/LPA[1]

Table 1 Difference between IMA and AIS/MIA/LPA

	Invasive Mucinous ADC	AIS/MIA/LPA
Female	~60%	~70%
Smoker	~45%	~46%
Clinical symptoms	Mucinous sputa	Mostly no symptom
Radiographic appearance	Majority consolidation; Air-bronchogram	Majority ground-glass attenuation
	Frequent multifocal & multi-lobar presentation	
Cell type	Mucin-filled, columnar and/or goblet	Type II pneumocyte &/or Clara cell
Phenotype		
CK7	Mostly positive (90%)	Positive (~95%)
CK20	Positive (~54%)	Negative (<5%)
TTF1	Mostly negative (<10%)	Positive (~65%)
CDX2	Possible to be positive	Negative
Genotype		
KRAS	Frequent (~75%)	Some (~15%)
EGFR	Almost none (<5%)	Frequent (~45%)

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant adenocarcinoma



Keywords: Histological subtype, adenocarcinoma variant, Pathology

ES12 LUNG CANCER PATHOLOGY IN THE AGE OF GENOMICS
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ES12.03 TUMOR HETEROGENEITY

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While intertumoral heterogeneity is well recognised in many solid tumours including NSCLC, intratumoral heterogeneity has only recently gained attention. Heterogeneity of tumor morphology, protein expression, gene expression, epigenetic or genetic alterations has the potential to impact optimal biopsy strategies, diagnostic assessment, treatment decisions and clinical outcome. Sequencing of NSCLC from multiple sites of disease shows frequent evidence of intratumoral heterogeneity in terms of genetic mutations, translocations and copy number alterations, although not to the same extent as seen in other tumor types, such as clear cell renal cell carcinoma. NSCLC studies have demonstrated a common pattern of intratumoral heterogeneity with main clonal driver mutations and branched evolutionary acquired mutations. Of clinical relevance, mutations in known lung cancer driver oncogenes (such as *EGFR*, *BRAF* and *MET*) are generally present in all tumor regions in keeping with early evolutionary events. This finding is consistent with the high response rates to tyrosine kinase inhibitors that target these genetic alterations, across multiple sites of disease. Later subclonal driver mutations are found commonly in NSCLC and include alterations in genes such as *PIK3CA* and *NF1*. Metastatic sites can exhibit mutational profiles closely related to specific spatial regions of the primary tumor demonstrating that subclones can determine the course of systemic disease resulting in subclonal diversification. Clonal evolution is driven by multiple factors including selective pressure from targeted therapies and adaptive mechanisms due to interaction with immune cells and the microenvironment. Treatment resistance can occur due to acquisition and/or selection of clones and contributes to temporal heterogeneity. The hierarchy of genetic alterations can be used to trace clonal intratumoral heterogeneity although adequate sequencing depth is required to accurately assess for subclonal mutations. Reassuringly, sequencing of a single region of a tumor should be sufficient to identify known targetable driver mutations as they generally occur early in the evolutionary course of the disease. The exact clinical significance of various subclonal mutations is less well understood. Intratumoral heterogeneity can potentially lead to sampling errors when single sites of disease are sampled for mutational events that may only exist in another metastatic site. For this reason, testing for genetic markers of treatment resistance may be more appropriately performed on circulating tumour DNA as the ctDNA may derive from multiple metastatic deposits, although lower sensitivity limits the effectiveness of this approach. Liquid biopsy approaches also have the advantage of providing a contemporaneous sample, more likely to reflect impact of most recent therapy. Further investigation of spatial and temporal tumoral heterogeneity by comprehensive deep sequencing of multiple spatially discrete sites of disease at different time points may assist in understanding the complexity

of intratumoral heterogeneity and could potentially impact optimal biopsy and treatment strategies, particularly when assessing for drug resistance.

Keywords: genetic heterogeneity NSCLC

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ES12.04 MACHINE LEARNING AND INTEGRATIVE MULTI-OMICS ANALYSIS IDENTIFY NOVEL MOLECULAR GROUPS OF LUNG NEUROENDOCRINE TUMORS

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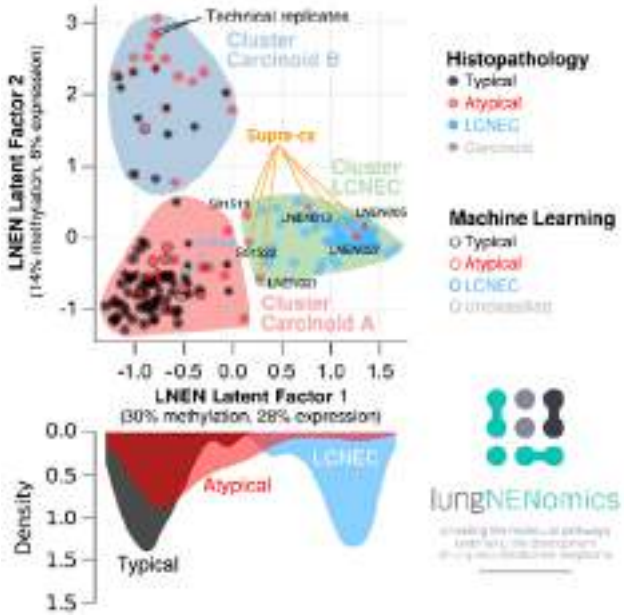
IARC, Lyon/France



This work is part of the lungNENomics project, a large multi-omic and multidisciplinary effort, built up on our previous published work (1-4). The lungNENomics project aims at the molecular characterization of rare lung neuroendocrine neoplasms through the integration of whole-genome sequencing, transcriptome sequencing and methylation data, as well as the correlation with epidemiological and clinical information, and taking advantage of unique biorepositories, advanced computational approaches, and state-of-the-art *in vitro* models. The talk would provide an overview of the global lungNENomics project, as well as presenting the identification of a novel molecular entity. The worldwide incidence of pulmonary carcinoids is increasing, but little is known about their molecular characteristics. Through machine learning and multi-omics factor analysis, we compared and contrasted the genomic profiles of 116 pulmonary carcinoids (including 35 atypical), 75 large-cell neuroendocrine carcinomas (LCNEC), and 66 small-cell lung cancers. Integrative analyses on 257 lung neuroendocrine neoplasms stratified atypical carcinoids into two prognostic groups with a 10-year overall survival of 88% and 27%, respectively. We identified therapeutically relevant molecular groups of pulmonary carcinoids, suggesting DLL3 and the immune system as candidate therapeutic targets; we confirmed the value of *OTP* expression levels for the prognosis and diagnosis of these diseases, and we unveiled the group of supra-carcinoids. This group comprises samples with carcinoid-like morphology yet the molecular and clinical features of the deadly LCNEC, further supporting the previously proposed molecular link between the low- and high-grade lung neuroendocrine neoplasms. Funding: U.S. National Institutes of Health (NIH), French National Cancer Institute (INCa), French Ligue Nationale contre le Cancer (LNCC), and the Dutch Cancer Society (DCS) Website: rarecancersgenomics.com Twitter: @CancersRare References 1. Peifer M*, Fernández-Cuesta L*, Sos ML, George J, Seidel D, Kasper LH, Plenker D, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012 PMID: 22941188 2. Fernandez-Cuesta L, Peifer M, Lu X, Sun R, Ozretić L, Seidal D, Zander T, et al. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. Nat Commun. 2014 PMID: 24670920 3. George J*, Walter V, Peifer M, Alexandrov LB, Seidel D, Leenders F, Maas L, Müller C, Dahmen I, Delhomme TM, Ardin M, Leblay N, Byrnes G, Sun R, De Reynies A, McLeer-Florin A, Bosco G, Malchers F, Menon R, Altmüller J, Becker C, Nürnberg P, Achter V, Lang U, Schneider PM, Bogus M, Soloway MG, Wilkerson MD, Cun Y, McKay JD, Moro-Sibilot D, Brambilla CG, Lantuejoul S, Lemaitre N, Soltermann A, Weder W, Tischler V, Brustugun OT, Lund-Iversen M, Helland Å, Solberg S, Ansén S, Wright G, Solomon B, Roz L, Pastorino U, Petersen I, Clement JH, Sänger J, Wolf J, Vingron M, Zander T, Perner S, Travis WD, Haas SA, Olivier M, Foll M, Büttner R, Hayes DN, Brambilla E, Fernandez-Cuesta L*, Thomas RK. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. Nat Commun. 2018 PMID: 29535388 4. Derks JL, Leblay N, Lantuejoul S, Dingemans AC, Speel EM, Fernandez-Cuesta L. New Insights into the Molecular Characteristics of Pulmonary Carcinoids and Large Cell Neuroendocrine Carcinomas, and the Impact on Their Clinical Management. J Thorac Oncol. 2018 Review. PMID: 29454048 5. Alcala N*, Leblay N*, Gabriel AAG*, Mangiante L, Hervas D, Giffon T, Sertier AS, Ferrari A, Derks J, Ghantous A, Delhomme TM, Chabrier A, Cuenin C, Abedi-Ardekani B, Boland A, Olaso R, Meyer V, Altmuller J, Le Calvez-Kelm F, Durand G, Voegele C, Boyault S, Moonen L, Lemaitre N, Lorimier P, Toffart AC, Soltermann A, Clement JH, Saenger J, Field JK, Brevet M, Blanc-Fournier C, Galateau-Salle F, Le Stang N, Russell PA, Wright G, Sozzi G, Pastorino U, Lacomme S, Vignaud JM, Hofman V, Hofman P, Brustugun OT, Lund-Iversen M, Thomas de Montpreville V, Muscarella LA, Graziano P, Popper H, Stojsic J, Deleuze JF, Herceg Z, Viari A, Nuernberg P, Pelosi G, Dingemans AMC, Milione M, Roz L, Brcic L, Volante M, Papotti MG, Caux C, Sandoval J, Hernandez-Vargas H, Brambilla E, Speel EJM, Girard N, Lantuejoul S, McKay JD, Foll M#, Fernandez-Cuesta L#. Integrative and comparative genomic analyses identify clinically relevant groups of pulmonary carcinoids and unveil the supra-carcinoids. Nat Commun. In Press

Keywords: lung neuroendocrine neoplasms, lungNENomics project, supra-carcinoids

ES12 LUNG CANCER PATHOLOGY IN THE AGE OF GENOMICS
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ES12.05 IMPACT OF STAS IN LUNG CANCER STAGING

W. Travis[1], R. Aly[2], T. Eguchi[1], N. Rekhtman[1], Y. Yagi[1], P. Adusumilli[1]

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Spread through air spaces (STAS) is an established histologic marker of poor prognosis found in 15-60% of lung cancers. The association with poor prognosis is supported by data from over 3500 patients from multiple multidisciplinary investigative groups worldwide. This prognostic significance has been demonstrated in all major types of lung cancer including adenocarcinoma, [1] squamous cell carcinoma, [2] small cell carcinoma, [3] large cell neuroendocrine carcinoma, [3], atypical carcinoid[3] and pleomorphic carcinoma.[4, 5] As this large volume of clinical data has accumulated some important issues that have arisen. 1) Importance of processing, 2) Role in Staging? 3) Limited resection vs lobectomy and 4) Frozen section. Criteria for STAS The original definition of STAS by Kadota et al and the 2015 WHO consisted of tumor cells within the first alveolar air spaces in the lung parenchyma beyond the edge of the main tumor. In adenocarcinoma it can occur as one of three morphologic patterns including 1) micropapillary structures within air spaces; 2) solid nests or tumor islands and 3) scattered discohesive single cells.[1, 6] In a recent paper we also proposed to require the presence of more than a single STAS cluster.[3] The solid nest pattern is characteristic in other lung cancer histologies such as squamous cell carcinoma and neuroendocrine tumors. 3-dimensional studies with serial histologic sectioning and microCT whole block imaging suggest that there may be two mechanisms of spread into the adjacent lung: 1) detachment, migration through air spaces and reattachment with vessel co-option and 2) tumor islands of continuous tumor spread into adjacent air spaces. An important component of the diagnostic criteria is the distinction from artifacts: 1) mechanically induced tumor floaters that are randomly situated often at the edge of the tissue section or out of the plane of section; 2) jagged edges of tumor cell clusters suggesting fragmentation or edges of a knife cut during specimen processing; 3) isolated tumor clusters at a distance from the tumor rather than spreading in a continuous manner from the tumor edge and 4) linear strips of cells lifted off alveolar walls. Importance of

Processing To assess for STAS histologic sections need to be taken in such a way to maximize the interface between the tumor and adjacent non-neoplastic lung parenchyma. For example, sections of subpleural tumors that maximize assessment of the visceral pleura or the interface with dense fibrotic scars or post-obstructive organizing are not well suited for assessment of STAS. This applies to both frozen and permanent sections. Role of STAS in Staging? Although the prognostic significance of STAS, has led some to suggest it might be included as a factor in staging,[7,8] there is insufficient data at this time to make such a recommendation. Tumor size should continue to be measured according to the gross and/or microscopically recognized edge of lung cancers rather than according to the maximum distance of furthest STAS. Although vascular (V) and lymphatic (L) invasion are recognized in TNM staging, only visceral pleural invasion (VPI) is officially incorporated as a T-factor in the 8th Edition. STAS is regarded as a sign of invasion similar to V, L and VPI, however, more data is needed before introducing this as a T-factor for staging. Limited resection vs lobectomy Evidence is accumulating that indicates an increased risk of recurrence and worse survival associated with STAS positive tumors treated by limited resection compared to lobectomy.[5,9] Role of Frozen Sections in Assessing STAS There is limited data evaluating pathologist's ability to recognize STAS in frozen section. Eguchi et al found the sensitivity and specificity of frozen section for prediction of STAS were 71% and 92%. respectively and interrater reliability across 5 pathologists was 0.67.[9] Walts AE et al studied frozen section for evaluation of STAS and recommended that current evidence did not warrant frozen section evaluation for STAS.[10] However, frozen section sensitivity to detect STAS positivity was 50%, with a 100% positive predictive value and an 8% negative predictive value. These studies suggest if a pathologist sees STAS on a frozen section there is a 92-100% likelihood it will be present on permanent sections. Both studies were retrospective so attention was not always given to including the tumor edge and adjacent lung. More studies are needed to evaluate the potential role of frozen section in detecting STAS and guiding intraoperative decisions by surgeons. REFERENCES 1. Kadota K, et al. Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences after Limited Resection for Small Stage I Lung Adenocarcinomas. J Thorac Oncol 2015;10:806-14. 2. Lu S, et al. Spread through Air Spaces (STAS) Is an Independent Predictor of Recurrence and Lung Cancer-Specific Death in Squamous Cell Carcinoma. J Thorac Oncol 2017;12:223-34. 3. Aly RG, et al. Spread Through Air Spaces (STAS) Is Prognostic in Atypical Carcinoid, Large Cell Neuroendocrine Carcinoma, and Small Cell Carcinoma of the Lung. J Thorac Oncol 2019. 4. Yokoyama S, et al. Tumor Spread Through Air Spaces Identifies a Distinct Subgroup With Poor Prognosis in Surgically Resected Lung Pleomorphic Carcinoma. Chest 2018;154:838-47. 5. Liu H, et al. Prognostic Impact of Tumor Spread Through Air Spaces in Non-small Cell Lung Cancers: a Meta-Analysis Including 3564 Patients. Pathol Oncol Res 2019. 6. Travis WD, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon: International Agency for Research on Cancer; 2015. 7. Uruga H, et al. Will spread through air spaces be a staging parameter in lung cancer? Journal of thoracic disease 2018;10:593-6. 8. Dai C, et al. Tumor Spread through Air Spaces Affects the Recurrence and Overall Survival in Patients with Lung Adenocarcinoma >2 to 3 cm. J Thorac Oncol 2017;12:1052-60. 9. Eguchi T, et al. Lobectomy Is Associated with Better Outcomes than Sublobar Resection in Spread through Air Spaces (STAS)-Positive T1 Lung Adenocarcinoma: A Propensity Score-Matched Analysis. J Thorac Oncol 2019;14:87-98. 10. Walts AE, et al. Current Evidence Does Not Warrant Frozen Section Evaluation for the Presence of Tumor Spread Through Alveolar Spaces. Arch Pathol Lab Med 2018;142:59-63.

Keywords: Spread through air spaces; limited resection;prognosis

ES13 GLOBAL POLITICAL, LEGAL, AND FINANCIAL STRATEGIES FOR TOBACCO CONTROL
SUNDAY, SEPTEMBER 8 15:15–16:45

ES13.01 TOBACCO CESSATION AND CANCER PATIENTS

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Smoking among cancer patients reduces the effectiveness of treatment, increases the risk of recurrence, and reduces survival time. One third of cancer patients continue smoking after diagnosis or during their treatment. Smoking is also common in patients with a cancer for which there is limited evidence for carcinogenicity of tobacco smoking. Cancer patients who smoke have greater risks, not only of the well known tobacco-related health problems, such as cardiovascular and respiratory diseases and further cancers, but also unfavourable cancer treatment outcomes. There is sufficient evidence to infer a causal relationship between cigarette smoking and adverse health outcomes, including all-cause mortality, cancer-specific mortality and further primary tobacco-related cancers among cancer patients. Poorer cancer treatment outcomes linked to tobacco use by cancer patients re related to altered cancer biology, altered drug metabolism, increased treatment-related complications, and increased tobacco-related comorbidity. Although smoking cessation is associated with better outcomes, this key and cost-effective preventive strategy is rarely addressed in health care services. Barriers to incorporating tobacco cessation interventions into hospitals include lack of knowledge, expertise, time, and organizational constraints. In addition, many cancer patients show higher rates of nicotine dependence, low self-efficacy, and higher levels of depression. The existing data support the conclusion that continued smoking negatively affects cancer treatment outcomes including survival, recurrence and quality of life and that, by quitting smoking, patients with cancer have the potential to improve their cancer treatment outcomes. At the population-level, there is a need to establish a basic infrastructure to provide tobacco cessation services to cancer patients who smoke, sustainable funding should be identified and allocated to dedicated tobacco cessation services (e.g. quitlines, available treatment for tobacco cessation) as well as tobacco treatment training programmes for health-care providers. At the individual-level, motivational interventions addressed to recognize the cancer-specific risks of smoking do increase patients' self-efficacy in quitting. Morover, cessation using the "5 A's model" provides good abstinence rates, and about 80% of smokers could be reached using this approach.

Keywords: smoking cessation, cancer patients, health outcomes

ES13 GLOBAL POLITICAL, LEGAL, AND FINANCIAL STRATEGIES FOR TOBACCO CONTROL
SUNDAY, SEPTEMBER 8 15:15–16:45

ES13.02 PURSUING CRIMINAL CHARGES AGAINST BIG TOBACCO

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ABSTRACT 1

Court of appeal rejects charges made against tobacco industry- The Court of Appeal in The Hague has declined to instruct the Netherlands Public Prosecution Service to bring criminal charges against cigarette manufacturers. The court concluded that it is up to the government, not the judiciary, to tackle the rigging of cigarettes. In other words, it's the government's move. On December 6th, 2018 the Court of Appeal in The Hague delivered its verdict in the proceedings brought by criminal lawyer Bénédicte Ficq on behalf of various individual complainants and a large number of legal entities who previously lodged complaints against cigarette manufacturers. Last February the Public Prosecution Service (OM) decided not to instigate legal proceedings, prompting the complainants to instigate an Article 12 procedure in an effort to force the OM to prosecute. In its verdict, the court writes that "the products of cigarette manufacturers are made and tested in accordance with stringent Dutch and European legislation and regulations. As long as the cigarette manufacturers respect these European and national rules, the member states must respect these rules and cannot prohibit the sale of cigarettes. Radical measures

against cigarette manufacturers can only be taken by the European regulator." In her reaction, lawyer Bénédicte Ficq draw attention to the significance of the court's comment, in its detailed motivation, that cigarette manufacturers deliberately market a deadly and harmful product with the sole objective of making money. The court writes: "The fact that smoking is harmful to your health, is a serious health risk, can cause serious illness and even death, and is moreover highly addictive, can in the opinion of the court be considered general knowledge and is not disputed by the defendants. The defendants supply cigarettes that they know are or can be addictive and harmful to the health of active and passive smokers. The court assumes that the defendants act with the aim of making a profit Here the lawyers note the similarities with verdicts reached against cocaine and heroin dealers. Ficq: "The court could have avoided making these remarks, but has instead chosen to make clear that there is a social evil that the court is powerless to address. In other words, the ball is in the government's court." Legislator must intervene In its conclusion the court expresses it very clearly once again: "Complainants have chosen to address a social problem concerning public health within a criminal framework. However, the court agrees with the Public Prosecution Service that criminal law offers no solution. Radical measures such as banning the production and sale of tobacco, which is produced in accordance with the legal directives, can only be taken by the legislator. The ultimate goal of the complainants, to ban cigarettes cannot be achieved through criminal law. It will instead have to involve an appeal to the European legislator." Conclusion:. "The court recognizes the scale of the social problem and the fact that cigarettes are extremely addictive and deadly, and should actually be banned, but it's up to the government to take action. That strengthens us in our demand that the Netherlands Food and Consumer Product Safety Authority and the government must take measures to tackle the phenomenon of 'rigged cigarettes' We feel as if we have ended up in a Kafkaesque situation in which it is patently obvious that cigarettes with holes in their filters release more toxic substances than legally allowed. But the legally prescribed smoking machines measure different levels, so cigarettes in their present form are permitted. Those responsible for passing legislation must now change this situation, especially since we've know that 'rigged cigarettes' cause more lung cancer. Time for government action!"

ABSTRACT 2

Tobacco Industry: first we fix the law, then we abide by it A little-known issue is the way that the tobacco industry has succeeded, over the years, in bending the implementation of anti-smoking laws to its own will. After all, in violation of all international laws, it exerts a strong influence on how the State determines emission values for cigarette smoke. As a result of that interference, the margins for enforcing the law are far too wide. According to Dutch law, every three years cigarette manufacturers must show the government how much tar, nicotine and carbon monoxide (TNCO) their cigarettes contain. These levels are controlled by the National Institute for Public Health and the Environment (RIVM). The RIVM then sends the results to the Dutch Food and Consumer Product Safety Authority (NVWA). If the legally set limits are exceeded, the NVWA must act. It must enforce the law. Those legal norms are unequivocally determined in the Law on Tobacco and Smoking Products. A cigarette may emit a maximum of 10 mg tar, 1 mg nicotine and 10 mg carbon monoxide. A smoker may not inhale more poison than that. The law also determines how levels are measured and the margins within which the legal norms must be met. However, the margins determined by law are very wide: 20% for tar and nicotine and 25% for carbon monoxide. This means that a cigarette with 12 mg tar (instead of 10), 1.2 mg nicotine (instead of 1) and 12.5 mg carbon monoxide (instead of 10) is still permissible. The NVWA will only intervene above those levels. The literature tells us that maximum margins of 10% are more than enough to conceal variations in measured levels. In developing and determining the measurements, the government has — following the example of the European lawmaker — used the services of two private organizations: the Netherlands Normalization Institute (NEN) and the *International Organization for Standardization* (ISO). These organizations consist entirely of representatives from the cigarette industry. The chairperson himself comes from Philip Morris. If you examine the explanation that accompanies the legal article, it turns out that the legal emission margins are statistically baseless. *"The conclusions within the report are based on practical experience of verifying these measurements in a number of different marketplaces underpinned by a theoretical consideration of the sources of statistical variation." (NEN-ISO 8243.2013, IDT)*

Keywords: Legislation, Anti Tobacco Industry, penal law and civil law

ES13.03 FOUNDATION FOR A SMOKE FREE FUTURE: FUNDING OPPORTUNITIES OR SMOKE SCREEN FOR THE TOBACCO INDUSTRY?

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The tobacco industry has long sought interactions with the health and medical communities that will enhance its legitimacy and augment profits. In the early 20thcentury, advertising involved the medical community emphasizing doctors who recommended cigarette smoking. From the mid 20thcentury, as scientific evidence developed, the tobacco industry contested restrictions vigorously as tobacco regulation intensified. The advent of ENDS products opened a new phase in marketing which stretched the limits of conventional tobacco control. The PMI Foundation, launched in 2017, targets the health and medical communities, promising research funding, the "Smoke-Free" aim and its interactions with high profile researchers. In the first few decades of the 20thcentury, tobacco companies involved physicians in advertising campaigns to promote health benefits and minimisation strategies for particular brands. Analysis of 1930s and 40s tobacco advertising in medical journals identified a number of strategies employed to involve doctors in promoting cigarettes including flattery, tobacco 'science', the advisory role to patients, less "irritating" brands and promotion of specific brands[1]. Analysis of tobacco advertising from the 1920s to the 1950s identified a focus on throat irritation, strategies to protect from harmful symptoms and portrayal of otorhinolaryngologists as promoters of cigarette-related benefits[2]. The "More Doctors smoke Camels" campaign[3]launched in the late 1940s by RJ Reynolds made a number of zealous health benefit claims, although landmark publications linking tobacco cigarettes to lung cancer led to scepticism from the health community and eventual banning of cigarette advertising and promotion in medical journals and at medical conventions[3]. From the mid-1960s, the paradigm for tobacco regulation shifted as evidence accumulated for the harmful effects. Additional key papers include a 1912 monograph, one of the first publications to link lung cancer with tobacco, early writings on lung cancer surgery and the 1964 US Surgeon General Report on Smoking and Health. Legislative efforts to control tobacco accelerated with, in the United States, the pivotal 1998 Master Settlement Agreement by which tobacco companies were obliged to pay compensation to 46 states to offset costs of smoking-induced illnesses[4]. In the early 21stcentury the WHO FCTC came in to force in 2005 with the launch of the MPOWER measures in 2008, setting up the tobacco framework that has characterised the last decade and a half and to which 181 countries are signatories. The emergence of e-cigarettes and other ENDS products has shifted tobacco control outside the current purview of the FCTC and opened up new areas of controversy as these products evade conventional regulation. E-cigarettes first appeared in the 20thcentury including designs from the 1960s from BAT and from the 1990s from PMI with the contemporary model attributed to an individual inventor[5]. The early designs were abandoned at least in part due to concerns about commercial viability[6,7]and it was not until the last decade or so that e-cigarettes have reached prominence. The emergence of highly appealing and commercially successful ENDS products such as the Juul device has stimulated concern at the level of the FDA and review of e-cigarette regulation. Companies such as Juul Labs (now owned by a tobacco corporation) and PMI advocate harm-minimization through their ENDS products while parent companies continue to sell conventional tobacco cigarettes in less tightly regulated markets. The Phillip Morris Foundation for a Smoke-Free World[8]was launched in 2017 and immediately prompted controversy. The stated aims of the Foundation include the funding of research, a focus on smoking cessation and harm reduction and the search for solutions to "unique challenges"[8]. Its launch prompted immediate debate and discussion, including a Lancet Viewpoint by the Foundation's director, advocating the benefits of reduced-harm products and expressing concern that full implementation of the FCTC would take many years. An editorial in the same Lancet issue raised strong concerns about involving the tobacco industry in tobacco control while acknowledging that (at the time of writing) the Foundation had yet to begin work[9]. An accompanying commentary piece questions the credibility of the Foundation and points out that the funding of research is used by the tobacco industry as a deliberate strategy that in fact acts as a "public relations" exercise while PMI, in this instance, continues to sell cigarettes as its core

product[10]. More recently, a review of the published tax returns from the Foundation suggest that it is having trouble both raising and spending funds, perhaps indicating some trouble engaging with the research community and multiple publications raise questions about its ethical robustness, the risks of long-term nicotine dependence and its commercial integrity. While the stated aims of the Foundation may appeal, concerns remain about engaging with the tobacco industry, about persistent global cigarette sales, about the use of the Foundation to divert attention from PMI's efforts to build its market for ENDs products and about the prioritisation of harm-minimisation (with accompanying profits) over genuine efforts to make the world free from tobacco. References 1. Jackler RK, Ayoub NF. "Addressed to you not as a smoker… but as a doctor": doctor-targeted cigarette advertisements in JAMA. Addict Abingdon Engl. 2018 Jul;113(7):1345–63. 2. Samji HA, Jackler RK. "Not one single case of throat irritation": misuse of the image of the otolaryngologist in cigarette advertising. The Laryngoscope. 2008 Mar;118(3):415–27. 3. Gardner MN, Brandt AM. "The doctors'' choice is America's choice": the physician in US cigarette advertisements, 1930-1953." Am J Public Health. 2006 Feb;96(2):222–32. 4. Schroeder SA. Tobacco control in the wake of the 1998 master settlement agreement. N Engl J Med. 2004 Jan 15;350(3):293–301. 5. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation. 2014 May 13;129(19):1972–86. 6. Risi S. On the Origins of the Electronic Cigarette: British American Tobacco's Project Ariel (1962-1967). Am J Public Health. 2017;107(7):1060–7. 7. Dutra LM, Grana R, Glantz SA. Philip Morris research on precursors to the modern e-cigarette since 1990. Tob Control. 2017;26(e2):e97–105. 8. Foundation for a Smoke-Free World [Internet]. [cited 2019 Mar 2]. Available from: https://www.smokefreeworld.org/ 9. Lancet T. Tobacco control: a Foundation too far? The Lancet. 2017 Oct 14;390(10104):1715. 10. Daube M, Moodie R, McKee M. Towards a smoke-free world? Philip Morris International's new Foundation is not credible. The Lancet. 2017 Oct 14;390(10104):1722–4.

Keywords: smoke-free, tobacco control, industry

ES13 GLOBAL POLITICAL, LEGAL, AND FINANCIAL STRATEGIES FOR TOBACCO CONTROL
SUNDAY, SEPTEMBER 8 15:15–16:45

ES13.04 COMPARING ENDS TO NRT FOR SMOKING CESSATION

H. Mcrobbie

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For people who smoke, quitting completely is associated with numerous benefits for current and future health. There are a range of effective stop smoking medicines that can increase long-term abstinence rates, compared with unassisted quitting. However, these rates remain low (eg. < 25%), with most people relapsing within 3-6 months. Over the past decade electronic nicotine delivery systems (ENDS), more commonly known as e-cigarettes or vaporisers, have become increasing popular among smokers, and in some countries are now the most commonly used tool to aid smoking cessation. Until recently the evidence for the effectiveness of ENDS in helping people stop smoking has been limited, with only two published randomised controlled trials (RCTs). There are now four RCTs; three show the superiority of nicotine containing ENDS, compared to those without nicotine, in helping smokers quit for at least six months and one found vaping to be associated with higher 12-month quit rates than nicotine replacement therapy (NRT; 18% vs. 10%; RR=1.83; 95% CI: 1.30-2.58). The difference in quit rates may have been due to ENDS providing greater withdrawal relief, providing better subjective effects, and smokers being able to self-titrate their nicotine intake. Among 12-month ex-smokers, rates of ongoing ENDS use were significantly higher than ongoing NRT use. This could raise concern if long-term ENDS use is associated with health risk. Alternatively, this could be beneficial if it prevents relapse and so risk-benefit analysis is required. Health professionals are often asked by their patients if ENDS can help aid quitting smoking and if they are safe. There are data to show that ENDS are an effective smoking cessation aid, and some evidence to support their superiority over NRT. Current data suggest that health risks associated with ENDS use are substantially less, overall, than risks associated with smoking tobacco. However, the health risks associated with long-term ENDS use remain unknown, and long-term cohort studies, especially regarding lung health in vapers, are needed. To mitigate concern over unknown health risks associated with long-term vaping ex-smokers can be advices to stop vaping as soon as they feel they are safe from relapse to smoking. This presentation will summarise the evidence of effectiveness of ENDS for smoking cessation, and provide an overview of possible health risks, to enable health professionals to better advise their patients who ask about using ENDS.

Keywords: smoking cessation, electronic nicotine delivery systems, nicotine replacement therapy

ES13 GLOBAL POLITICAL, LEGAL, AND FINANCIAL STRATEGIES FOR TOBACCO CONTROL
SUNDAY, SEPTEMBER 8 15:15–16:45

ES13.05 STIGMA AND IMPACT OF TOBACCO CONTROL POLICY

A. Borondy Kitts

Lahey Hospital & Medical Center, USA/United States of America

Figure 1 A - Breast Cancer People

Figure 1 B – Lung Cancer People

A simple quick google search on breast cancer people and lung cancer people is enough to show the impact of stigmatizing smoking on people with lung cancer (Figure 1). Breast cancer people are perceived as pink, young, healthy, cheerful, supportive and happy although that is not an accurate depiction of the breast cancer journey. In contrast, lung cancer people are seen as diseased and dying, sad, concerned, bleak, and alone with little support. The stigma associated with smoking stops people from going to the doctor because they are afraid the doctor will think they are stupid for continuing to smoke, it stops people from getting screened for lung cancer because they blame themselves for smoking and feel they deserve the disease or because they are afraid their loved ones will blame them for getting sick. The stigma reduces the funding available for lung cancer research. In the US, federal funding for lung cancer research per lung cancer death is only 15% of the funding amount for breast cancer per breast cancer death. People with lung cancer, regardless of their smoking status, encounter stigma on a regular basis.(1) Often after disclosing a lung cancer diagnosis for themselves or for a loved one the first comment is not, I'm so sorry you have this awful disease. The first comment is invariably "I didn't know you smoked" or "Was he a smoker" or "He smoked a lot. It's not surprising he got lung cancer" or "It's to be expected since you are a smoker" In a Global Lung Cancer Coalition survey, one in five people (21%) agreed with the statement that they have less sympathy for people with lung cancer than for people with other types of

cancer. Studies have shown that the stigma encountered by people with lung cancer reduces quality of life, increases depression and negatively impacts outcomes.(2) Probably most disturbing is that stigmatization of smokers has the greatest impact on the socioeconomically deprived, the disadvantaged populations.(3) These populations have the highest prevalence of smokers and encounter the stigma of their race or disadvantage (poverty, disability, sexual preference, behavioral health etc.) in addition to the stigma associated with smoking.(4) One could argue that tobacco control (tobacco denormalization efforts) may be tolerable if they resulted in short term stigma but increase tobacco cessation for these disadvantaged populations resulting in an overall public health benefit. Unfortunately, studies show that tobacco control efforts have the least impact on socioeconomically deprived populations thus actually increasing the health inequity (and stigma) for this already marginalized population. Smoking related stigma may actually help reinforce smoking in this population by being perceived as resistance to the norms of society. In other words, tobacco control efforts may not work and may actually have the opposite effect. (5,6,7) This stigmatization leads people who smoke to be less likely to seek medical care when they have symptoms, more likely to lie about their smoking, more likely to be refused access to care including curative surgery for early stage lung cancer unless they quit smoking, less likely to be offered smoking cessation help if they are uncomfortable disclosing their smoking status due to stigma and bias from their healthcare professional.(5,6) Tobacco control and stigmatization of smokers has resulted in stigmatizing all people with lung cancer regardless of smoking history or socioeconomic status. It's time to stop stigmatizing people who smoke and people with lung cancer but rather to promote and implement policies that have been shown to work in deterring tobacco use and helping people quit.(8) These include increased age limits for tobacco purchase and use, increased taxes on tobacco sales, free access to tobacco cessation counseling, nicotine replacement products and prescription smoking cessation medications. 1. Hamann HA, Howell LA, McDonald JL. "You did this to yourself": causal attributions and attitudes toward lung cancer patients. *J Appl Soc Psychol.* 2013;43:E37–E45. doi:10.1111/jasp12053. 2. Cataldo, JK, & Brodsky, JL. Lung cancer stigma, anxiety, depression and symptom severity. *Oncology (Switzerland)*. 2013;85(1):33-40. http://dx.doi.org/10.1159/000350834 3. Bell K, Salmon A, Bowers M, Bell J, McCullough L. Smoking, stigma and tobacco 'denormalization': Further reflections on the use of stigma as a public health tool. A commentary on Social Science & Medicine's Stigma, Prejudice, Discrimination and Health Special Issue (67: 3). *Social Science & Medicine*. 2010;70(6):795-799. https://doi.org/10.1016/j.socscimed.2009.09.060 4. Borondy Kitts AK. The patient perspective on lung cancer screening and health disparities. J Amer Coll Rad. 2019;16(4):601-606. https://doi.org/10.1016/j.jacr.2018.12.028. 5. Evans-Polce RL, Castaldelli-Maia JM, Schomerus G, Evans-Lacko SE. The downside of tobacco control? Smoking and self-stigma: A systematic review. *Social Science & Medicine*. 2015;145:26-34. https://doi.org/10.1016/j.socscimed.2015.09.026 6. Kirsten Bell K, Salmon A, Bowers M, Bell J, McCullough L. Smoking, stigma and tobacco 'denormalization': Further reflections on the use of stigma as a public health tool. A commentary on Social Science & Medicine's Stigma, Prejudice, Discrimination and Health Special Issue (67: 3). *Social Science & Medicine*. 2010; 70(6):795-799. https://doi.org/10.1016/j.socscimed.2009.09.060. 7. Lozano P, Thrasher JF, Forthofer M, Hardin J, Reynales Shigematsu LM, Santillán EA, Fleischer NL. Smoking-related stigma: A public health tool or a damaging force?, *Nicotine & Tobacco Research*, nty151, https://doi.org/10.1093/ntr/nty151 8. Hill S, Amos A, Clifford D, et al. Impact of tobacco control interventions on socioeconomic inequalities in smoking: review of the evidence. *Tobacco Control*. 2014;23:e89-e97.

Keywords: stigma, tobacco control policy, lung cancer

ES14 WHAT FIRST LINE IN ONCOGENE ADDICTED NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

ES14.01 FIRST LINE IN EGFR MUTATED PATIENTS

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Precision medicine is currently applied for almost all cancer types, especially, in NSCLC which is the prototype of successful targeted therapy. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the first effective targeted drug found in NSCLC for treatment in *EGFR*-mutation positive patients. *EGFR* (also termed human epidermal growth factor receptor 1 [HER1] or ErbB1) is a member of the ErbB family of cell surface receptor tyrosine kinase1. It is a 170 kDa RTK with an extracellular ligand binding domain, a transmembrane region and an intracellular tyrosine kinase. The RTKs form homodimers and heterodimers after binding to specific ligands, leading to autophosphorylation of tyrosine residues on the intracellular TK domain. This interaction recruits a diverse set of signal transduction cascades including the phosphoinositide 3 kinase (PI3K)/protein kinase B (AKT)/ mammalian target of rapamycin (mTOR), signal transduction and transcription (STAT) transcription and RAS/RAF/ mitogen activated protein kinase (MAPK) proliferation pathway1. In 2004, somatic mutations in the TK domain of EGFR, found most frequently in adenocarcinomas from patients in Asia who were never or former smokers, were strongly correlated with sensitivity to EGFR-TKIs[1]. The prevalence of *EGFR* mutation in NSCLC patients is higher in Asian population compared to the other population (50-55% vs. < 20%). These mutations are mostly distributed in four exons (exon18 to exon21)[2]. In frame deletions of exon19 (44%; *E746 A750deletion*) and *L858R* substitutions in exon21 (41%) are the most prevalent mutations associated with sensitivity to EGFR-TKIs. The point mutations in exon18 (G719C, G719S and G719A) and exon20 (V765A and T783A) are less frequent; 5% and 1%, respectively1. Presence of the "classical" mutations in exon19 and 21 are the best predictive biomarker for the efficacy of EGFR-TKIs with superior response rate (RR) of 60-70%, progression free survival (PFS) of 9-18.9 months, and overall survival (OS) more than 2 years compared with conventional chemotherapy in patients with tumors harboring EGFR sensitive mutations making EGFR-TKI is the first-line treatment[3]. Currently, there are 3 generations of EGFR-TKIs approved in the market. The strategy of first-line treatment in *EGFR*-positive patients can be categorized into 2 strategies. The first one is treating by the single agent EGFR-TKIs. The first and second-generation EGFR-TKIs have the efficacy in term of PFS of 9-14.7 months in first-line treatment, but if starting with third generation EGFR-TKI, the PFS is longer (18.9 months)[3-4]. The ORR is similar either starting with 1st, 2nd, or 3rd generation EGFR-TKIs (60-70%). The acquired resistance could be occurred after 9-14 months of treatment by 1stand 2nd-generation EGFR-TKIs and the majority of resistance mechanism is *T790M* (50-60%) which is now we have the 3rd-generation EGFR-TKI for overcoming this resistance. Moreover, the other bypass tracts (*MET* amplification, *BRAF, HER2* mutation etc.)[5] could be the mechanism of resistance as well and we have the potential targeted drugs in the clinical studies which some of them will be approved in the near future. The mechanism of resistance if we start the 1st-line treatment with 3rd-generation EGFR-TKI is different from the previous one. Recently, exploratory data from FLAURA study was reported. They found no T790M detected in the patients whom had progressive disease after 1st-line treatment with 3rd-generation EGFR-TKI. The most common detected acquired resistance genes in the blood were C797S and MET amplification. The other mechanism included HER2 amplification, PIK3CA and RAS mutations. Furthermore, the 3rd-generation EGFR-TKI has the significant strong evidence of better in survival outcome and CNS response in patient whom had the CNS metastases disease[6]. The second strategy is starting 1st-line treatment with the combination therapy. The recent studies reported in ASCO2018 and ASCO2019 showed the longer PFS (16-19 months) in combination of 1st-generation EGFR-TKI and anti-angiogenesis agents and also longer PFS (16-20 months) in combination of 1st-generation EGFR-TKI with doublet platinum-based chemotherapy compared to single agent 1st-generation EGFR-TKI.[7-9] Definitely, there were more adverse events for the combination treatment. The rate of occurring *T790M* as the acquired resistance and the CNS efficacy are the issues to concern for the combination treatment (Figure 1). The most proper sequence of the treatment in EGFR-positive NSCLC is needed to explore more in the clinical studies. It has pros and cons in each approach and it depends on several factors such as; the patients' performance status,

the location of tumor (CNS metastases?), types of *EGFR* mutations, acquired resistance, toxicities, treatment after progression, cost of treatment and the reimbursement issue in each country. In summary, *EGFR* mutation is the crucial oncogenic-driven mutation in NSCLC with effective EGFR-TKI treatment making the patient has good quality of life (QOL) even though they have the advanced-stage disease. The journey of treatment in this group of patients is still underway of development and it is the good prototype for the other targeted drugs development in the clinical studies. I believe that there will be the other effective novel targeted treatments for NSCLC approved in the near future which would improve the long-term survival and QOL for patients. References: 1. Salomon DS, et al. Crit Rev Oncol Hematol 1995 2. Lynch TJ, et al. N Engl J Med 2004 3. Reungwetwattana T, et al. Journal of Carcinogenesis 2013 4. Soria JC, et al. N Engl J Med 2018 5. Papadimitrakopoulou V, et al. ESMO Congress 2018 6. Reungwetwattana T, et al. J Clin Oncol. 2018 7. Furuya N, et al. ASCO Congress 2018 8. Nakamura A, et al. ASCO Congress 2018 9. Nakagawa K, et al. ASCO Congress 2019 **Figure 1: The survival outcome of each approach for EGFR-positive NSCLC**

Keywords: EGFR mutation, NSCLC, first-line treatment

ES14 WHAT FIRST LINE IN ONCOGENE ADDICTED NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

ES14.02 FIRST LINE IN ALK TRANSLOCATED PATIENTS

A. Shaw

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Chromosomal rearrangement of ALK defines a distinct subset of non-small cell lung cancer (NSCLC) with marked sensitivity to small molecule ALK tyrosine kinase inhibitors (TKIs). Currently, five ALK TKIs are approved as standard therapies for advanced ALK-positive NSCLC, including the first generation ALK/ROS1/MET inhibitor crizotinib, the second generation ALK inhibitors ceritinib, alectinib and brigatinib, and most recently the third generation ALK/ROS1 inhibitor lorlatinib. In three randomized phase 3 studies (J-ALEX, global ALEX, and ALESIA), alectinib has demonstrated superior efficacy compared to crizotinib, and has replaced crizotinib as the standard first-line therapy for advanced ALK-positive NSCLC. Recently, in a planned interim analysis of the ALTA-1L phase 3 study, brigatinib has also shown superior efficacy to crizotinib as first ALK TKI in advanced ALK-positive NSCLC. In this talk, we will review all the available first-line data with ALK TKIs, with a focus on next-generation ALK inhibitors. In addition to discussing second-generation ALK TKIs, we will also highlight available data with lorlatinib in the first-line setting. The phase 3 study of lorlatinib vs crizotinib as first-line therapy (CROWN) has completed accrual, with results expected within the next year. Finally, we will discuss the potential role of investigational combinations as first-line therapy in advanced ALK-positive NSCLC. These investigational strategies hold the promise of further extending front-line progression-free survival as well as overall survival for this molecular subgroup of patients.

Keywords: ALK, Targeted therapy

ES14 WHAT FIRST LINE IN ONCOGENE ADDICTED NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

ES14.04 FIRST LINE FOR RARE MUTATIONS (RET, BRAF, HER2)

D. Planchard

Institut Gustave Roussy, Villejuif/France

Systemic therapy for non-small cell lung cancer (NSCLC) has undergone a dramatic paradigm shift over the past decade. In the recent years a number of other oncogenic drivers beyond EGFR, ALK, and ROS1 inhibition have emerged as novel molecular targets with potential therapeutic implications, including mutations in the genes BRAF, HER2, as well as RET rearrangements. A great number of clinical trials are currently underway, evaluating agents specifically designed to target these alterations. Here, we discuss both established and emerging targeted therapy approaches, as well as ongoing challenges for the treatment of NSCLC patients harboring these oncogenic alterations.

Keywords: HER2, RET, braf

ES14 WHAT FIRST LINE IN ONCOGENE ADDICTED NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

ES14.05 PATIENTS HARBOURING A DRIVEN-MUTATION: PRO AND PATIENT'S PERSPECTIVE

K. Reckamp

City of Hope Comprehensive Cancer Center, Duarte/United States of America

Genomic alterations in non-small cell lung cancer (NSCLC) define distinct subtypes with specific mechanisms leading to constitutive activity of a gene pathway, and tumor growth and metastasis. Targeted therapy for NSCLC with oncogenic driver mutations or alterations, usually with small molecule tyrosine kinase inhibitors (TKIs), has changed the paradigm for treatment of patients. New genetic alterations continue to be described with potential therapeutic interventions, and over 60% of patients with the adenocarcinoma subtype of NSCLC have a defined molecular alteration[1]. The perspective of the clinician and patient merges on the ideal that treatment for NSCLC should provide a long duration of cancer control (ideally tumor shrinkage) with limited side effects, and improvement in quality of life. Some aspects of treatment with targeted therapy may be more important to the treating physician, while patients may have a differing viewpoint during care. This will be explored. From a clinician's lens, the treatment for patients with NSCLC harbouring an alteration that can be treated with a targeted therapy involves an algorithm that includes the ideal sequencing of therapy. This requires determining the best front line therapy based on progression free survival (PFS) and overall survival while including the toxicity profile into the algorithm, and also assessing possible mechanism of resistance and options for subsequent therapy. A front line option should not be withheld based on second line options, but sequencing of therapy to increase survival and quality of life becomes an important part of the treatment decision (Table 1). This may be best exemplified in the case of *EGFR* mutant NSCLC, in which osimertinib demonstrated clear PFS benefit over erlotinib or gefitinib.[2] In this case, mechanisms of resistance are still being elucidated and subsequent therapy becomes chemotherapy combinations. Recent studies have shown PFS benefit with first generation EGFR TKIs in combination with ramucirumab or chemotherapy, but were not directly compared to osimertinib. Furthermore, the toxicity with the combination therapy was also increased. Therefore, the choice of osimertinib as front line therapy is optimal for most patients. Another important aspect in the physician choice of front line therapy is brain penetration, which most TKI therapy is able to achieve, but some are better than others. Importantly, patients will not be treated with novel targeted therapies if they are not tested. Testing can include single gene testing by PCR and FISH, NGS testing and hotspot analysis either on blood or tissue. The utility of liquid biopsies to identify alterations in the metastatic front line setting has been shown, [3] and detection has led to actionable therapy.[4] Patients expect their physicians to be advocates for their therapy and their lives, and want a reason to hope. Most would like to avoid chemotherapy if possible in the course of treatment. They want the most current, and extensive testing done to determine the right therapy, but also encounter the economic

impact of diagnosis and treatment of oncogene-driven NSCLC. Untangling the clinical trial data to provide the therapy most likely to prolong quality of life and survival is essential. Inadequate testing up front can lead to inappropriate treatments, and increased anxiety associated with additional tests and time required to find the right treatment. A NSCLC patient who is also a physician provides valuable insight into the patient perspective, "Everyone with lung cancer needs to have their cancer tissue tested for genetic mutations... That biopsy may lead to identifying mutations that can be successfully targeted. All therapies, whether conventional or targeted, provide bridges to keep you alive for the next therapy, to get to the next bridge. My ultimate goal is not necessarily to cure the disease, but to successfully manage the disease. Very much like the way HIV/AIDS and diabetic patients manage their disease for many, many years....to convert a death sentence to a chronic illness."[5] References

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Oncogene	Mutation prevalence	Approved drugs	First-line drug of choice
Driver-oncogenes with approved agents			
EGFR	Asian 30-40%/ Caucasian 10-20%	Erlotinib Gefitinib Afatinib Osimertinib	Osimertinib
ALK	1-7%	Crizotinib Ceritinib Alectinib Brigatinib Lorlatinib	Alectinib
ROS1	1.7%	Crizotinib Ceritinib	Crizotinib
BRAF	2%	Dabrafenib/ trametinib	Dabrafenib/ trametinib
NTRK	<1%	Larotrectinib	Larotrectinib

Keywords: genetic mutation, Targeted therapy, front line

ES15 THE MANAGEMENT OF CANCER TREATMENT IN THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 15:15–16:45

ES15.01 MANAGEMENT OF COGNITIVE CHANGES IN ONCOLOGY PATIENTS

N. Duma

University of Wisconsin, Madison/United States of America

Over the past two decades, we have seen significant advances in the treatment of thoracic malignancies, from targeted therapy to the introduction to immune checkpoint inhibitors. Secondary to these advances, we have the fortune of observing an increasing number of cancer survivors, something that may have been unthinkable in the past. Cancer survivorship starts the day of cancer diagnosis and entitles many aspects of our patients' lives with cognitive changes being one of them. Cognitive deficits can be secondary to the treatment effects of cytotoxic therapy/immunotherapy and also secondary to the changes our patients experience in their daily lives, living with a chronic disease and for many of our survivors changing to a new way of life with frequent doctors' visits, medication side effects and the fear of early mortality. Often called "chemobrain" or "chemofog" are the cognitive changes that persist long after treatment has ended. The mechanisms by which cancer and cancer treatment impact cognitive function have not been well described. Some investigators have proposed that cancer treatment can either shift the trajectory of normal cognitive aging or accelerate the aging process [1]. Many factors likely contribute to the cognitive decline in our patients with cancer, including inflammation, diffuse decrease in the gray and white matter, direct toxic effects from chemotherapy, and psychosocial challenges related to survivorship [2,3]. Our patients may bring issues related to cognitive decline in several ways, like reporting short term memory loss, difficulty multi-tasking, or living with a "fog" over their heads. Cognitive evaluation of our patients with thoracic malignancies is not standard practice; due to this, it is difficult to quantify the cognitive decline after completion of therapy. Since the etiology of potential cognitive inefficiencies post-cancer treatment is not well established, it is difficult to identify possible modifiers. Interventions are focused on behavioral strategies and psychopharmacological approaches. Most of the data come from studies in breast cancer or hematologic malignancies. Behavioral strategies vary, but all of them have the same goal, compensate for the cognitive deficits. Examples include relaxation techniques with a focus on mindfulness; some studies have reported improvement on patients' quality of life with these techniques [4]. Other alternatives include brain-training programs in combination with occupational therapy, more cancer centers across the United States are offering these programs to our patients surviving with thoracic malignancies. These are usually composed of a standard cognitive rehabilitation program with mental exercises using online tools or devices, the challenges with this type of interventions include insurance coverage, the repetitive visits to the rehabilitation center and the lack of data supporting these interventions in our patients with thoracic malignancies. Exercise has been linked with cognitive improvement in several studies [5]. Physical exercise interventions have been reported to improve quality of life and other adverse events secondary to chemotherapy [6]. Support groups are also an essential resource of our patients with cancer and cognitive changes due to therapy; they provide the sense of community and the opportunity to learn from other survivors about coping strategies and behaviors [7]. Other behavioral interventions also include electroencephalography biofeedback and cognitive behavioral therapy [3]. Pharmacologic interventions can be included in the treatment approach for our patients with cognitive deficits due to cancer therapy. However, the data supporting this is limited. Central nervous stimulants like Modafinil and methylphenidate have been evaluated in this patient population with some data suggesting improvement in cognitive function, including speed of memory, mean continuity of attention and quality of episodic memory, indicating a potential benefit of modafinil for the alleviation of attention and memory problems for survivors [8]. Donepezil is a reversible acetylcholinesterase inhibitor that was studied in a phase II study in patients with primary central nervous system malignancies; the study reported patients experienced improvement in their attention/concentration verbal and figural memory after taking the medication for 24 weeks compared to their baseline [9]. Paroxetine hydrochloride has also been studied in this setting in a study of 781 patients with cognitive deficits secondary to chemotherapy; authors reported statistically significant differences in alleviating some of the cognitive challenges experienced by the patients in the study. Further studies, including double-blinded randomized trials, are necessary to examine the benefits of these and other psychotropic agents, especially in combination with behavioral interventions. It is crucial to notice and act on the adverse cognitive effects that cancer-directed therapy can have on our patients with thoracic malignancies. Awareness and education remain the cobblestone to the problem; patients should be informed of the possible cognitive deficits secondary to systemic and radiation therapy and be educated about compensating mechanisms and to bring up the challenges they are experiencing during their doctors' visits. Our survivors need us; cancer treatment does not end with the last dose of chemotherapy. 1. Ahles TA. Brain vulnerability to chemotherapy toxicities. *Psycho-Oncology.* 2012;21(11):1141-1148. 2. Hurria A, Somlo G, Ahles T. Renaming "chemobrain". *Cancer Investigation.* 2007;25(6):373-377. 3. Jean-Pierre P. Management of cancer-related cognitive dysfunction—Conceptualization challenges and implications for clinical research and practice. *US Oncology.* 2010;6:9. 4. Lerman R, Jarski R, Rea H, Gellish R, Vicini F. Improving symptoms and quality of life of female cancer survivors: a randomized controlled study. *Annals of Surgical Oncology.* 2012;19(2):373-378. 5. Hartman SJ, Nelson SH, Myers E, et al. Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory

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Keywords: chemobrain, survivorship, cognitive deficits

ES15 THE MANAGEMENT OF CANCER TREATMENT IN THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 15:15–16:45

ES15.02 TOXICITIES OF RADIATION AND IMMUNOTHERAPY: WHAT WE KNOW

B. Lok

Princess Margaret Cancer Centre, Toronto/Canada

Radiotherapy is one of the longstanding pillars of cancer treatment. Immunotherapy is being established a new cancer treatment pillar and represents a momentous advance in the armamentarium of the cancer care health professional. As such, how these two modalities interact with each other is important to understand to allow the healthcare team to identify and manage the accompanying side effects. The objectives of this session are to cover a brief overview of basic radiotherapy, basic tumor immunology, followed by a more extensive review on the current status of radiotherapy and immunotherapy in clinical practice with a significant focus on reviewing the toxicities of radiotherapy, immunotherapy and their combination. The goal is to equip all members of the healthcare team to delivery optimal care for patients that receive these treatment modalities.

Keywords: Immunotherapy, radiotherapy, toxicities

ES15 THE MANAGEMENT OF CANCER TREATMENT IN THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 15:15–16:45

ES15.03 MANAGING SLEEP DIFFICULTIES AND CANCER

M. Ftanou

Peter MacCallum Cancer Centre, Melbourne/Australia

This paper discusses evidence-based interventions for managing sleep difficulties in people with cancer. Insomnia is a common sleep problem in people with cancer. Insomnia refers to the difficulty of falling asleep, staying asleep and early morning awakenings. It causes distress or impairment in important areas of functioning, such as relationships and employment. It is estimated that between 30-60% of cancer survivors experience significant sleep disturbances that can persist for up to five years post treatment. Aside from greatly impacting on quality of life, poor sleep is associated with anxiety, depression, concentration and memory difficulties, higher rates of pain, increased use of sedatives and poorer work performance [1-3]. People with lung cancer are at an increased risk of experiencing sleep difficulties because of their generally older age, compromised respiratory function, increased disease burden and the impact of treatments [4]. Sleep difficulties also have economic and social impacts on the broader community, due to increased health system costs, productivity losses and wellbeing costs [5]. Cognitive Behaviour Therapy (CBT) is considered to be the first-line treatment for insomnia [6]. CBT targets dysfunctional attitudes, beliefs and habits that interfere with sleep. CBT for insomnia commences with a comprehensive assessment about the nature and duration of sleep complaints, the impact on daytime functioning, compensatory behaviours, the person's beliefs about sleep and any other biopsychosocial factors that might be impacting on sleep. Common screening tools used to assess the impact of sleep difficulties include the Insomnia Severity Index (ISI), the Epworth Sleepiness Scale (ESS) and the Pittsburgh Insomnia Rating Scale (PIRS). These tools are self-reporting and easy to administer. CBT for insomnia is a multi-component intervention and includes psychoeducation, sleep hygiene, stimulus control, sleep restriction, relaxation, cognitive strategies and relapse prevention strategies. It is usually delivered between four to eight session modules. CBT is effective in improving sleep disturbance, fatigue, pain and quality of life. The effects of CBT are durable, with benefits lasting up to three years post-treatment [7, 8]. CBT is suitable for most adults with insomnia, however, it works best with people who are motivated and have the cognitive capacity to learn and adopt CBT strategies. CBT can be effectively provided in group settings, individually, via telephone, video or online methods. Over three quarters of patients achieve remission or significant reduction of sleep disturbance after CBT treatment [9]. CBT has been found to be more effective than mindfulness, massage, exercise and acupuncture intervention. CBT has been found to be as effective as pharmacological intervention in the short-term and more beneficial than medication in the longer term. CBT is also more cost-effective than pharmacological or non-treatment of sleep difficulties [10]. Despite the benefits of CBT, access for people with cancer is limited due to lack specialist availability, cost and awareness of the benefit of CBT. To improve access to evidence-based interventions for people with cancer, stepped-care approaches (where face-to-face CBT is reserved for the most complex cases while less burdensome and less costly self-managed interventions are available for less complex cases) could help translate evidence into clinical practice. Conclusion Sleep difficulties are highly prevalent in people with cancer, however, access to evidenced-based interventions are limited. Embedding evidence based-screening and CBT into routine care is essential to improving quality of life and care for people with cancer. 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Keywords: Sleep, Insomnia, Cognitive Behaviour Therapy

ES15 THE MANAGEMENT OF CANCER TREATMENT IN THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 15:15–16:45

ES15.04 NURSING ROLE IN MANAGING TOXICITY AND EXPECTATIONS OF TREATMENT

J. Mcphelim

NHS Lanarkshire, Glasgow/United Kingdom

This presentation will discuss the clinical patient care and management of patients receiving immunotherapies. A team approach to patient management including patient education, pre asessment, toxicity management and follow up will be presented. This team consists of Oncologists, specialist nurses and cancer care pharmacists, who work together in a dedicated clinic. The benefits to patients will be presented as well as demonstrating efficient use of clinical time.

Keywords: immunotherapy, management, teamworking

ES15 THE MANAGEMENT OF CANCER TREATMENT IN THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 15:15–16:45

ES15.05 THE ROLE OF MICROBIOME RESTORATION IN CHEMOTHERAPY AND IMMUNOTHERAPY

A. Chan

National Cancer Centre Singapore, Singapore/Singapore

Microbiomes are composed of bacteria, viruses, fungi, protozoa and archaea that reside on the surface of our body's epithelial barrier. There is increasing evidence to suggest microbiomes' role in carcinogenesis as well as cancer treatment efficacy and toxicity. In this presentation, we will focus on the impact of gut microbiome on efficacy of chemotherapy and immunotherapy. We will also discuss strategies to restore gut microbiome, with the potential on improving the delivery of chemotherapy and immunotherapy.

ES16 MODERN RADIOTHERAPY IN STAGE III NSCLC
MONDAY, SEPTEMBER 9 11:00–12:30

ES16.01 PROTON THERAPY

C. Faivre-Finn

The Christie-University of Manchester, Manchester/United Kingdom

Proton therapy is an attractive option for the treatment of lung cancer patients due to the physical properties of proton beams. Proton therapy allows a focused delivery of radiation at the Bragg peak, with very steep decline of the radiation dose beyond the target volume. These properties offer the possibility to 1) reduce toxicity by reducing the integral dose and the dose to adjacent normal tissues and 2) escalate the dose to the target in some patients. In this talk, I will summarise briefly the physics/radiobiology of protons and the need for adaptation. I will also discuss the rationale for the use of protons in patients with lung cancer, including reduction in integral dose, cardiac toxicity and reduction in haematological toxicity. The clinical trial evidence supporting the use of protons will be presented in early stage and locally advanced non-small cell lung cancer as well as in small-cell lung cancer. Finally I will discuss future research directions, including preclinical and drug-proton combination research, ongoing clinical trials, the model based-approach and the need for biomarkers. REFERENCES Liao Z, Lee JJ, Komaki R, eat l. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(18):1813-1822 Chang JY, Jabbour SK, De Ruysscher D, et al; International Particle Therapy Co-operative Group Thoracic Subcommittee.Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016;95(1):505-16. Vyfhuis MAL, Onyeuku N, Diwanji T, Mossahebi S, Amin NP, Badiyan SN, Mohindra P, Simone CB 2nd. Advances in proton therapy in lung cancer. Ther Adv Respir Dis. 2018 Jan-Dec;12:1753466618783878 C, Pawelke J, Seidlitz A, Peitzsch C, et al; "Radiobiology of Proton Therapy": Results of an international expert workshop.Lühr A, von Neubeck Radiother Oncol. 2018; 128(1):56-67 Jin, J.Y., et al., Higher Radiation Dose to Immune System is Correlated With Poorer Survival in Patients With Stage III Non-small Cell Lung Cancer: A Secondary Study of a Phase 3 Cooperative Group Trial (NRG Oncology RTOG 0617). International Journal of Radiation Oncology Biology Physics, 2017. 99(2): p. S151-S152. Joseph, N., et al., Post-treatment lymphocytopaenia, integral body dose and overall survival in lung cancer patients treated with radical radiotherapy. Radiotherapy and Oncology, 2019. 135: p. 115-119. Durante, M., D.J. Brenner, and S.C. Formenti, Does Heavy Ion Therapy Work Through the Immune System? Int J Radiat Oncol Biol Phys, 2016. 96(5): p. 934-936. Lee, H.J., Jr., J. Zeng, and R. Rengan, Proton beam therapy and immunotherapy: an emerging partnership for immune activation in non-small cell lung cancer. Translational lung cancer research, 2018. 7(2): p. 180-188. Dess, R.T., et al., Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol, 2017. 35(13): p. 1395-1402. McWilliam, A., et al., Radiation dose to heart base linked with poorer survival in lung cancer patients. Eur J Cancer, 2017. 85: p. 106-113. Schulz-Ertner, D. and H. Tsujii, Particle radiation therapy using proton and heavier ion beams. J Clin Oncol, 2007. 25(8): p. 953-64. Gameiro, S.R., et al., Tumor Cells Surviving Exposure to Proton or Photon Radiation Share a Common Immunogenic Modulation Signature, Rendering Them More Sensitive to T Cell-Mediated Killing. Int J Radiat Oncol Biol Phys, 2016. 95(1): p. 120-30.

ES16 MODERN RADIOTHERAPY IN STAGE III NSCLC
MONDAY, SEPTEMBER 9 11:00–12:30

ES16.02 MRI-BASED RADIOTHERAPY

F. Mcdonald

Insitute of Cancer Research, London/United Kingdom

One key potential advance for radical radiotherapy indications in lung cancer is the integration of magnetic resonance imaging (MRI) in the treatment pathway, giving anatomical and functional detail without additional radiation exposure to the patient. Incorporating anatomical MRI into the treatment planning may improve target volume and organs at risk delineation reproducibility. Functional MRI may facilitate heterogeneous dosing of target volumes and assessment of normal tissue toxicity to assist adaptive strategies. Four-dimensional MRI has the potential to complement 4D CT and 4D F-18-FDG PET with superior spatial resolution. MR-guided radiotherapy delivery machines are increasing in number internationally, providing novel hybrid technology that continues to evolve with various technical challenges to overcome. It is anticipated that the clinical benefits of MR-guided radiotherapy will lie the ability to adapt treatment in real-time. Research is ongoing to develop trials of MR-guided adaptive treatment schedules in lung cancer patients.

Keywords: Magnetic Resonance Radiotherapy

ES16 MODERN RADIOTHERAPY IN STAGE III NSCLC
MONDAY, SEPTEMBER 9 11:00–12:30

ES16.03 OPTIMAL INTEGRATION OF RADIOTHERAPY, TKIS AND I/O

U. Ricardi

University of Turin, Turin/Italy

Umberto Ricardi, Serena Badellino, Cristina Mantovani, Donatella Caivano, Stefania Martini, Marzia Cerrato, Giuseppe Carlo Iorio Department of Oncology, University of Turin, Italy Approximately one third of patients affected by non-small cell lung cancer (NSCLC) present with 'locally advanced' disease at diagnosis. Most patients are considered inoperable due to disease extension, and chemo-radiotherapy (CT-RT) still represents the standard therapeutic option, with unsatisfactory results in terms of overall survival (OS) despite advances in staging and technological evolution in radiation therapy planning and delivery. Besides radiation dose escalation, a logical step for improving survival in inoperable stage III patients was to evaluate the combination of concurrent/sequential RT-CT with targeted agents (tyrosine kinase inhibitors, TKI; mono-clonal antibody against EGFR; ALK/ROS1 inhibitors) and/or anti- angiogenic therapies, following the positive results obtained in stage IV disease (1, 2). Since the early 2000s, when first-generation TKIs were first approved for clinical use, several studies have been conducted in an attempt to demonstrate the efficacy of targeted therapies combined with radiotherapy (3, 4, Table 1). These studies were testing mainly the feasibility and the tolerability of this combination, with not statistical significant benefit in terms of outcomes (4, Table 1). Mature results of an international trial testing the contribution of TKIs with chemoradiotherapy in patients affected with stage III NSCLC harboring sensitive mutations are still waited. Immunotherapy, and in particular immune-checkpoint inhibitors targeting the PD-1/PD-L1 axis, gained wide popularity for NSCLC in light of the positive findings of several trials in metastatic disease (1, 5). Radiation therapy combined with immunotherapy represent a new therapeutic opportunity, given the role of RT in reversing immunosuppressive barriers within the tumor microenvironment (6). The growing enthusiasm for immune-oncology and its possible applications in radiation oncology led to a remarkable expansion of pre-clinical and clinical studies testing various combinations of immunotherapeutic agents and radiation. Stage III unresectable NSCLC is an interesting setting for the combined use of chemo-radiation and immunotherapy, also considering the multiple experimental evidences in favor of a synergistic effect between radiation and immune checkpoint inhibitors, with the potential of enhancing immuno-modulating

effects and overcoming resistance. The PACIFIC trial (PD-L1 inhibitor Durvalumab vs placebo, unresectable stage III NSCLC who did not progress following concurrent platinum-based chemo-radiotherapy) showed a major improvement in 2-year PFS and OS, which holds promise for an improved cure rate (7). Even the use of Pembrolizumab (anti-PD-1 agent) is under investigation in a series of trials. A number of studies (e.g. INSPIRE study) investigated the role of Tecemotide (anti-tumor vaccine inducing a specific immune response against MUC-1, glycoprotein overexpressed in NSCLC) (8) in Stage III NSCLC. More evidence is awaited regarding the optimal timing when combining immunotherapy and CT-RT, considering the possibility to improve this synergism even further. Several ongoing trials are testing multiple schedules (5). A predominance of the consolidation/adjuvant/maintenance setting is evident, however many studies also integrated immunotherapy at the beginning of chemo-radiation. The latter schedule should be one of the most efficient ways to fully harness the synergistic effects of chemo-radiation and immunotherapy in terms of boosting the immune-stimulating effects, particularly when using anti-PD-L1 agents, given that enhanced expression of PD-L1 during RT may be one of the main causes of radioresistance. Some attention should also be paid to those trials introducing anti-PD-1 agents before chemo-radiation, as neo-adjuvant: this innovative approach could be promising, by integrating radio-chemotherapy in a tumor micro-environment already modified by immunomodulators, and with a subsequent consolidation phase. When using anti-PD-L1 agents in this setting, PD-L1 expression levels would probably be necessary to stratify patients as highlighted in the PACIFIC trial post-hoc analysis (9). REFERENCES Filippi AR, Di Muzio J, Badellino S, Mantovani C, Ricardi U. Locally-advanced non-small cell lung cancer: shall immunotherapy be a new chance? J Thorac Dis 2018;10(Suppl 13):S1461-S1467. doi: 10.21037/jtd.2017.12.53. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Jan 30. doi: 10.1093/annonc/mdy474. 3. Arcangeli S, Jereczek-Fossa BA, Alongi F, Aristei C, Becherini C, Belgioia L, Buglione M, et al. Combination of novel systemic agents and radiotherapy for solid tumors - Part II: An AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment toxicity. Crit Rev Oncol Hematol. 2019;134:104-119. doi: 10.1016/j.critrevonc.2018.11.006. Kordbacheh T, Honeychurch J, Blackhall F, Faivre-Finn, Illidge. Radiotherapy and anti-PD-1/PD-L1 combinations in lung cancer: building better translational research platforms. Ann Oncol. 2018 Feb 1;29(2):301-310. doi: 10.1093/annonc/mdx790. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol. 2009 Jul;10(7):718-26. doi: 10.1016/S1470-2045(09)70082-8. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018; 379:2342-2350 DOI: 10.1056/NEJMoa1809697. Wu YL, Park K, Soo RA, et al. INSPIRE: A phase III study of the BLP25 liposome vaccine (L-BLP25) in Asian patients with unresectable stage III non-small cell lung cancer. BMC Cancer 2011;11:430. Kim YH. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2019 Mar 7;380(10):989-990. doi: 10.1056/NEJMc1900407.

Table 1. Major studies on Radiotherapy and TKIs in LA-NSCLC.

Author and year	Study type	Number of patients	RT technique/ dose/ fractionation	Combination (concomitant, other)	Primary Endopoint	Treatment outcome
Martinez et al (2016)	Phase II Randomised, NSCLC	90	3D-CRT 66 Gy/33 fx	RT alone vs RT+Erlotinib	Feasibility/ Tolerabily	Median OS: 11.4 vs 8.9 (p=0.835)
Lilenbaum et al (2015)	Phase II, unresectable NSCLC	75	3D-CRT 66 Gy/33 fx	Induction Carbo/Paclitaxel® RT+ Erlotinib	OS	Median OS: 17 months. 1-yy OS: 57%
Ramella et al (2013)	Phase I-II, unresectable NSCLC	60	3D-CRT 59.4 Gy/33 fx	CT-RT+Erlotinib	Feasibility/ Tolerabily	Median OS:23.3months. Median PFS: 4.7 months

ES16 MODERN RADIOTHERAPY IN STAGE III NSCLC
MONDAY, SEPTEMBER 9 11:00–12:30

ES16.04 MOLECULAR BIOLOGY OF RADIATION TOXICITY

F. Hegi-Johnson

Peter MacCallum Cancer Centre, Melbourne/Australia

Molecular Biology of Radiation Toxicity Radiotherapy causes damage to normal and malignant cells, resulting in the cell death of tumour cells and radiation toxicity. Historically, the damage caused by radiotherapy has been described by the linear quadratic(LQ) model; a model of cellular survival derived by observing the effects of fractionated radiotherapy on cell cultures. However, it is increasingly understood that radiation toxicity is a complex event mediated by both the DNA damage modelled in the LQ model, and contributory factors such as immune and inflammatory upregulation and vascular dysfunction (see Figure 1). In this talk we will review the role of DNA damage immune and inflammatory mediated reactions on the development of radiation toxicity. DNA damage and cell death Radiotherapy effects damage on normal cells by both direct and indirect means. Direct damage to DNA by either secondary electrons or reactive oxygen species (ROS) causes the initiation of DNA damage responses (DDR). This can result in varying effects depending on individual variation in the efficiency of the DDR pathways, the severity of the insult, and the type of normal cell (2). For example, haematological cell death is usually mediated through primary apoptosis within a few hours of exposure; the majority of non-haematological cells die when they enter mitosis inappropriately (mitotic catastrophe). Several key mediators of DDR have been identified. The 2 most important genetic modulators of DDR appear to be TP53, which mediates cell cycle arrest, facilitating both apoptosis and mitotic catastrophe, and ATM, which encodes the main kinase responsible for repairing double-strand DNA breaks (3). P53 works through downstream targets such as PUMA and p21, with evidence suggesting that different pathways are significant in different systems. In murine models of GI induced radiation toxicity, loss of PUMA is protective, whilst p53 and p21 loss increases toxicity (4). In contrast, in slowly replicative systems, such as the CNS and salivary glands, non-lethal radiation dose induced p53 activation may result in cell cycle arrest and altered differentiation (1); the survival of these damaged cells may lead to stem cell ageing and second malignancies. Immune and Inflammatory system upregulation during radiotherapy and the impact on radiation toxicity Radiotherapy exposure results in global upregulation of the immune system, increasing immune activity by increasing tumour cell-surface expression of major histocompatibility complex (MHC) class 1, increasing expression of tumour-associated antigens, activating dendritic cells, and changing the T cell repertoire, with a consequent reduction in the immune suppressive regulatory T-cells and an increase in active CD8 populations (5). These responses underpin the positive outcomes seen in immunoradiotherapy trials, but the relationship between radiotherapy and the immune system is likely to have complex effects both on tumour control and radiation toxicity. Under normal circumstances dying cells are phagocytosed by macrophages and an anti-inflammatory pathway mediated by IL-10, TGF-b, platelet-activating factor, and prostaglandin E2 (PGE2) suppresses inflammation (6). During radiation the high levels of DNA damage results in the release of a high concentration of pro-inflammatory “damage-associated molecular patterns”(DAMPS) including oxidized DNA, adenosine triphosphate (ATP) heat shock proteins (HSPs) and high -mobility group box 1 (HMGB1)(7), leading to upregulation of inflammatory pathways through activation of

TLR's and triggering of pro-inflammatory cytokine cascades (8). This acute inflammatory reaction contributes to several of the hallmarks of acute radiation toxicity, including erythema, ulceration and oedema (9). Finally, chronic inflammatory responses induced by radiotherapy contribute to radiation fibrosis; a result of imbalance in the creation and destruction of extracellular matrix components mediated by the upregulation of pro-inflammatory cytokines (TNFα, IL1, IL-4, IL6) and fibrogenic cytokines (TNFβ) (10). Summary Our understanding of the molecular biology of radiation toxicity continues to evolve, but is increasingly seen to be the result of the complex interplay of dysregulated DDR, immune and inflammatory responses. These pathways will provide a rich source of future therapies to increase both the efficacy and safety of radiotherapy treatment. References De Ruysscher D, Niedermann G Burnet N Siva S, Lee A, Hegi-Johnson F. Radiotherapy Toxicity, Nature Reviews Disease Primers (2019) 5:13 Lomax M, Folkes L, O'Neill P. 2013. Biological consequences of radiation induced DNA damage: relevance to radiotherapy. Clin Oncol (R Coll Radiol). 25:578–585. Morgan, M. A. & Lawrence, T. S. Molecular pathways: overcoming radiation resistance by targeting DNA damage response pathways. Clin Cancer Res 21: 2898-2904 (2015). Qiu, W. et al. PUMA regulates intestinal progenitor cell radiosensitivity and gastrointestinal syndrome. Cell Stem Cell 2, 576–583 (2008) Vanpouille-Box, C. et al. DNA exonuclease Trex1regulates radiotherapy-induced tumour immunogenicity. Nat. Commun. 8, 15618 (2017). Chung EY, Kim SJ, Ma XJ. 2006. Regulation of cytokine production during phagocytosis of apoptotic cells. Cell Res; 16: 154-161. Gehrke N, Mertens C, Zillinger T, Wenzel J, Bald T, Zahn S, T€uting T, Hartmann G, Barchet W. 2013. Oxidative damage of DNA confers resistance to cytosolic nuclease TREX1 degradation and potentiates STING-dependent immune sensing. Immunity 39:482–495. Piccinini A, Midwood K. 2010. DAMPening inflammation by modulating TLR signalling. Mediat Inflamm. 2010:672395. Sprung et al 2015. Immmunological markers that predict radiation toxicity. Cancer Lett 368:191-197 Yamada M, Kubo H, Ota C, Takahashi T, Tando Y, Suzuki T, Fujino N, Makiguchi T, Takagi K, Suzuki T. 2013. The increase of microRNA-21 during lung fibrosis and its contribution to epithelial-mesenchymal transition in pulmonary epithelial cells. Respir Res. 14:95.

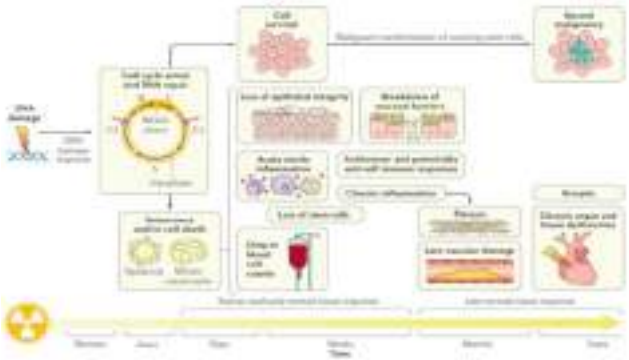

Figure 1: Cellular and Tissue Damage to Radiation Therapy. Taken from De Ruysscher D, Niedermann G ... Hegi-Johnson F. Radiotherapy Toxicity, Nature Reviews Disease Primers (2019) 5:13 (1)

Keywords: radiotherapy, toxicity, Radiobiology

ES17 MOLECULAR ALTERATIONS AND HETEROGENEITY IN MESOTHELIOMA
MONDAY, SEPTEMBER 9 11:00–12:30

ES17.01 MESOTHELIOMA EVOLUTION

E. Hollox

University of Leicester, Leicester/United Kingdom

Malignant pleural mesothelioma (MPM) is mostly caused by prior exposure to asbestos fibres. It has a long but variable latency period following exposure, with a median of around 40 years but a range between 20-70 years, possibly reflecting the length and level of asbestos exposure as well as other environmental and genetic causes. Upon diagnosis, there are limited treatment options, and median survival time is a year, although, again, this is highly variable. Understanding the genetic events in the mesothelium between asbestos exposure and diagnosis of MPM is important for two reasons. Firstly, it will inform the biology of MPM tumour growth and potentially highlight different environmental and genetic factors that cause the variation in latency. Secondly, it will help identify key early driver mutations in MPM informing biology and candidate changes for developing approaches for early detection of the cancer. Evolutionary genetics is based on inferring past events from current genetic/genomic sequences. It has long been recognised that the development of cancer is an evolutionary process, and the availability of large amounts of DNA sequence data have facilitated an understanding of evolution of tumours using methods mostly borrowed from evolutionary genetics. One powerful approach compares a matched tumour and normal genome, infers the somatic mutations in the tumour, and uses the ratio of mutations that change an amino acid to mutations that don't change an amino acid (dN/dS ratio) across all genes to identify particular genes that have been positively selected during tumour evolution. This approach can also shed light on overall evolutionary processes that have occurred in the tumour. Genomic sequences from multiple regions of the same tumour not only emphasise the molecular heterogeneity of tumours but allow an explicit phylogenetic tree of the evolution of the tumour for each patient, distinguishing somatic mutations that happened early in the tumour's evolution (and are therefore present throughout the tumour) from those that happened late in the tumour evolution. Here, I report preliminary findings from a British Lung Foundation/Mesothelioma UK-funded project entitled MEDUSA - Mesothelioma Evolution: Deciphering drUgable Somatic Alterations as potential targets for synthetic lethal therapy. This project uses multiregional sampling of MPMs, together with matched whole blood, to infer a phylogenetic tree of MPMs. The preliminary data presented focuses on the first 20 patients, with between 4 and 5 regions of the tumour analysed per patient. Using whole exome sequencing, the project aims to identify truncal changes, that is, mutations that happened early in the tumour and are present throughout the tumour that can be potential targets for drugs, with the aim of developing personalised, effective tumour treatment for each patient. We focus on copy number changes (deletions and duplications of genes) and confirm that MPM is highly heterogeneous with extensive copy number changes in the genome. We focus on truncal copy number changes in ~20-25% of patients affecting the known mesothelioma tumour suppressor genes *BAP1*, *MTOR*, *CDKN2A* and *SETD1*. Distinguishing patients that have truncal copy number changes in these genes, in contrast to those patients with copy number changes in the terminal branches of the evolution of the tumour, helps to tailor individualised drug therapies. Our approach emphasises the importance of multiregional sampling of tumours to account for MPM heterogeneity. For example, by sampling the posterior costophenic angle of these MPM from these 20 patients, we would find 10 deletions of *CDKN2A*, of which only 5 are truncal, with the other five localised to only part of the tumour. Multiregional genomic analysis and evolutionary genetics approaches can illuminate the history of a tumour and have the potential to guide therapy. They also provide the framework for follow-on studies in a patient, such as analysing the origin of metastases and identifying the effects on the tumour of treatment. The extra information provided by multiregional sampling supports the idea that this approach should become routine in tailoring the treatment to the tumour in MPM.

Keywords: evolution, Mesothelioma, Genomics

ES17 MOLECULAR ALTERATIONS AND HETEROGENEITY IN MESOTHELIOMA
MONDAY, SEPTEMBER 9 11:00–12:30

ES17.02 MOLECULAR HETEROGENEITY

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Molecular heterogeneity in Malignant Pleural Mesothelioma Malignant Pleural Mesothelioma (MPM), a rare thoracic tumor strongly linked to asbestos exposure, is one of the most aggressive cancer with a very poor prognosis. Clinical trials have highlighted MPM diversity in terms of prognosis and patients' response to anti-cancer agents, suggesting an underlying tumor heterogeneity. As current treatment options are rarely curative, a better characterization of inter and intra-tumor heterogeneity is essential for the identification of new therapeutic strategies, and for the implementation of precision medicine with the aim to improve the cure to this dreadful cancer. The first level of inter-tumor heterogeneity in MPM is histologic with three main histologic types i.e. epithelioid, sarcomatoid and biphasic. The latter is also an evidence of intra-tumor heterogeneity as the biphasic histologic

type is a mix of variable proportion of epithelioid and sarcomatoid tumor cells. The histologic heterogeneity is even more complex with the characterization of several histologic subtypes (1). Large-scale omics and NGS (Next Generation Sequencing) studies also highlighted MPM heterogeneity at the molecular level. MPM show a complex pattern of chromosomal abnormalities and mutations, so it is difficult to take into account this molecular heterogeneity of MPM solely on the basis of chromosomal or genetic alterations. We and others, using unsupervised hierarchical clustering based on transcriptomic or integrated multi-omics data, defined molecular classification in 2 and 4 tumor subtypes (2-4). These molecular subtypes are related to histology and associated to prognosis, to specific mutations in genes such as *BAP1* and to the deregulation of specific signal pathways such as epithelial-mesenchymal transition (EMT). Smaller and highly homogeneous subtypes were also defined by taking into account molecular subtypes and mutation profiles such as the one characterized by a double inactivation in the two tumor suppressor genes related to Hippo signal pathway, *NF2* and *LATS2* (5). Interestingly, based on preclinical studies, a potential target therapy has been proposed for this subtype illustrating the interest to define homogenous tumor subtypes in order to develop new therapeutic approaches. However, these molecular classifications in subtypes have some limitations. First, they take into account only inter-tumor heterogeneity but not intra-tumor heterogeneity, which is poorly described at the molecular level in MPM (6). Second, a meta-analysis comparing all molecular subtypes obtained by unsupervised hierarchical clustering of several different transcriptomic dataset highlighted only two main subtypes, which are highly correlated in all datasets. Apart from these two opposite subtypes corresponding to pure epithelioid and sarcomatoid phenotypes, intermediate subtypes could simply reflect various cut-offs of a continuum combining epithelioid and sarcomatoid entities, which could be better defined using molecular gradients (7). For these reasons with the aim to better characterize MPM molecular heterogeneity, we used a deconvolution method that decomposes the MPM transcriptomic profile of each tumor as a combination of epithelioid and sarcomatoid components. We determined the proportion of these epithelioid and sarcomatoid components (E.score and S.score, respectively) in large series of tumors. These two opposite histo-molecular gradients were related to histology types and to subtypes of MPM molecular classification (7). The underlying oncogenic pathways driving the establishment of the epithelioid and sarcomatoid related cell entities were specified. Integration of transcriptome, methylome and miRNome data showed the strong contribution of epigenetic regulation. We also highlighted the link between the histo-molecular gradients and the tumor microenvironment and the immune contexts. A strong positive correlation was observed between the S.score and the infiltration of T lymphocytes, monocytes, fibroblasts and endothelial cells, while the E.score was linked to natural killer cells infiltration and complement pathway. These results suggested the presence of an adaptive immune response in tumors with a high S-score and of an innate immune response in tumors with a high E-score. The S.score was also strongly correlated with high expression of most immune checkpoint inhibitors, including *CD274* (*PDL1*) and *CTLA4* (7). More importantly, we highlighted the potent clinical impact of histo-molecular gradients on prognosis and on personalized therapeutic strategies in MPM. First, we showed that the S.score has a strong prognostic value, higher than histologic and molecular classifications. Second, our data supported that these histo-molecular gradients might be used to guide therapeutic strategies such as targeted therapies by performing preclinical studies. Third, the strong correlation of the S.score with T lymphocytes infiltration and immune checkpoint inhibitors expression supports that a high S.score could be predictive of immunotherapy based on anti-PDL1 and anti-CTLA4 inhibitors (7). Prediction of patients responding to these inhibitors is particularly important given the recent promising results of this immunotherapy for some MPM patients (8). More recently, we have performed a genetic profiling, focusing on the main key genes altered in mesothelial carcinogenesis, of a large collection of MPM with complete clinical annotations and well-characterized for heterogeneity using current available tumor classifications. The unpublished results provided a comprehensive overview of the genetic landscape of MPM taking into account the histologic and molecular heterogeneities. References: 1. Husain A. N. *et al.* Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013, *137*: 647-667. 2. Bueno R. *et al.* Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet. 2016, *48*: 407-416. 3. de Reynies A. *et al.* Molecular classification of malignant pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res. 2014, *20*: 1323-1334. 4. Hmeljak J. *et al.* Integrative Molecular Characterization of Malignant Pleural Mesothelioma. Cancer Discov. 2018, *8*: 1548-1565. 5. 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Keywords: Molecular classification, Histo-molecular gradient, tumor heterogeneity

ES17 MOLECULAR ALTERATIONS AND HETEROGENEITY IN MESOTHELIOMA
MONDAY, SEPTEMBER 9 11:00–12:30

ES17.03 HETEROGENEITY & IMMUNE CHECKPOINT EXPRESSION

A. Mansfield

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Mesothelioma is a spatially complex malignancy. Morphologic heterogeneity is commonly identified, especially with surgical resection that can unmask distinct histologic components across sites of disease. Molecular analyses of *HUMARA* methylation patterns on the X-chromosome, *CDKN2A* deletions, and single nucleotide variants from multiple tumor sites all suggest that mesothelioma is polyclonal with multiple genetic subclones within each tumor. Temporal histologic heterogeneity has also been reported with sarcomatoid differentiation during progression of disease. The selective pressures of the microenvironment and therapies may further drive tumor heterogeneity. With the application of immune checkpoint inhibitors for the treatment of this disease, the expression of immune checkpoints and the immunologic milieu of mesothelioma has been increasingly investigated. Whereas most studies report immune checkpoint expression from a single site of disease obtained from a single time point, distinct immunologic patterns have been observed within tumors from different sites. The molecular and immunologic heterogeneity of mesothelioma may have prognostic and therapeutic implications.

Keywords: Mesothelioma, Heterogeneity, PD-L1

ES17 MOLECULAR ALTERATIONS AND HETEROGENEITY IN MESOTHELIOMA
MONDAY, SEPTEMBER 9 11:00–12:30

ES17.04 NEW INSIGHTS INTO THE MOLECULAR CHARACTERISTICS AND INTRA-TUMOR HETEROGENEITY OF MALIGNANT PLEURAL MESOTHELIOMA FROM THE MESOMICS PROJECT

L. Fernandez-Cuesta

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Malignant pleural mesothelioma (MPM) is a rare but deadly disease, which molecular characteristics have only recently been uncovered through large-scale genomic studies (Bueno Nat Genet 2016; Hmeljak Cancer Discov 2018). Although insightful and important, many questions are still unanswered, which could be addressed with additional comprehensive and integrative genomic analyses. In addition, we have recently performed a reanalysis of the transcriptome data of the two aforementioned cohorts with no assumption of discretness, in which we have uncovered the importance of angiogenesis and the immune system for understanding the diversity of MPM molecular phenotypes (Alcala et al. under review). Intra-tumour heterogeneity (ITH) is commonly reported in MPM at the histopathological level; however, the question of the molecular ITH of this disease has not been comprehensively addressed so far. Only one recent study has highlighted the

enormous ITH at the microenvironment level (Thapa et al. JTO 2017), suggesting that MPM experience spatially heterogeneous selective pressures, or possibly that there exist MPM clones that differentially alter their micro-environment. In close collaboration with the French MESOBANK/MESOPATH, we have started the MESOMICS project aiming at performing a molecular characterization of a large series of MPM through the integration of muti-omic data and detailed epidemiological and clinical information in order to better understand this understudied and deadly disease. For this we have collected 130 fresh frozen tumors and their matched-normals from all the three MPM types (epithelioid, biphasic, sarcomatoid) and the main morphological subtypes of the epithelioid MPM. We have performed whole-genome sequencing, transcriptome sequencing and 850K methylation arrays in all these samples. For 12 of them we had access to several regions of the tumor, which allowed us to perform ITH analyses. The preliminary analyses of these data will be presented and discussed. Website: RareCancersGenomics.com Twitter: @CancersRare

Keywords: MESOMICS, genomics, intra-tumor heterogeneity

ES18 ACQUIRED RESISTANCE TO TKIS: THE REBIOPSY CASE AND THE FUTURE OPTIONSES
MONDAY, SEPTEMBER 9 11:00–12:30

ES18.01 REBIOPSY IN ONCOGENE ADDICTED NSCLC AT PROGRESSION

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As we have defined piecharts of different oncogenes at diagnosis in NSCLC, each oncogene, under the selection pressure of an active targeted agent may develop acquired resistance after initial benefit in a number of different ways, allowing intra-oncogene piecharts of acquired resistance mechanisms to be described. Key features to consider when considering a rebiopsy - either of the tumor or of a surrogate of the tumor (cf-DNA) is the ease and risks of rebiopsy, its false positive and false negative rates and the potential 'actionability' of the data generated. These factors allow rebiopsies for research purposes to be differentiated from those that could inform changes in clinical care immediately. Rebiopsies of systemic disease, became standard when osimertinib was used post 1st- or 2nd-generation EGFR TKIs to look for T790M. With the move of osimertinib to the first line setting, the need to detect T790M has becoem less, but other mechanisms of resistance in the post 1/2nd generation EGFR TKI setting, separate from T790M, and in the post-osimertinib setting including small cell transition and MET amplification are also likely to change clinical management and maintain the role for biopsies in EGFR mutant disease. In ROS1 rearranged lung cancer - the lack of efficacy of lorlatinib and crizotinib to G2032R clinically, but the possible activity of repotrectinib in trials, can make the case for a rebiopsy and reanalysis post-crizotinib or lorlatinib in ROS1+ disease. Actionable second drivers remain under exploration. In ALK rearranged lung cancer, on target mutations are multiple - preclinical data suggesting specific drugs for specific mutations post-crizotinib can be identified remains partially determined, with multiple caveats about the preclinical-clinical transferability of data. The ALK master protocol will address some of these issues. However, perhaps the biggest issue relates to the potential for non-ALK related second drivers to be actionable, suggesting the methodology of testing in the acquired resistance setting, as in EGFR, should be broad. Rebiopsies performed in the setting of CNS progression, in the absence of prior overt CNS benefit, are of limited practicality or use at present, however, with the advent of CNS penetrant drugs for key oncogenes, true CNS acquired resistance may emerge and some form of CNS sampling may become relevant.

ES18 ACQUIRED RESISTANCE TO TKIS: THE REBIOPSY CASE AND THE FUTURE OPTIONSES
MONDAY, SEPTEMBER 9 11:00–12:30

ES18.02 WHEN TO SWITCH TO A NEW TKI:IMAGING BASED CRTIERIA OR POSITIVE LIQUID BIOPSY?

J. Yang

National Taiwan University Hospital, Taipei/Taiwan

The discovery of specific mutations and associated addicted pathways in lung adenocarcinoma cells has led to the development of many targeted therapies useful for corresponding activating mutation. In addition, conventional chemotherapy and novel immunotherapy such as PD1/PDL1 antibodies are also very effective for lung cancer patients with or without specific driver mutation. Patients with metastatic lung cancer nowadays can be treated with multiple lines of effective treatment. Patients who receive more lines of therapy tend to live longer than those who had only receive limited number of treatment. In order to maximize the overall survival outcome of metastatic lung cancer patient who receives systemic treatment, it is important to find out the best first line choices and the best timing to change the treatment regimen to second line and so forth. Tumor reduction or stabilization by imaging criteria has been used widely for a long time in chemotherapy and targeted therapy era. RECIST (Response evaluation criteria in solid tumors) has been adopted as a uniform criteria for cancer clinical trial to classify the tumor response to certain treatment. However, in order to accommodate different cancer types and sites of metastasis, several variants of RECIST emerged to better evaluate the treatment response and necessity of maintain the present treatment. In daily practice, changes of tumor size in the image provide the best guidance for clinicians to continue or change regimen for the patients. In patients who has no reliable evaluable radiological image for follow up, such as patients who presented with effusion, bone metastasis, leptomeningeal metastasis or tumor with poor margin, patients' clinical performance and alterations in tumor markers occasionally can provide clinicians information for judgement. The introduction of cell free plasma tumor DNA for the molecular diagnosis of cancer gave us a new change of how to manage the patients properly when changing regimen to prolong patients chance to survive or improving quality of life are attainable. There are a least 3 important applications for cell free tumor DNA detection. First is to provide information of specific mutation at the time of diagnosis or progression, so that a corresponding targeted therapy can be chosen as the best treatment of choice. Second is to use quantitative amount of specific mutation found in plasma cell free DNA to follow patient's tumor. The presumption is the amount of specific mutation may represent the tumor load of the treated patients. The 3rd possible application is to use the novel mutations detected in the plasma at the time of diagnosis or during treatment follow up to select a theoretical best combination for patients. There are ample of analysis reported in the literature for the first and second possible applications of plasma cell free DNA. The evidence for the 3rd possible application is accumulating. However, there is no emphasis of using this vast information gathered in the plasma to guide the right timing to switch regimen. In addition, there has been a trend to continue original treatment in slow progressing patients beyond imaging progression, or to treat oligo-progressing sites with local irradiation or surgery in order to keep the original treatment. These approaches certainly will further complicate the rationale decision of right timing to change regimen. Thus, a few options exist for patients who are receiving targeted therapies. One is to use conventional ways of RECIST progression by imaging studies to change the treatment to further lines. The treatment outcome may be more predictable, because most of the clinical trials follow this dogma. A second choice is to treat patients beyond progression by RECIST and follow physicians judgment to switch the regimen. Several recent clinical trials use this criteria to change regimen and collect the treatment time as duration-of-treatment, or time-to-treatment-failure. The 3rd possible timing is to switch regimen according to plasma DNA alterations, for example, emergence of activating mutation when plasma tumor DNA was previously eradicated by current targeted therapy; add another targeted therapy when a new parallel pathways amplification is predicted from the plasma sample analysis. This strategy lack the support of prospective clinical trial data and was purely based on direct scientific deduction or instinct and a few case reports. Therefore, studies specifically designed to address the switch timing is very important. Unfortunately, the effort devoted to this area is lacking.

ES18 ACQUIRED RESISTANCE TO TKIS: THE REBIOPSY CASE AND THE FUTURE OPTIONSES
MONDAY, SEPTEMBER 9 11:00–12:30

ES18.03 NEW STRATEGIES TO OVERCOME RESISTANCE IN EGFR MUTATED NSCLC

P. Bunn, Jr

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Activating EGFR mutations occur in 15-50% of lung adenocarcinomas with a higher frequency in never or light smokers and individuals of East Asian origin. First and second generation EGFR tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, afatinib and dacomitinib are associated with high response rates (50-75% and median progression free survival rates of 9-14 months. Failure in the CNS is frequent because these agents have poor CNS penetration and the most frequent cause of systemic failure is the development of T790M resistance mutations. Other reported mechanisms of resistance to first and second generation EGFR TKIs include small cell transformation, AXL overexpression, HER2 mutation and overexpression, Wnt pathway overexpression and other less common alterations. Standard platinum doublet chemotherapy is generally used for those with small cell transformation and these cases usually have Rb loss and p53 mutation. The addition of cetuximab to first or second generation EGFR TKIs did not appear to improve outcomes. Osimertinib is a third generation EGFR TKI whose advantages include high sensitivity to both activating EGFR mutations and T790M mutations with lesser sensitivity to wild type EGFR. Osimertinib also crosses the blood brain barrier. A randomized phase III trial, AURA3, demonstrated that osimertinib was superior to chemotherapy and was associated with decreased CNS relapse in the second line setting after failure on a first generation EGFR TKI due to T790M. These data with second line osimertinib led to a first line phase III randomized trial, FLAURA, comparing osimertinib to either gefitinib or erlotinib. Osimertinib was associated with a significantly longer PFS, a significantly longer time to CNS progression, a significantly longer duration of response and a longer overall survival that had not reached significance at most recent analysis. Patterns of resistance to first line osimertinib are only emerging now but include alterations that have specific targeted therapy such as MET amplification (15%), BRAF mutations (3%), HER2 amplification (1%), ALK fusions (1%), PI3K mutations (3%), KRAS mutations (2%), C797s or other resistance mutations (2%), SCLC transformation (5%), CDK and cell cycle alterations (2-5%). Because these have specific non-chemotherapy treatment options, NGS testing should be done on blood ctDNA and if negative on tissue at the time of progression. For those without these actionable alterations, chemotherapy is the next standard therapy although combinations of chemotherapy with checkpoint inhibitors with or without anti-VEGF agents is under investigation due to a positive subset analysis of the IMPOWER 150 trial. The addition of checkpoint inhibitors to first line TKIs has proven to have increased toxicity with low activity. Another way to delay or prevent resistance is to use combinations in the first line therapy. Combinations of EGFR TKIs with anti-VEGF therapies, with anti-MET therapies, with anti-EGFR antibodies, and with chemotherapy are in progress. Initial trials combining erlotinib with bevacizumab demonstrated improved PFS but not OS. Current trials are combining newer EGFR TKIs such as osimertinib with anti-VEGF antibodies such as bevacizumab or ramicirumab are in progress. Trials using anti-VEGFR TKIs are also in progress. Preclinical studies indicated that combining anti-EGFR antibodies such as cetuximab or necitumumab with EGFR TKIs could overcome some resistance led to other ongoing clinical trials combining these agents. Amplification of MET is a common mechanism of resistance to EGFR TKIs, so the combination of MET TKIs with EGFR TKIs is rational and trials are ongoing. Understanding the mechanisms by which EGFR mutant cells can persist in the presence of initial EGFR TKIs remains a priority for future investigation. The adjuvant use of EGFR TKIs after surgical resection of early stage NSCLC patients with EGFR mutations has clearly established superiority in recurrence free survival but not in overall survival. It appears that there is insufficient cell kill to lead to an increase in the cure rate but additional survival based adjuvant trials such as "ALCHEMIST" are ongoing. Neoadjuvant studies could provide downstaging because the response rates are high. It is not clear whether this would be more likely to provide an increase in cure rates compared to adjuvant use of these agents. These neoadjuvant trials are providing surgical samples to explore mechanisms by which cells persist after EGFR TKI therapy. This incredibly important information could lead to rational combinations that could increase pCR rates in early stage patients and improved outcomes in advanced stage patients.

Keywords: EGFR, TKI resistance

ES18 ACQUIRED RESISTANCE TO TKIS: THE REBIOPSY CASE AND THE FUTURE OPTIONSES
MONDAY, SEPTEMBER 9 11:00–12:30

ES18.04 NEW STRATEGIES TO OVERCOME RESISTANCE IN ALK REARRANGED NSCLC

S.-H. Ou

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Since the discovery of ALK+ NSCLC in 2007, there are now 6 ALK TKI have been approved or in clinical development. These 6 ALK TKI can be generally divided into 3 generations. First-generaion (Crizotinib). Second-generaion (Alectinib, Ceritinib, Brigatinib, Ensartinib). Third-generation (Lorlatinib). The advantages of the second-generation ALK TKI or beyond is better potentcy an excellent improved CNS penetration. The mode of progression in ALK+ NSCLC are 4 fold and can be single or combination according to individaul patients: developed of acquired second site ALK mutations, CNS progression, bypass activation, and histological transformation. For second site ALK mutations, sequencing ALK TKIs that will overcome the particular second site mutation(s) or proceed to the most potent ALK TKI is likley be successful. For CNS progression, lorlatinib has demonstrated CNS activity in CNS progression from second generation ALK TKIs (ceritinib, alectinib). Additionally the use of stereotactic radiation (SRS) or whole brian radiation can contral CNS progression but clinicians should look out for radiation necrosis. For second bypass activation such as (i.e. RAS, SRC, EGFR, Kit) in vritro pre-clinical modles of combining specific bypass inhibitor and ALK TKI were albe to inhibit growth of these resistance cell lines or patient dervied PDX model, clinical trials are on-going but to date clinical data are lacking. Additional the use of chemotherapy especailyl pemetrexed-based chemotherapy in addition to ALK TKI has showen to be more efficacious than just switching to chemotherapy while discontinuing ALK TKI For histologic transformation most commonly small cell transformation, the switching to small cell regimen is only viable option at this point. The addition to immunotherapy to chemotherapy (e.g. IMpower133 regimen) or IO + IO combination (e.g. chckmate-032) should be explored in small cell tranformation as mode of progression in ALK+ NSCLC.

ES19 RECENTLY DIAGNOSED MALIGNANT PLEURAL EFFUSION
MONDAY, SEPTEMBER 9 14:00–15:30

ES19.01 BENEFITS AND LIMITATIONS OF SYSTEMIC THERAPY FOR MALIGNANT PLEURAL EFFUSION

A. Tsao

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Systemic therapy for metastatic non-small cell lung cancer is directed by molecular profiling. Ideally, genetic sequencing and PD-L1 immunohistochemistry should be performed on tumor cells obtained from malignant pleural effusions where the diagnosis of non-small cell lung cancer is evident. This discussion will review the recommended up to date testing practices and the subsequent systemic therapy decisions for patients with metastatic non-small cell lung cancer.

Keywords: systemic therapy, non-small cell lung cancer

ES19 RECENTLY DIAGNOSED MALIGNANT PLEURAL EFFUSION
MONDAY, SEPTEMBER 9 14:00–15:30

ES19.02 BEST ENDOSCOPIC TOOLS FOR THE BEST RESULTS

M. Munavvar

Lancashire Teaching Hospitals, Preston/United Kingdom

Undiagnosed pleural effusion is an increasingly common clinical problem and represents significant burden of disease both to patients and healthcare resources. With the increase in annual incidence of both primary and secondary pleural malignancies, better diagnostics and treatment options are very much needed. Medical thoracoscopy, also known as local anaesthetic thoracoscopy [2], is a procedure where a rigid or semi-rigid scope is inserted into the pleural cavity via a port for direct visualisation of the pleura and biopsy of abnormal areas, besides completion of talc poudrage, where appropriate. It is usually performed under conscious sedation and local anaesthesia. This procedure avoids risks of general anaesthesia and single lung ventilation, required for video-assisted thoracoscopic surgery (VATS) and therefore can be performed in patients who are unfit for anaesthesia/surgery. The procedure of thoracoscopy is performed in a controlled environment such as in an operating theatre setting, endoscopy suite or treatment room with adequate staffing. Diagnostic advantage A significant number of cases of pleural effusion are undiagnosed after a single diagnostic pleural aspiration and the diagnostic yield of pleural fluid cytology is only approximately 60% [3]. A second aspiration only modestly increases diagnostic yield by 15% and a third sample is non-contributory [3]. A blind pleural biopsy (also known as closed pleural biopsy) increases the diagnostic yield above pleural fluid cytology by only 7-27% [3]. In mesothelioma however, the diagnostic yield of pleural fluid cytology is even lower, at around 32% [4]. A blind pleural biopsy only increases sensitivity to around 50% [5]. Medical thoracoscopy is substantially superior in diagnostic power compared to pleural fluid cytology and blind pleural biopsy. As it allows direct visual assessment of the pleura and subsequent biopsy of the abnormal areas, it maximises diagnostic yield to >90% in malignant pleural diseases [5,6]. Rigid thoracoscopy generates similar diagnostic yield compared to semirigid thoracoscopy in exudative pleural effusions but larger biopsy samples can be obtained during rigid thoracoscopy [5,6].The sensitivity of medical thoracoscopy in malignant mesothelioma appears to be equally good and the efficacy of rigid medical thoracoscopy in regards to diagnosis in pleural malignancy is as high as VATS [2]. With the increasing need to secure an accurate diagnosis and plan optimal treatment in possible pleural malignancy, medical thoracoscopy offers a high diagnostic yield earlier in the patient journey. Therefore, this is the preferred procedure where the option exists and helps to reduce the need for repeated diagnostic procedures and reduces the time taken to establish diagnosis and commence appropriate treatment. Medical thoracoscopy as a therapeutic procedure Another advantage of medical thoracoscopy is that it is a diagnostic and therapeutic procedure in the same setting. Complete drainage of pleural fluid can be achieved during the procedure and talc poudrage can also be performed during medical thoracoscopy. It is a highly effective method of pleurodesis with an efficacy of 84% at 1 month, which is at least equivalent to talc slurry via a seldinger chest drain, with possibly increased efficacy in the subgroup of patients who have breast or lung carcinoma and without trapped lung [2]. Medical thoracoscopy is also effective in the management of TB pleurisy and empyema. Septations and adhesions in complex infected effusions can be divided during thoracoscopy which can facilitate accurate chest tube placement and drainage. Advanced Thoracoscopy Techniques Narrow Band Imaging- using Semirigid Thoracoscope Autofluorescence Rigid Thoracoscopy Biopsy- with Insulated Tip Diathermy Knife Cryobiopsy- using Semirigid Thoracoscope Rigid Thoracoscope Semi-rigid Thoracoscope References: Diacon AH, Van de Wal BW, Wyser C, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J 2003;22:589e91. Rahman NM, Ali NJ, Brown G, Chapman SJ, O'Davies RJ, Downer NJ, Gleeson FV, Howes TQ, Treasure T, SinghS and Phillips GD Local anaesthetics thoracoscopy: British Thoracic Society pleural disease guideline 2010. Thorax 2010;65(Suppl 2):ii54-ii60 Mohan A, Chandra S, Agarwal D, Naik S and Munavvar M. Utility of semirigid thoracoscopy in the diagnosis of pleural effusions: a systematic review. Journal of Bronchology and Interventional Pulmonology 17 (3), 195-201 Munavvar M, Khan MAI, Edwards J, Waqaruddin Z and Mills J. The autoclavable semirigid thoracoscope: the way forward in pleural disease? 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Keywords: Rigid Thoracoscopy, Semi-rigid Thoracoscopy, Advanced Techniques

ES19 RECENTLY DIAGNOSED MALIGNANT PLEURAL EFFUSION
MONDAY, SEPTEMBER 9 14:00–15:30

ES19.03 RCT'S ON MALIGNANT PLEURAL EFFUSION TALC PLEURODESIS MANAGMENT

N. Maskell

University of Bristol, Bristol/United Kingdom

This talk will focus on 2 recently completed multicentre RCT's in talc pleurodesis for malignant pleural effusions; IPC plus trial (NEJM 2018) and the TAPPS trial (in submission). A summary of these 2 trials is below: IPC Plus - *Methods:* Over a period of 4 years, we recruited patients with malignant pleural effusion at 18 centers in the United Kingdom. After the insertion of an indwelling pleural catheter, patients underwent drainage regularly on an outpatient basis. If there was no evi- dence of substantial lung entrapment (nonexpandable lung, in which lung expansion and pleural apposition are not possible because of visceral fibrosis or bronchial ob- struction) at 10 days, patients were randomly assigned to receive either 4 g of talc slurry or placebo through the indwelling pleural catheter on an outpatient basis. Talc or placebo was administered on a single-blind basis. Follow-up lasted for 70 days. The primary outcome was successful pleurodesis at day 35 after randomization. *Results:* The target of 154 patients undergoing randomization was reached after 584 patients were approached. At day 35, a total of 30 of 69 patients (43%) in the talc group had successful pleurodesis, as compared with 16 of 70 (23%) in the placebo group (haz- ard ratio, 2.20; 95% confidence interval, 1.23 to 3.92; P=0.008). No significant be- tween-group differences in effusion size and complexity, number of inpatient days, mortality, or number of adverse events were identified. No significant excess of blockages of the indwelling pleural catheter was noted in the talc group. *Conclusions:* Among patients without substantial lung entrapment, the outpatient administration of talc through an indwelling pleural catheter for the treatment of malignant pleural effusion resulted in a significantly higher chance of pleurodesis at 35 days than an indwelling catheter alone, with no deleterious effects. (Funded by Becton Dickinson; EudraCT number, 2012-000599-40.) TAPPS - *Methods* We recruited patients with malignant pleural effusion from 17 United Kingdom hospitals over 5 years. On an open-label basis, patients were randomly assigned to receive either 4g talc poudrage at thoracoscopy under conscious sedation, or chest tube insertion under local anesthetic followed by 4g talc slurry. Follow-up lasted for six months. The primary outcome was pleurodesis failure rate three months after randomization, defined as the need for further pleural intervention during follow-up. Secondary outcomes including mortality and cost-effectiveness were also assessed. *Results* The target of 330 patients was reached after 583 were approached. At three months, pleurodesis failure rate was 36/161 (22%) with poudrage and 38/159 (24%) with slurry (adjusted odds ratio (OR) 0.91, 95% confidence interval (CI) 0.54-1.55, p=0.74). No statistically significant differences were noted in any secondary outcome. Numbers of adverse events were similar between groups. Using a standard threshold, poudrage had a 36% probability of being cost-effective. *Conclusions* In patients with malignant pleural effusion, there appears to be no additional clinical or cost-effectiveness benefit to choosing talc poudrage at physician-led thoracoscopy over talc slurry through chest tube. *(Funded by the United Kingdom National Institute for Health Research).*

Keywords: Malignant pleural effusion, Pleural effusion, Talc pleurodesis

ES19 RECENTLY DIAGNOSED MALIGNANT PLEURAL EFFUSION
MONDAY, SEPTEMBER 9 14:00–15:30

ES19.04 HOW TO DEAL WITH A TRAPPED LUNG

Y.C.G. Lee

Sir Charles Gairdner Hospital, Perth/Australia

Trapped lung, now also called nonexpandable lung, refers to the observation when an underlying lung fails to fully expand upon removal of pleural fluid or air [1]. It occurs in ~30% of patients with malignant pleural effusions (MPEs) and may arise from thickened visceral pleura (inhibiting lung expansion) or from endobronchial tumor obstruction. The pleural space in patients with nonexpandable lung is usually under high negative pressure. This can lead to transudative fluid accumulation by Starling's equation, in addition to the underlying MPE formation. This condition is often difficult to manage as fluid often keep recurring to fill up the trapped lung space. Patients with MPE and trapped lung often present with breathlessness. It is important to recognize that removal of the fluid can still provide symptom relief despite the nonexpendable underlying lung [2]. A trial of fluid drainage to determine if the patient has symptoms benefits is worthwhile. The current belief is that breathlessness from MPE is a result of altered respiratory mechanics when the hemithorax expands to accommodate the volume of the effusion (see our review [2] for details). Patients with nonexpandable lungs usually do not benefit from pleurodesis due to the lack of apposition of the visceral and parietal pleura. Indwelling pleural catheter (IPC) is now a recognized first choice management of MPE in patients with a nonexpendable lung, as recommended in the latest American thoracic Society MPE guidelines (2018) [3]. Several large randomized studies in recent years have testified to the benefits of IPC management of MPEs. The TIME-2 study [4] showed that IPC offered benefits to breathlessness and chest pain similar to conventional talc slurry pleurodesis. The AMPLE trial [5] showed that patients with MPE managed with IPC spent fewer days in hospital and required fewer pleural invasive procedures in their remaining life while enjoying the same level of symptom and quality-of-life improvements as those patients treated with talc pleurodesis. The recently published AMPLE-2 study [6] compared daily catheter drainage vs symptom-guided drainage in patients with MPEs and an IPC. Interestingly 50% of those with initial trapped lung who underwent daily drainage eventually developed spontaneous pleurodesis that allow removal of the catheter. The numbers however were small and the results require verification. Conventionally it is believed that surgical decortication of the lung in MPE patients with visceral pleural thickening may allow the lung to re-expand and thus permit successful pleurodesis. Limited objective data exist to support this belief (see our recent review [7]). In the VATS-Meso trial [8] and other observational series, patient who underwent VATS pleurodesis +/- pleurectomy have higher risks of complications especially prolonged post-operative air-leak and thus hospitalization. The planned AMPLE-3 randomized trial will compare IPC treatment with surgical pleurodesis for MPE. Patients with MPEs and underlying nonexpandable lung are often excluded in clinical trials and thus their optimal management remains unclear. They represent a sizeable subset of MPE patients and deserve specific attention in future research. REFERENCES 1. Light RW, Lee YCG. *Textbook of Pleural Dieaseas.* 3rd ed. USA: Taylor & Francis; 2016. 2. Thomas R, Jenkins S, Eastwood PR*, et al.* Physiology of breathlessness associated with pleural effusions. *Curr Opin Pulm Med.* 2015;21(4):338-45. 3. Feller-Kopman DJ, Reddy CB, DeCamp MM*, et al.* Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2018;198(7):839-49. 4. Davies HE, Mishra EK, Kahan BC*, et al.* Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA.* 2012;307(22):2383-9. 5. Thomas R, Fysh ETH, Smith NA*, et al.* Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. *JAMA.* 2017;318(19):1903-12. 6. Muruganandan S, Azzopardi M, Fitzgerald DB*, et al.* Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *Lancet Respir Med.* 2018;6(9):671-80. 7. Fitzgerald DB, Koegelenberg CFN, Yasufuku K*, et al.* Surgical and non-surgical management of malignant pleural effusions. *Expert Rev Respir Med.* 2018;12(1):15-26. 8. Rintoul RC, Ritchie AJ, Edwards JG*, et al.* Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. *Lancet.* 2014;384(9948):1118-27.

Keywords: malignant effusion, pleural, Breathlessness

ES19 RECENTLY DIAGNOSED MALIGNANT PLEURAL EFFUSION
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ES19.05 SURGICAL MANAGEMENT OF MALIGNANT PLEURAL EFFUSION

A. Sihoe

The University of Hong Kong, Hong Kong/Hong Kong PRC

At first glance, it would seem that the thoracic surgeon has little role to play nowadays in the management of malignant pleural effusion (MPE). Substantial advances have been made in the understanding of the pathophysiology of MPE and its diagnosis. There is broad consensus that pleurodesis should generally be given at the bedside rather than in the operating theatre, while intractable cases can be managed with indwelling catheters. Even where interventions into the chest are required, the advent of 'medical' thoracoscopy appears to have diminished the role of surgeons in managing MPE. However, it would be wrong to presume that thoracic surgeons may be completely excluded from the MPE scene. There remain situations were surgery is still required for a definitive diagnosis or effective palliation. Surgeons continue to have more extensive experience with biopsy, drainage, and 'rapid pleurodesis' – yielding high rates of success. More importantly, minimally invasive Video-Assisted Thoracic Surgery (VATS) has evolved significantly in recent years. Uniportal VATS is becoming increasingly utilized, and is often complemented by technological advances such as non-intubated anesthesia. The latest advances in minimally invasive thoracic surgery have ensured that the high success rate of surgery is now coupled with surprisingly little – if any – functional or physiological 'cost' to the patient with MPE. The 'VATS' available today is not the same VATS from even a few years ago. This presentation provides an overview of the current surgical options available in the management of MPE. The modern thoracic surgeon remains fully equipped and prepared to contribute to the multi-disciplinary care of patients with this complication.

Keywords: Pleural effusion, surgery, thoracoscopy

ES20 STRATEGIES FOR CANCER PATIENTS TO HAVE OPTIMAL OUTCOMES
MONDAY, SEPTEMBER 9 14:00–15:30

ES20.01 WHY IT MATTERS FOR PATIENTS TO QUIT - WHAT WE'VE DONE

A. Shankar

DRBRAIRCH, All India Institute of Medical Sciences, NEW DELHI/India

Smoking after a cancer diagnosis causes adverse outcomes including increasing overall mortality, cancer specific mortality, and risk for second primary cancer. Continued smoking is also associated with increased toxicity from cancer treatment. The best method to prevent the adverse effects of smoking is to assist patients with quitting. However, large surveys consistently demonstrate that while most providers ask about tobacco use and advise patients to quit, most oncologists unfortunately do not provide assistance. Predictive barriers to providing assistance with quitting include a lack of time, education, and resources. Continued smoking after a diagnosis can result in substantial added cancer treatment costs, which can be used to justify resources to assist patients with quitting. Methods to assist patients include counseling and pharmacotherapy. Considering in person or phone based approaches to cessation support is important to implement effective and sustainable changes within each practice setting. As approaches are implemented, significant opportunity exists to increase the efficiency of smoking cessation in cancer care. Additional opportunities exist for identifying optimal cancer treatment strategies for cancer patients who smoke. The key to realizing the clinical and financial benefits of addressing tobacco use in cancer care is the systemic incorporation of standardized

approaches to identifying tobacco use, providing assistance for patients to quit, and tracking tobacco use after diagnosis in combination with monitoring clinical outcomes."

Keywords: Smoking, Cancer, quitting, Outcome

ES20 STRATEGIES FOR CANCER PATIENTS TO HAVE OPTIMAL OUTCOMES
MONDAY, SEPTEMBER 9 14:00–15:30

ES20.02 TOBACCO CONTROL INTEGRATION IN CANCER CARE: THE CANADIAN EXPERIENCE

W. Evans[1], R. Truscott[2], E. Cameron[2], C. Timmings[3], M. Haque[2], M. Halligan[3], S. Rana[2], D. Keen[3], L. Rabeneck[2]

[1]*McMaster University, Hamilton/Canada,* [2]*Cancer Care Ontario, Toronto/Canada,* [3]*Canadian Partnership Against Cancer, Toronto/Canada*

The evidence that smoking cessation improves outcomes for cancer patients is irrefutable. Continued smoking after a diagnosis of cancer can increase all-cause and cancer-specific mortality, result in increased adverse treatment effects and cause a higher incidence of recurrence and second malignancies (1,2). In 2011, Cancer Care Ontario (CCO) noted the potential benefits of smoking cessation in two seminal papers (3,4) and established a Steering Committee to create an implementation framework for a provincial smoking cessation initiative. The framework provided guidance on standard program elements, optional regional initiatives and central administrative support (5). Required elements included screening of all new ambulatory cancer patients using a standardized tobacco screening question to identify current and recent smokers (smoked within past six months); appointment of regional smoking cessation Champions; training for healthcare providers on the health benefits of smoking cessation for cancer patients; referral of patients willing to accept help in quitting; and submission of performance metric data. Optional elements of the framework were the intensity of the regional smoking cessation intervention and location of smoking cessation services (cancer centre or host hospital vs external provider). Central administrative support included a secretariat within the division of Prevention and Cancer Control, and a central database within Analytics and Informatics. Patients were to be screened for smoking status by a nurse or physician using the 5As (ask, advise, assess, assist, arrange) model of smoking cessation. The screening question asked is "Have you used any form of tobacco in the last six months?" To assess a patient's willingness to quit, the question asked is "Are you interested in learning about what is available to help you avoid smoking/using tobacco in the future?" Centres were to develop an inventory of regional smoking cessation resources. Potential resources included the Canadian Cancer Society's Smokers' Helpline – a quit line accessible by phone, web and text-based messages (6), trained pharmacists and family physicians, public health units and hospital and community-based smoking cessation clinics. In 2016, based on the Ontario initiative, the Canadian Partnership Against Cancer (CPAC) offered funding to all provinces to plan, implement or evaluate smoking cessation initiatives within cancer centres. Seven provinces and two territories made submissions in response to CPAC's request for proposals, leading to multiple new efforts within cancer agencies across Canada to assist cancer patients to stop smoking (7). Cancer Care Ontario used funding from CPAC to implement educational initiatives for both providers and patients (e.g., development of posters, multilingual brochures and videos), and to conduct a survey to determine best implementation processes. Monthly teleconferences with the regional Champions and annual face-to-face meetings to review progress and celebrate successes were critical success factors. Other factors that contributed to a successful implementation were strong leadership from the Steering Committee (now Advisory Committee), commitment from CCO executive and clinical leadership and the use of performance metrics and performance management. The initial five key performance metrics were: 1) proportion of ambulatory cancer patients screened for smoking status; 2) proportion of those screened who were current or recent smokers; 3) proportion of smokers advised to quit smoking; 4) proportion of those advised to quit who were recommended a referral to smoking cessation services; and 5) proportion of those offered a referral who accepted a referral. Two metrics (tobacco use screening and accepted a referral) are reviewed on a quarterly basis by senior CCO executives with the regional cancer centre leaders in order to drive change. Targets are set and performance metrics on smoking cessation are used, amongst others, to determine the overall ranking of a cancer centre within the province of Ontario. Most of the 14 regional cancer centres are achieving the target of 75% of new ambulatory cancer patients screened for tobacco use but fall below the target of 25% for acceptance of a cessation referral. This poor performance led to the adoption of an "opt-out" approach in which patients are automatically referred to smoking cessation services unless they specifically refuse. It is critical that busy oncologists not be overburdened, and that other frontline staff assume responsibility for implementing the smoking cessation program. "Scripts" can communicate to patients that the physician wants them to stop smoking in order to get the best results from treatment. Using 3As (ask, advise, act) also minimizes the burden on staff. CPAC has disseminated these learnings across Canada and engaged all 10 provinces and three territories in a 2019-21 funding initiative requiring an evaluation plan with 15 quality indicators. Already, a 10% increase in the level of implementation of evidence-based tobacco cessation programs within ambulatory cancer settings across Canada has occurred (56% adoption in 2017/18; 66% adoption in 2018/19). The approaches to smoking cessation vary by jurisdiction (7,) but the culture within cancer centres is evolving with a growing realization that it is never too late for a cancer patient to stop smoking, and acceptance that smoking cessation must be integrated into cancer treatment for it to be truly considered quality cancer care. References: Toll BA, Brandon TH, Gritz ER et al. AACR subcommittee on tobacco and Cancer. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Cancer Clin Cancer Res 2013; 19:1941 – 1948. Health consequences of smoking – 50 years of progress: a report of the Surgeon General, 2014. Available at http://www.surgeongeneral.gov/library/reports/50-years-of-progress/ Parson A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. 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ES20 STRATEGIES FOR CANCER PATIENTS TO HAVE OPTIMAL OUTCOMES
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ES20.03 TOBACCO CONTROL INTEGRATION IN CANCER CARE: THE JORDAN EXPERIENCE

F. Hawari

King Hussein Cancer Center, Amman/Jordan

Tobacco control is an integral component of any action plan that aims to reduce cancer incidence and mortality. Efforts at King Hussein Cancer Center, the only comprehensive cancer center in Jordan and the region, started 10 years ago. We sought to address the tobacco epidemic in Jordan on multiple fronts. In Jordan, tobacco prevalence exceeds 60%. About 50% of patients presenting with a cancer diagnosis are smokers. Integrating tobacco control in general and tobacco dependence treatment in patients suffering from cancer is pivotal. Smoking in patients with cancer has been shown to impact cancer treatment, increase complications from cancer treatment, increase cancer recurrence, increase the odds of development of secondary malignancies and eventually decrease overall long-term survival. Throughout the last 10 years our tobacco dependence tretament program grew in services and scope. The program addressed three major components required for tobacco control in cancer patients: First, patient-centered clinical tobacco dependence treatment service. Second, tobacco dependence treatment training and education for health-care providers. Third, research that addresses tobacco dependence in cancer patients. Our program provides 6 smoking cessation clinics every week dedicated mainly to our cancer patients. We have managed to address training needs for our staff by establishing a tobacco treatment specialist training program, the first ever to be accredited by The Council

for Tobacco Treatment Training Programs outside the USA. We studied outcomes of our treatment program and developed means to improve referral to smoking cessation clinics as well as improve the abstinence of our patients. In addition, we studied knowledge, attitude and perception of our health care providers working at our institution; a step especially important in a country where significant numbers of health care providers are smokers. Finally, we studied the impact of our tobacco dependence treatment program on the survival of our patients. Understanding the impact of smoking cessation on short-term survival of patients with cancer (2 years) highlights the importance of integrating such programs as part of the acute treatment phase of these patients. Cancer registry and smoking cessation clinic data for cancer patients diagnosed between 2012 and 2016 were analyzed. Approximately 19% of cancer patients were seen at the smoking cessation clinic. In a sub-sample of 2,387 patients, a significant two-year survival advantage was observed for smokers who had visited the smoking cessation clinic and confirmed that they had not smoked on at least two of their 3, 6 or 12-month follow-up visits (HR 2.8, 95% confidence interval [CI] = 1.7–4.5) relative to those who never went to the smoking cessation clinic. Those at the smoking cessation clinic who were abstinent at only one follow-up point also exhibited a survival advantage (non-abstainers at the smoking cessation had comparable survival to those who were not seen at the clinic). In conclusion, tobacco control in patients with cancer has an important role in the outcome and survival of these patients and must be integrated in their short and long-term plan of care.

Keywords: Tobacco, Cessation, cancer

ES20 STRATEGIES FOR CANCER PATIENTS TO HAVE OPTIMAL OUTCOMES
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ES20.04 TOBACCO CONTROL IN INDONESIA

S. Andarini

Faculty of Medicine University of Indonesia Persahabatan Hospital, Indonesia, Jakarta/Indonesia

Indonesia is the largest archipelago country of more than 17,000 islands over 5,200 km width, with population over 260 million makes it fourth most populated country in the world. As the largest economy in South East Asia, and member of G20 country, Indonesia's economy growth is second fastest growing economy after China. A changing in socioeconomic profile of Indonesia is in paralel with increase prevalence of tobacco smoking. Current data showed prevalence of current adult male tobacco smoking is 64.9% which predicted to increase to 79% in the year of 2030, while youth male prevalence of current tobacco use is 23.0% and current cigarette smoking is 21.4%. This number is highest for daily smoking rate in male, and two third Indonesian women are regularly exposed to second-hand tobacco smoke. Indonesia's life expectancy increased between 1990 and 2016 at 8 years to 71.7 years (7.4 years for male and 8.7 years for female). Double health burden due to mix of communicable and noncommunicable diseases. Of all proportional mortality, 35% are cardiovascular diseases, 12% cancer, 6% chronic respiratory diseases, 21% communicable, maternal, perinatal and nutritional conditions, 6% injuries, 6% diabetes. Noncommunicable disease are estimated to responsible for 73% of all death in Indonesia. The increasing leading causes of DALYs in 2017 as compared to 1990 are ischaemic heart disease, cerebrovascular diseases, diabetes, COPD, lung cancer. Tobacco listed as fourth risk factor of cause of death after high systolic blood pressure, dietary risks, high fasting plasma glucose. Tobacco control remains contradictionary within the country, despite strong national tobacco control program and government law implementation, Indonesia has yet to sign the WHO Framework Convention on Tobacco Control. National tobacco control program in Indonesia were transformed into specific national government objectives in tobacco control, such as national agency of technical unit for tobacco control, through MPOWER activities. **M**onitor tobacco use and prevention policies were implemented in Indonesian Law Article 26/2009 for Health and translated in Goverment Ordinant Article 109/2012 for the Security and Restriction of Addictive Substance of Tobacco and other several Presidential Decrees and Ministerial Decrees. **P**rotect people from tobacco smoke were implemented in Ministerial Decree, and Provincional Decree for for Tobacco Smoke Free policy. **O**ffer help to quit tobacco use were included in Ministerial of Health Decree and implemented in National Smoking Cessation Program. **W**arn about the dangers of tobacco were translated in Ministrerial Decrees Article 56/2017 for tobacco health effect warning in tobacco products and pictorial warning of tobacco smoke. **E**nforce bans on tobacco advertising, promotion and sponsorship were implemented through Indonesian Broadcasting Law Article 46 Clause 3B prohibits promotion of addictive substances, and **R**aise taxes on tobacco were implemented in Ministry of Finance Decree article 222/2017 regarding using, monitoring and evaluation of tobacco tax income. Moreover, Presidential Decree article 44/2016 and Ministry of Industry Decree Article 64/2014 for Regulation and Control of tobacco industry. Tobacco and related indutries argued against tobacco control policy by mentioning largescale effects of tobacco industry for Indonesian economy, and controlling tobacco industry will create massive unemployment, and economic crisis. Ministry of Industry of Republic Indonesia mentioned that tobacco industry creates 5.98 million employments, in which 4.28 million in manufacture and distribution, and 1.7 million people working in tobacco farming. In 2018, export rate of tobacco as cigarettes and cigar were 931.6 million USD, increasing 2.98% as compared to 2017. Tobacco company links closely to small medium enterprises as the tobacco company's social responsibility (CSR) program. One CSR program as retail community, was founded in 34 provinces, 408 cities which included 60,000 small business retail. Other tobacco related industry's CSR are including sports, youth and creative activities nationwide. Since 1968, Indonesia National Health insurance system was only implemented for formal sector, individual, civil servants, police and military member, but, since 2014, Indonesian Government launched Universal Health System called Jaminan Kesehatan Nasional (JKN) for all Indonesian. In 2017 approximately 180.7 million people are insured through JKN, 70% of total population and planned to reach 95% target in 2019. While tobacco industry tax income were IDR 153 trillion (approximately USD 10.9 billion) in the year of 2018, tobacco related lost due to early death and disease were IDR 4,200 trillion (one third of national GDP), and economy related lost due to tobacco consumption were approximately IDR 596 trillion. This should be bear in mind, that amount of tax income from tobacco company is incomparable to high burden loss due to tobacco related morbidity and mortality. 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Keywords: Tobacco Control

ES20 STRATEGIES FOR CANCER PATIENTS TO HAVE OPTIMAL OUTCOMES
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ES20.05 TOBACCO CESSATION AFTER CANCER DIAGNOSIS: DECLARATION FROM IASLC

J. Jassem

Medical University of Gdańsk, Gdańsk/Poland

Tobacco Cessation After Cancer Diagnosis: Declaration from IASLC Tobacco use is a well established cause of cancer, contributing to about 1 in 3 cancer deaths annually. Whereas detrimental effects of smoking are well recognized, the harms of continued smoking after a cancer diagnosis are undervalued (1). Smoking by cancer patients and survivors causes adverse treatment outcomes, including increased overall mortality, cancer related mortality and risk for second primary cancer, and considerably increases cancer treatment toxicity (2,3). The clinical effects of smoking after a cancer diagnosis has a substantial effect on increased cancer treatment costs (4). Smoking cessation after a cancer diagnosis can improve cancer treatment outcomes (1), but most cancer patients who smoke at the time of diagnosis persist in a smoking habit during long term follow-up (5). Unfortunately, oncologists often do not work with their patients to quit, and do not provide tobacco cessation assistance for continuing tobacco users (6,7). Large analyses of IASLC members demonstrate that although most oncologists recognize that smoking

causes adverse outcomes, approximately 90% ask about tobacco use and 80% advise patients to quit, only few offer assistance with quitting (8). There is a clear and unmet need to address tobacco use in patients with cancer. The diagnosis of cancer is "the teachable moment", allowing health care professionals the best opportunity to discuss with patients their lifestyle habits, including nicotine addiction (9). An enhanced focus on smoking cessation at the time of a cancer diagnosis and its active promotion may increase patients' motivation to quit. All patients should be screened for tobacco use and advised on the benefits of tobacco cessation. In patients who continue smoking after diagnosis of cancer evidence-based tobacco cessation assistance should be routinely and integrally incorporated into multidisciplinary cancer care. Smoking status should be a required data element for all prospective clinical studies, and clinical trials of patients with cancer should be designed to determine the most effective tobacco cessation interventions (10). Recognizing the critical importance of smoking cessation to increase the efficacy of cancer treatment, these postulates will be a subject of IASLC Declaration presented at the 20th World Conference On Lung Cancer in Barcelona. References: 1. Warren GW, Simmons VN. Tobacco Use and the Cancer Patient. In: Lawrence TL. editor. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 11th ed. Philadelphia, PA: Lippincott, Williams, & Wilkins, 2018. 2. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention, 2014. 3. Jassem J. Tobacco smoking after diagnosis of cancer: clinical aspects. Transl Lung Cancer Res 2019. doi: 10.21037/tlcr.2019.04.01 4. Warren GW, Cartmell KB, Garrett-Mayer E, et al. Attributable failure of first-line cancer treatment and incremental costs associated with smoking by patients with cancer. JAMA Netw Open 2019;2:e191703. 5. Westmaas JL, Newton CC, Stevens VL, et al. Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. J Clin Oncol. 2015;33:1647-52. 6. Burke L, Miller LA, Saad A, et al. Smoking behaviors among cancer survivors: an observational clinical study. J Oncol Pract 2009; 5: 6-9. 7. Warren GW, Marshall JR, Cummings KM, et al. Addressing tobacco use in patients with cancer: a survey of American Society of Clinical Oncology members. J Oncol Pract 2013; 9: 258-62. 8. Warren GW, Marshall JR, Cummings KM, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. J Thorac Oncol. 2013;8:543-8. 9. Gritz ER, Fingeret MC, Vidrine DJ et al. Successes and failures of the teachable moment: smoking cessation in cancer patients. Cancer. 2006 Jan 1;106:17-27. 10. Toll BA, Brandon TH, Gritz ER, et al. Assessing tobacco use by cancer patients and facilitating cessation: An American Association for Cancer Research Policy Statement. Clin Cancer Res 2013; 19: 1941-8.

Keywords: Tobacco Cessation, cancer

ES21 CURRENT STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH OLIGOMETASTATIC NSCLC
MONDAY, SEPTEMBER 9 15:45–17:15

ES21.01 OPTIMAL IMAGING FOR STAGING OF OMD

K. Irion[1], B. Hochhegger[2]

[1]*Manchester University NHS Foundation Trust, Manchester/United Kingdom,* [2]*Pontificia Universidade Catolica do Rio Grande do Sul (PUCRS), Porto Alegre/Brazil*

The role of imaging in oligometastatic disease in NSCLC: The current guidelines include a contrast-enhanced CT of the chest and upper abdomen as the baseline imaging investigation of lung cancer patients. A contrast-enhanced CT or MRI of the brain is indicated in patients who present with neurological signs/symptoms[1]. An additional investigation with PET-CT and MRI could be considered, "but only if their results could alter the treatment strategy"[2]. Lung cancer patients who are candidates to a radical treatment should be referred to a PET-CT if the initial investigations indicate a potentially curable disease[2]. Not infrequently, the identification of unsuspected metastasis on the PET-CT changes the initial staging to a stage IV, in a significant number of cases. A radical treatment can be considered for those with oligometastatic disease (OMD), which is defined by the National Cancer Institute as: "a small number of metastatic tumors in one or two other parts of the body"[3]. Discerning additional lung lesions as benign or malignant can be improved with the use of MRI[4,5]. Considering the limitations of PET-CT for detecting brain and liver metastases, MRI should be considered to avoid a futile extended radical treatment in this select group of patients[5]. This presentation will discuss the role of imaging in OMD patients being considered for extended radical treatment. 1. NICE. https://www.nice.org.uk/guidance/ng122/chapter/Recommendations#diagnosis-and-staging 2. Planchard D. et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology (2018) 29(4): iv192–iv237. 3. NCI. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/oligometastasis. 4. Basso Dias A. et al. Fluorine 18–FDG PET/CT and diffusion-weighted MRI for malignant versus benign pulmonary lesions: a meta-analysis. Radiology (2019) 290:525–534 5. Hochhegger B. et al. MRI in lung cancer: a pictorial essay. BJR (2011) 84:1003, 661-668

Keywords: NSCLC, imaging, Metastases

ES21 CURRENT STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH OLIGOMETASTATIC NSCLC
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ES21.02 BIOLOGICAL DISEASE CHARACTERIZATION OF OMD

D. Gerber

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Variation in the characterization of OMD

Trial	OMD characteristics	OMD timing
Iyengar et al (2017)	· ≤6 sites of extracranial disease (including primary) · ≤3 sites in liver or lung ·Up to 2 contiguous vertebral metastases considered a single site	After first-line therapy and without progression
Gomez et al (2016)	· ≤3 metastatic sites · Any N1-3 thoracic nodes considered a single site · Satellite lesions counted as separate sites	After first-line therapy and without progression
Parikh et al (2014)	· ≤5 metastatic sites	After first-line therapy and without progression
Cheruvu et al (2011)	· ≤8 metastatic sites	At time of initial staging
Khan et al (2006)	· 1-2 metastatic sites · Definitive (surgery and/or chemoradiation) treatment of thoracic disease	After treatment of thoracic disease

Recent years have seen a marked increase in interest in the concept of oligometastatic disease (OMD) in non-small cell lung cancer (NSCLC). Lacking a precise and consistent definition, OMD is generally considered to represent a relatively favorable clinical state, with more indolent biology, a limited number of disease sites, and potential for prolonged periods of disease control. Discussions of oligometastatic NSCLC area inexorably linked with management considerations, specifically the use of local therapies such as surgery and radiation therapy. There are numerous clinical and biological rationales to support such approaches: (1) disease progression most commonly occurs in original sites of gross disease[1]; (2) metastatic sites may propagate secondary metastases (parallel progression model)[2]; (3) solid tumors are composed of faster growing (sensitive) and slower growing (resistant) cell populations (Norton-Simon hypothesis)[3]; (4) resistance depends on spontaneous mutations and therefore increases with time (Goldie-Coldman hypothesis).[4] Nevertheless, several questions regarding the characterization and optimal management of OMD remain (Table 1). Up to how many sites of disease constitute an oligometastatic state? Does a "site" of disease comprise a single lesion or neighboring tumors? Does the anatomic site matter? For instance, brain metastases have historically been considered a more favorable location for definitive treatment of OMD, and their emergence may reflect pharmacokinetic failure rather than molecular evolution.[5,6] Additionally, there are likely meaningful clinical differences between OMD states depending on whether they are defined at diagnosis (de novo), after initial exposure to systemic therapy (induced), recurrence, or progression. OMD may

also have a distinct biologic phenotype. The metastatic cascade includes loss of cellular adhesion, increased motility, primary tumor invasiveness, entry into and survival in the circulation, and entry into and colonization of distant organs.[7] Tumor dormancy, regulated in part by interferon signaling, may impact the number, location, and timing of metastases.[8] Expression of genes that positively regulate the cell cycle may determine whether cancer growth occurs as polymetastasis versus oligometastasis. Ideally, ongoing and future clinical trials will collect biospecimens for discovery and validation of OMD biomarkers, thereby enabling the identification of cases most likely to benefit from OMD treatment paradigms. References: 1. Rusthoven KE, Hammerman SF, Kavanagh BD, Birtwhistle MJ, Stares M, Camidge DR. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 2009;48:578-83. 2. Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer 2009;9:302-12. 3. Norton L, Simon R. Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat Rep 1977;61:1307-17. 4. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727-33. 5. Hu C, Chang EL, Hassenbusch SJ, 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 2006;106:1998-2004. 6. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro Oncol 2011;13:1364-9. 7. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell 2006;127:679-95. 8. Dunn GP, Koebel CM, Schreiber RD. Interferons, immunity and cancer immunoediting. Nature reviews Immunology 2006;6:836-48.

Keywords: Oligometastatic, Non-Small Cell Lung Cancer, stereotactic radiation therapy

ES21 CURRENT STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH OLIGOMETASTATIC NSCLC
MONDAY, SEPTEMBER 9 15:45–17:15

ES21.03 INTERPRETING THE CURRENT DATA FOR LOCAL CONSOLIDATIVE TREATMENT IN THE SETTING OF OLIGOMETASTATIC DISEASE: WHERE DO WE STAND?

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Over the past 15 years, several retrospective and single arm prospective studies suggested a benefit for local consolidative therapy (surgery, radiation therapy, or interventional radiologic ablation) in the setting of oligometastatic disease. More recently, a small number of randomized trials have provided further data regarding the utility of an agressive approach with regard to progression free and overall survival. With the considerable amount of emerging evidence, it can be difficult to aggregate and interpret the major themes across studies. This presentation will discuss the composite data of local consolidative therapy in oligometastases, with a particular focus on high impact non-randomized studies and the limited randomized trials addressing this topic. The presentation will then provide major conclusions that can be the basis for analysis going forward. Attendees will thus be provided with a summary of the current evidence in the oligometastatic disease context and a basis for future directions.

ES21 CURRENT STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH OLIGOMETASTATIC NSCLC
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ES21.04 OPTIMAL SYSTEMIC TREATMENT OF OMD

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A series of randomized trials (1-3), 2 of them specifically conducted for non-small cell lung cancer (NSCLC) patients (2,3), have shown that those with OMD could get clinical benefit from the addition of local ablative therapy to the standard systemic treatment. All 3 trials demonstrated improvement of progression-free survival (PFS), and 2 of them suggested overall survival (OS) benefit (1,2). OS was the primary endpoint of the 2 studies. In each of the trials, however, the "standard systemic treatment" was not specified; in fact, it was merely described that the systemic therapy was determined by the treating oncologists from a set of "standard-of-care options" (3). It would be easy to imagine that the "standard-of-care options" for OMD in these trials would be no different from those for other stage IV diseases. For NSCLC, they are cytotoxic chemotherapies according to histologic subtypes, appropriate target-based therapies when the tumors have druggable targets, and, more recently, immune-oncology (IO) drugs when the tumors have potentially predictive markers, such as PD-L1 (4) or tumor mutation burdens (5). The question is, is the optimal systemic therapy of OMD really exactly same with the "standards" of other, more advanced, poly-metastatic stage IV NSCLC? First of all, let me suppose that the disease is truly oligo-metastatic, meaning there are no other metastatic foci than those which are detected by the image scans. In this scenario, you do not require systemic therapy at all; the disease is "cured" by a series of local ablative therapies, since no other diseases exist. However, in the vast majority of the patients, this would not be the case. Instead, there should be some other "microscopic" metastases which are undetected by the scans, evade the local therapies, and get relapsed without systemic treatment. By focusing on the "microscopic metastases" status, you could make analogy to post-operative adjuvant therapy. After the apparently curative surgery, without no "macroscopic" metastases in sight, we usually use conventional chemotherapies for prevention of recurrence. It is hoped that these "cytotoxic" drugs would eradicate the residual cancer cells, leading to true "cures". The long-tails of the survival curves, with increased number of long-term survivors with the adjuvant chemotherapy (6), show that this theory actually works. On the other hand, use of target-based drugs as post-operative adjuvant therapy has so far had only limited success (7,8). The PFS is elongated, without OS benefit (7). It appears that the patients do as good with the use of "targeted" drugs after relapse, and those drugs suppress tumors only as long as they are taken (9). In other words, they appear "cytostatic" and unable to "cure" the disease. Results of IO adjuvant trials are not yet available, but the "long-tails" of the survival curves of IO treatment make us hope for strong cytotoxic, "cure-oriented" effect. Therefore, when you aim at "cure" of the OMD, you should choose cytotoxic chemotherapies and/or IO drugs. However, if you are to "control" the disease and get some OS improvement, target-drugs are strong candidates. Let me see the topic from another viewpoint. The "local ablative" therapies employed in OMD are surgery and (stereotactic) radiotherapy. Which systemic therapy would make a better partner to which local therapy? Almost all target drugs are eventually turned ineffective, due to acquired resistance. However, in some cases, you could elucidate the resistance mechanism and conquer it (10), with modification of the target-based "precision" medicine. At present, investigation of the tumor itself is the most certain method, as expressed in the "tissue is the issue" slogan. Very often, however, tiny pathological specimens obtained from transbronchial or CT-guided biopsies are insufficient for the full molecular analysis. Surgical resection of the tumor has advantages both in terms of curative therapy and supply of ample specimens. It also minimizes the late effect on pneumonitis, which is a rare but dreadful toxicity of target-based tyrosine kinase inhibitors. Taken together, use of surgery would be (more) appropriate when you use target-based drugs in OMD. On the other hand, there are some clinical data that prior use of radiotherapy is associated with better outcome of IO therapy, implying the so-called "abscopal" effect (11). Investigations are on-going, which are aimed at showing synergistic effect of stereotactic radiotherapy and IO treatment (12,13). This could be applied in the management of OMD. So, in conclusion, what is the optimal systemic treatment of OMD? It depends on the aim of the therapy, cure vs elongation of PFS/OS, as well as on the choice of main local therapy, surgery vs radiotherapy. Future studies should specify the aim of the clinical investigation, not only to maximize the efficacy of local therapies and benefit to the patients, but to increase the statistical power of the clinical trials. References 1. Palma DA, et al. Lancet 2019 2. Gomez DR, et al. J Clin Oncol 2019 3. Iyenger P, et al. JAMA Oncol 2018 4. Sacher AG, Gandhi L. JAMA Oncol 2016 5. Goto Y. J Clin Oncol 2018 6. Pignon J-P, et al. J Clin Oncol 2008 7. Kelly K, et al. J Clin Oncol 2015 8. Zhong WZ, et al. Lancet Oncol 2018 9. Pennell NA, et al. J Clin Oncol 2019 10. Jänne PA, et al. New Engl J Med 2015 11. 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Keywords: Target-based therapy, cytotoxic chemotherapy, Immune-Oncology

ES21 CURRENT STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH OLIGOMETASTATIC NSCLC
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ES21.05 CLINICAL TRIALS TO ADVANCE THE FIELD OF OMD

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Oligometastatic disease (OMD) in non-small cell lung cancer (NSCLC) is a complex pathology. Four settings can be displayed where synchronous OMD (sOMD), occurring at the time of initial diagnosis, was the most evaluated in clinical trials. Other potential situations are oligorecurrence (rOMD), developed after optimal local control of a localised tumour, oligoprogression (pOMD) corresponding to a progression in a limited number of metastatic sites, and oligopersistant disease (peOMD) after/on systemic therapy. Several non-randomised phase II studies demonstrated the feasibility adding local ablative therapy (LAT) to systemic therapy in sOMD. Design, number of metastatic sites, type of LAT (chemoradiotherapy [CTRT], surgery, stereotactic radiotherapy [SBRT]) and endpoints largely differed among studies. A first pilot study (1) showed that surgery at the primary and the single metastatic sites after induction chemotherapy (CT) was feasible with 57% complete resection (R0) and 11 months median survival (MST). The same approach was recently confirmed in another prospective study with 71% R0 and 46.5% 5-years survival (2). Later, a phase II study conducted in The Netherlands and recently updated (3) demonstrated, when combining LAT (surgery or radiotherapy) to systemic therapy, MST of 13.5months but more essential, 5 and 6-years survival rates of 7.7% and 5.1% respectively. Other phase II studies, including NSCLC with <6 metastases, confirmed those results whether considering overall survival (4), metabolic response (5) or progression-free survival (PFS) (6). The first randomised phase II trial (RCT) compared, in sOMD with < 3 metastases non-progressing after CT, LAT (surgery, SBRT, CTRT) plus maintenance to maintenance only. The study closed early after first interim analysis and 49 randomised patients. Updated data confirmed improved PFS (14.2 months vs 4.4 months; p = 0.022) and MST (41.2 months vs 17 months; p = 0.017) favouring the LAT arm. A second small-sized phase II RCT closed early after interim analysis (8). 29 sOMD patients (≤5 metastases) not progressing after CT were randomised between SBRT plus maintenance or maintenance. Also median PFS improved from 3.5 months to 9.7 months (p = 0.01) in the LAT arm. All these data need confirmation in larger RCT. Four phase III trials are or will be ongoing. SARON (NCT02417662) is comparing standard CT alone to CT plus SBRT in sOMD with ≤ 3 metastases. In the OMEGA trial (NCT03827577), patients with synchronous or metachronous oligometastatic NSCLC (1-3 metastatic lesions) were considered for LAT (surgery or RT) or not in addition to systemic therapy. SINDAS (NCT02893332) is assessing the role of SBRT in addition to tyrosine kinase inhibitor in sOMD EGFR muted NSCLC with ≤ 5 tumoral sites (inclusive primary site; lymph nodes being considered as a metastatic site). Finally, HALT (NCT03256981) is a phase II-III RCT evaluating SBRT for pOMD during targeted therapy in NSCLC harbouring activating mutations. All these studies are presenting with various designs and primary endpoints, but also differences in staging procedures resulting in major difficulties for definite conclusions on the usefulness of LAT in OMD patients. In order having similar populations among clinical trials, we need that a common definition is used by all investigators. In this way, the EORTC Lung Cancer Group proposed a definition for sOMD based on a consensus from thoracic oncology experts (8). Using common definition and staging assessment, and finding predictive factors for a better patient's selection should be addressed in future clinical trials. 1. 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Keywords: Oligometastasis, non-small cell lung cancer

ES22 IMMUNOTHERAPY - DISCOVERING NEW AREAS
MONDAY, SEPTEMBER 9 15:45–17:15

ES22.01 IMMUNOTHERAPY IN RESECTABLE NSCLC

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Immune checkpoint blockade with inhibitors of the PD-1/PD-L1 interaction have improved survival substantially for patients with advanced non-small cell lung cancer. Despite many clinical trials of different combination regimens, the benefit from perioperative platinum doublet chemotherapy in resectable lung cancer is modest with an approximate 5% improvement in 5 year survival over surgery alone. This session will review the background of systemic therapy for resectable lung cancer and data reported to date with single agent PD-1 blockade, PD-(L)1-based immunotherapy combinations, and chemotherapy combined with anti-PD-1. Ongoing phase 3 clinical trials of neoadjuvant and adjuvant immunotherapy will be discussed and future directions both in novel science and clinical trials explored.

Keywords: immunotherapy, resectable, lung cancer, early stage lung, surgery immunotherapy

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ES22.02 A MILESTONE IN LOCALLY ADVANCED NSCLC

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Stage III NSCLC encompasses locally advanced tumours with infiltration of locoregional nodes and central thoracic structures and accounts for about a third of newly diagnosed NSCLC[1]. It represents the most advanced stage of NSCLC in which treatment is delivered with curative intent, but eventually more than 60% of patients die from their disease. Stage III NSCLC patients must strictly be discussed in a multidisciplinary tumor board, whereat the definition of resectability suffers from a certain heterogeneity across centers. Resectability is usually defined by the degree of invasion of lymph nodes, most often excluding multilevel or bulky N2 and N3 disease as well as invasion of the oesophagus, aorta and myocardium. Controversy exists on the role of surgery in stage III NSCLC since two large randomized trials investigated either induction chemoradiation therapy followed by resection versus radiotherapy[2], or induction chemotherapy followed by resection versus radiotherapy[3]. Both studies failed to demonstrate a difference in survival[2-5], however these treatment strategies are evidence-based and can be pursued in restectable NSCLC[6]. In the surgical scenario, randomised trials and meta-analyses have consistently shown that either adjuvant or neoadjuvant chemotherapy added to surgery results, with a better survival than surgery alone[7,8]. Adding preoperative radiotherapy to chemotherapy in patients with stage IIIA/N2 NSCLC did not improve the clinical outcome in a phase 3 randomised trial[9]. The role of adjuvant radiotherapy in stage IIIA/N2 after neoadjuvant chemotherapy followed by surgery has been evaluated in a unique randomized trial with awaited results (Lung ART, NCT00410683). Early NSCLC stages offer a theoretical unique curative scenario for the development of immunotherapy startegies, with limited disease volumes, a relative immune system preservation as well as unique oportunities for the investigation and assessment of new biomarkers. Perspectives, rational, hopes and ongoing attempts to combine immunotherapy in the surgical setting or alterenatively complementary to chemoradiation will be discussed, with a focus on locally advanced disease. References 1. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: What does it mean on main street? J Thorac Cardiovasc Surg 2018;155:356-9. 2. Albain

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Keywords: Stage III NSCLC, chemoradiation, neo-adjuvant immunotherapy

ES22 IMMUNOTHERAPY - DISCOVERING NEW AREAS
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ES22.03 NEW HOPE IN SCLC?

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Lung cancer is the leading cause of cancer-related death worldwide. Small cell lung cancer (SCLC) accounts for approximately 15-20% of cases. This aggressive tumor is characterized by rapid growth, early development of disseminated disease and dramatic responses to first line chemotherapy. For decades, first line therapy has traditionally included four to six cycles of platinum-based chemotherapy. While up to 80% of patients respond to first-line chemotherapy, the majority eventually relapse with a median survival of 8 to 12 months for patients with extensive stage disease and 12 to 20 months for those with limited stage disease. Until recently, topotecan was the only FDA approved second line therapeutic option. The shortcomings of traditional chemotherapy, as well as the limited role of targeted therapy in SCLC, led to the investigation of novel mechanisms to target lung cancer and specifically the discovery of immune checkpoint inhibitors. Immune checkpoint inhibitors work by blocking interactions between T cells and antigen presenting cells (APCs) or tumor cells. By inhibiting this interaction, the immune system is effectively upregulated and T-cells become activated against tumor cells. There are three major classes of checkpoint inhibitors. Ipilimumab and tremelimumab inhibit T-lymphocyte antigen-4 (CTLA-4); nivolumab and pembrolizumab target the programmed cell death-1 receptor (PD-1); and atezolizumab, durvalumab, and avelumab block PD-L1, the ligand of PD-1. Prior studies have shown lack of PD-L1 expression on tumor cells in patients with pulmonary and extra pulmonary SCLC. While PD-1 and PD-L1 are expressed in the tumor stroma of small cell carcinomas. [1] In addition PD-L1 has been shown to be prognostic in patients with SCLC.[2] The aggressive nature of SCLC is underscored by its high mutational burden, including loss of the tumor suppressor genes p53 in 75%–90% and retinoblastoma in almost 100% of tumors.[3] Higher tumor mutation burden has been associated with outcome in patients with select tumors treated with checkpoint inhibitor therapy, including non-small cell lung cancer. [4] Recently singly agent nivolumab and combination nivolumab and ipilimumab were shown to have activity in the second and third line setting for patients with advanced SCLC with response rates of approximately 10% and 20% respectively. Combination nivolumab and ipilimumab appeared particularly promising in patients with tumors with high tumor mutation burden and in 2018 nivolumab received approval in the third line setting for patients with advanced SCLC. [5] However, disappointingly Chekckmate 331, a large phase III trial of patients who had progressed on first line platinum-based chemotherapy, found nivolumab was not superior to topotecan or amrubicin in the second line setting. Recently a combined analysis of patients treated on the Keynote 158[6] and 028 trial[7] with pembrolizumab in the second line setting demonstrated a response rate of approximately 20% in patients, with a greater benefit in patients with tumors that were PD-L1 positive. In the first line setting, a single arm phase II trial demonstrated no benefit to maintenance pembrolizumab following induction chemotherapy in patients with advanced SCLC with a progression free survival of less than 2 months. [8] Earlier this year, a phase III trial (Checkmate 451) also found maintenance nivolumab with or without ipilimumab following induction chemotherapy in patients with advanced small cell lung cancer was not superior to placebo, suggesting this is not the optimal strategy in patients with advanced stage disease. Importantly, he Impower 133 phase III trial demonstrated combination chemotherapy with carboplatin, etoposide and atezolizumab was superior to chemotherapy alone in patients with advanced SCLC with a significant improvement in progression free and overall survival leading to FDA approval and a new standard of care for patients with advanced disease. [9] Two large phase III trials Keynote 604 and Poseidon are comparing a similar strategy with pembrolizumab and durvalumab respectively, with data anticipated in the upcoming year. While progress has finally been made. Limited tissue specimens in patients with SCLC remain a challenge and many unanswered questions remain including the optimal patient population in which these agents will have benefit (PD-L1 positive or negative, tumor mutation high or low), the optimal duration of therapy, the appropriate combinations (can we improve upon chemotherapy with a different checkpoint inhibitor), and the safety of these agents long term, particularly in patients with comorbid disease. References: 1. Schultheis, A.M., et al., *PD-L1 expression in small cell neuroendocrine carcinomas.* Eur J Cancer, 2015. 51(3): p. 421-6. 2. Ishii, H., et al., *Significance of programmed cell death-ligand 1 expression and its association with survival in patients with small cell lung cancer.* J Thorac Oncol, 2015. 10(3): p. 426-30. 3. Byers, L.A. and C.M. Rudin, *Small cell lung cancer: where do we go from here?* Cancer, 2015. 121(5): p. 664-72. 4. Rizvi, N.A., et al., *Cancer immunology. 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ES22 IMMUNOTHERAPY - DISCOVERING NEW AREAS
MONDAY, SEPTEMBER 9 15:45–17:15

ES22.05 ROLE IN THYMIC EPITHELIAL TUMOURS

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Although thymic epithelial tumours (TETs) are rare, they are the commonest primary tumours of the anterior mediastinum. TETs are heterogenous with histological classification into thymoma and thymic carcinoma. Subtypes of thymomas include A, AB, B1, B2 and B3 depending on the presence of spindle cells, the relative proportion of lymphocytes and abnormal epithelial cells. The commonest histological subtype of thymic carcinoma is squamous cell, others include sarcomatoid, adenocarcinoma, basaloid etc. The traditional Masaoka-Koga staging system is widely used to stage TETs (I: no breaching of capsule; II: invasion through capsule to involve surrounding fatty tissue; III: invasion into nearby organs; IV: pleural/pericardial spread or distant metastases), while TNM staging (T1a: with or without invasion into mediastinal fat; T1b: mediastinal pleura; T2: pericardium; T3/T4: nearby organs; N1: peri-thymic anterior mediastinal nodes; N2: deep thoracic or cervical nodes; M1a: separate pleural or pericardial nodules; M1b: distant metastases) has been introduced more recently. The prognosis of TETs depends on both histology and disease extent. Thymomas are usually more indolent with 10- year overall survival rate of >80% for

stage I and II, but thymic carcinoma confers poorer prognosis with 5-year survival of around 50% for stage III and 25% for stage IVa. The treatment of choice for early stage disease is surgical resection with curative intent. Concurrent chemoradiation can be considered for unresectable locally advanced TETs. 10-15% of resected TETs recur and radical radiation may be appropriate for local recurrence. In unresectable stage III and IV disease with spread to pleural and pericardial cavities or beyond, standard first-line systemic treatment is platinum-based chemotherapy, usually with cisplatin, doxorubicin and cyclophosphamide. Although TETs are reported to be chemo-sensitive with a response rate (ORR) of 50% for thymomas and around 20% for thymic carcinoma, they ultimately will progress and research into second-line treatments besides chemotherapy is important. Targeted therapies including sunitinib and everolimus with disease control rate (DCR) of >80% in previously treated TETs have been reported. Cancer treatment landscape has been rapidly evolving in recent years due to the successful development of PD1 blockade in many cancer types including melanoma, non-small cell lung cancer, bladder cancer, renal cell cancer, head and neck cancer, etc. The function of thymus during childhood in the production, differentiation and maturation of immunocompetent T cells together with the observation of high level of PD-L1 expression in normal thymus and TETs suggest a possible role of immunotherapy in TETs. Of 40 eligible patients with chemotherapy refractory thymic carcinoma in a phase 2 study, pembrolizumab provided an ORR of 22.5%, DCR of 75%, median progression-free survival (PFS) of 4.2 months, and median overall survival (OS) of 24.9 months with 1-year OS rate of 71%. Exploratory analysis in this study suggested an association of high-level PD-L1 with longer PFS and OS. A similar phase 2 study of pembrolizumab after at least 1 line of chemotherapy in Korea included 7 patients with thymoma and 26 patients with thymic carcinoma achieving an ORR of 27% with DCR of 100% in thymoma and ORR of 19% with DCR of 73% in thymic carcinoma. A phase 1 study with avelumab showed confirmed ORR of 29% with DCR of 86% in 7 thymoma patients and stable disease in the 1 thymic carcinoma patient. As thymus is involved in positive and negative T cell selection process for self-major histocompatibility complex molecules, thereby inducing self-tolerance avoiding auto-immunity, one third of thymoma is associated with autoimmune diseases, the commonest being myasthenia gravis. Other associated autoimmune conditions include systemic lupus erythematosus, pure red cell aplasia, syndrome of inappropriate anti-diuretic hormone secretion, bullous dermatoses autoimmune blistering diseases, polymyositis, dermatomyositis, pernicious anaemia, haemolytic anaemia, scleroderma, Sjogren's syndrome, rheumatoid arthritis, ulcerative colitis, Takayasu syndrome, Grave's disease etc. However, autoimmune disorders are much less likely to occur in thymic carcinoma. It is not surprising that a significant incidence of immune-related adverse events (irAE) is evident with immune-checkpoint inhibitors in the treatment of TETs with higher frequency of irAE in thymoma than in thymic carcinoma. 71% of patients with thymoma and 15% of patients with thymic carcinoma treated with pembrolizumab in the Korean study experienced grade 3-4 irAE including 12% hepatitis, 9% myocarditis, 6% myasthenia gravis, 3% thyroiditis, colitis, nephritis and myoclonus. The other phase 2 pembrolizumab study in patients with thymic carcinoma also reported similar incidence of 15% severe irAE with 5% myocarditis. IrAE was observed in 63% of patients in the phase 1 avelumab study with 38% myositis and 13% enteritis. PD-L1 status did not predict irAE. In conclusion, the main issue of PD1 blockade in TETs is common irAEs with higher frequency in thymomas. Therefore, immunotherapy is still not standard of care, needing further research to identify possible biomarkers to spare patients with less likelihood to benefit taking the risk of serious irAEs. There may be a role of immunotherapy in advanced TETs with aggressive pathology after failing chemotherapy, but thorough discussion with patients about the potential irAEs is warranted. References: Girard N, Ruffini E, Marx A, et al. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26:v40-v55. Miyamoto K and Acoba J. 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Keywords: thymic epithelial tumors, Immunotherapy, Immune-related adverse events

ES23 OPTIMAL MANAGEMENT OF N2 DISEASE IN THE ERA OF IO
TUESDAY, SEPTEMBER 10 11:30–13:00

ES23.01 MEDIASTINOSCOPY WITH INVASIVE STAGING: ARE THEY STILL CRUCIAL?

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There are more multiple treatment strategies for non-small cell lung cancer(NSCLC) that should be selected based on staging of the disease. Nodal status indicates N component of staging and studies invariably show that upfront surgical resection of patients with mediastinal lymph node involvement (i.e., N2 or N3) is not recommended. Evidence suggest that, T1-4N2-3M0-1c patients should firstly receive oncological treatment; otherwise, surgical treatment could be deemed to be futile. Accordingly, mediastinal lymph node involvement prediction as accurate as possible is recommended before any treatment planning. PET-CT, Endobronchial ultrasonography-transbronchial aspiration (EBUS-TBNA), endoscopic ultrasound-guided-fine-needle aspiration(EUS-FNB) have all inherent limitations. Mediastinoscopy has been defined to be gold standard for preoperative disclosure of mediastinal lymph node metastasis. However, small biopsy material due to being an incisional biopsy, practically low number of explored mediastinal stations (usually median number of 2 or 3) led to approximately 10% of false negativity rate. Also studies showed that, even the fact that, mediastinoscopy has been recommended to be performed in all patients except the patients with non-discrete lymph node involvement or in the patients with peripheral cT1a-cN0M0 patients, a fraction of thoracic surgeons prefer to comply with the published guidelines. Video-assisted mediastinoscopy lymphadenectomy(VAMLA) was developed to reduce the false negativity rate below statistically non-significant levels (below 5%). It involves dissection of at least 5 lymph nodes stations and some evidence suggest that, VAMLA is associated with better survival rate beyond selection bias phenomenon. Transcervical extended mediastinal lymphadenectomy (TEMLA) is a technically more advanced mediastinal lymph node dissection procedure that is a definition of a resection of lymph nodes from #1-9 bilaterally including aorticopulmonary and anterior mediastinal lymph nodes. The accuracy of TEMLA has been reported to be 98.4%. Taking all those achievements into consideration, VAMLA or TEMLA or at least video-mediastinoscopy should be performed before selecting a therapeutical option in a patient with potentially resectable operable NSCLC. However, recent advancements in computational science could propose us that, possibly, there is enough information for us to predict mediastinal lymph node positivity without performing any invasive procedure. Artificial Intelligence (AI) is accomplished by computers that use algorithms, pattern matching, rules, deep learning and cognitive computing to approximate conclusions using previously defined analog or digital parameters. AI aimed to mimic the brain's neural networks. It uses multiple layers of non-linear processing units to teach itself how to understand data classifying the record or making predictions. In a study, we aimed to evaluate the value of artificial neural network(ANN) for mediastinal nodal metastasis, by using only clinical and radiologic data. In our data set, ANN predicted mediastinal nodal involvement perfectly (AUC:1) in both training and test groups. When we used 'traditional' univariate and multivariate analyses, younger age (<65) (AUC:0.59) and higher SUVmax (>2.5)(AUC:0.67) were associated to be mediastinal nodal involvement. ANN prediction was better and it was even more sensitive than VAMLA! However, specificity of ANN resulted to be less than 0.9 in some training analyses. The major limitations of ANN include its variability, non-transparency and non-consistency. Nevertheless, there is a possibility that, ANN could provide better predictions and it may help us to identify and narrow down the patients who need invasive staging. However, the usage of ANN in medicine has been continuously expanding. Future studies are needed to understand the exact place of ANN in mediastinal staging.

Keywords: Artificial Intelligence, Non-small cell lung cancer, Mediastinal staging

ES23.02 WHICH N2 PATIENTS ARE CANDIDATES TO SURGERY IN THE ERA IF I/O?

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The role of surgery in patients with pre-resection documented N2 disease remains a subject of controversy. In some institutions, any clinical N2 disease identified preoperatively is considered non-surgical and these patients are offered upfront definitive chemoradiation therapy (DefCRT) without planned resection. In other institutions, a selective approach to N2 patients will consider surgery as part of a multimodality approach where surgery may be offered first followed by adjuvant cytotoxic chemotherapy (AC) with or without sequential post-operative radiation therapy (PORT), or where surgery will be offered after induction chemotherapy or induction chemoradiation therapy. Due to variability in N2 disease presentation, factors determining this selective approach vary between institutions and may include the bulk of N2 nodal involvement (size), extent of N2 involvement (single vs multistation, microscopic vs macroscopic), the presence or absence of extracapsular nodal involvement, the need to perform a pneumonectomy or not, and mediastinal sterilization after induction therapy. Historically, response to induction therapy with clearance of N2 nodal involvement following induction therapy has been shown to bode for a better prognosis after surgical resection. Unfortunately, even after complete resection following induction therapy, many patients develop distant metastases, with brain metastases prevailing. In 2018, the PACIFIC trial showed that adding an immune checkpoint inhibitor (IO) durvalumab for up to one year after completion of DefCRT in non-surgical stages cIIIa and cIIIB patients led to a significant and unprecedented overall survival in this population of patients. (Antonia, NEJM 2018) In patients with resectable NSCLC (cIIIA and less), recent small phase I clinical trials of either single-agent induction IO (Forde, NEJM 2018) or concurrent induction chemoimmunotherapy (Provencio, JTO abst. 2018) given before surgery have demonstrated feasibility, acceptable toxicity, and unprecedented pathological response rates. It remains to be seen if these pathologic responses will translate into improved overall survival in this patient population. Extrapolating from these early observations, one may think that induction IO (likely with concurrent cytotoxic chemotherapy) may possibly allow us to offer surgery to a larger proportion of patients with clinical N2 disease in the future as we observe higher response rates to induction therapies which may translate in better survival. Others may want to extrapolate from the Pacific trial results and hypothesize that surgery followed by adjuvant IO may become a desirable option. Though encouraging, there is a paucity of data to help guide us in the incorporation of IO therapy perioperatively for patients with clinical N2 disease. As such, the role for IO in multimodality treatment for N2 disease remains undefined. Unknown are the true impacts of periop IOs in this patient population and what is the optimal combination and timing of these multimodality treatments. There are more unanswered questions than established guidelines: (1) whether "IO first then surgery" is superior to "surgery first then adjuvant IO", (2) whether an induction IO strategy followed by resection would be superior to DefCRT followed by IO in this population of potentially resectable cN2 IIIA patients, (3) if induction IO is shown to be superior, how many cycles preop, (4) do we need to continue IOs post op, if so, for how long, (5) whether there will be a role for surgery after major response to IO, and (6) how will we select patients for resection when major pathological response rates will be in the 80% range (7) do we need to utilize biomarkers, tumor mutation burden, or genotyping in patient selection, (8) What is the best biomarker to predict response, among other questions. The easy answer at this stage is to treat these patients on trials where the impact of IOs can be rigorously studied. Ideally, I personally would want to compare: (1) Induction vs adjuvant IOs for surgical patients with cN+ disease, (2) Induction IO followed by resection vs DefCRT followed by IO. The duration of periop IO also needs to be evaluated and these studies should include cost analysis as well. For the surgeons, as systemic treatments improve, our duty is to perform sound oncological surgery with minimal morbidity and minimal to absent mortality. I believe that preop IO may allow us to consider surgical resection for a larger proportion of cIIIA N2 patients in the future.

Keywords: Immunotherapy, stage IIIA NSCLC, surgery

ES23.03 IS CT/RT FOLLOWED BY I/O THE STANDARD OF CARE FOR ALL N2 AND SELECTED N3 PATIENTS?

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Background: Immunotherapy consolidation with PD-L1-Ab has changed the current standard treatment for unresectable patients with stage III NSCLC (in Europe with PD-L1-exp by IHC > or = 1%) who are not progressing following definitive chemoradiotherapy[1,2,3]. More and more issue comes up for which patients this new strategy should be adopted, and for whom these data do not represent the new standard. Here we will try to analyze current evidence of stage selection for this multimodality approach. Methods: We analyzed the existing evidence on outcome results of stage III NSCLC subsets based on the new 8th-version of the IASLC/UICC staging classification and expert consensus[4,5] and current outcome data on stage III subsets within large landmark randomized trials[6,7,8,9,10] and possible permutations of chosen multimodality treatment approaches. Results: The PACIFIC Trial included only unresectable patients with stage IIIA and stage IIIB (based on the old UICC7 staging classification)[1,2,3]. No detailed data on T- and N-subgroups as well as transferring the data to the new UICC8 stage subsets IIIA/IIIB/IIIC were given in the manuscript[1]. Definition of "unresectable stage IIIA and IIIB" was probably best carried out as "individual local descision within tumor boards including thoracic surgeons to define disease resectability status". Nevertheless, no clear definition on selection for unresectable disease is given in the trial description of the PACIFIC publication. The overall two- and three-year-survival results were excellent and showed a significant and clinically meaningful benefit for patients receiving PD-1-antibody consolidation for one year[2,3]. Based on current evidence and consensus[4,5] about 15 to 20% of stage III patients are still ocnsidered to be potentially resectable. The majority of these belong to the IIIA(N2) diasease subset. Only one recently published clinical phase-III trial included subgroups with T4N0 (stage IIIB UICC7/stage IIIA/UICC8)[8]. Outside of multimodality groups with specific expertise, stage IIIB(UICC8) and stage IIIC(UICC8) are considered unresectable and would definitely be put on definitive chemoradiotherapy protocols. Only three large randomized trials[6,7,8] included resectable patients subsets of stage IIIA(N2)-disease (INTERGROUP 0137, SAKK, ESPATUE). The treatment strategies within these trials were induction chemotherapy followed by surgery versus induction chemotherapy followed by radiation and followed by surgery[6], induction chemoradiotherapy followed by surgery versus definitive chemoradiotherapy[7]or induction chemotherapy followed by concurrent chemoradiotherapy and surgery versus induction chemotherapy followed by concurrent chemoradiotherapy and definitive chemoradiation boost[8]. All three trials including surgery in at least one of the randomization arms gave a detailed description of T- and N-subgroups in their overall patient characteristics. All three clinical trials had PET-CT and detailed mediastinal staging techniques included into the initial patient selection descision (either mediastinoscopy or recently EBUS). All three trials had excellent overall survival outcomes in each of their randomization arms. Five-year survival results were somewhere betweeen 20% and 44% observed in the three randomized trials. In all three trials no significant difference was noted for OS between the different randomization arms while the OS results in all treatment groups of the studies can be considered excellent. However, in all three trials a low accrual rate was generally noted, and the overall duration of the clinical trials was around six to eight years in all three, pointing to a considerable selection procedure of patient inclusion. The two large randomized clinical phase-III trials investigating modern chemoradiation techniques[9,10] included per definition only "unresectable stage IIIA and IIIB patients subsets" (following the old UICC7/UICC6 classification). However, in both trials (PROCLAIM and RTOG 0617) no detailed TN-subgroups were given, but they included rather IIIA and IIIB definitions based on PET-CT staging as well as biopsy confirmation of N2- or N3-tumor-positive lymph nodes at staging work-up. FIve-year overall survival data turned out somewhere around 30% of the initially included patient groups within the two trials. The only group that showed a significantly worse outcome was that with the higher total radiation dose of 74 Gy in the RTOG study (no comment on this issue here). Nevertheless, all survival outcomes showed overall excellent five-year survival data in these two chemoradiation trials, too. Median OS data were between 25 and 29 months observed. There are considerable difficulties to compare all six randomized trials (PACIFIC, RTOG

0617, PROCLAIM, SAKK-TRIAL, INTERGROUP 0139, ESPATUE) based on the difficulties to compare patient selection and included TN-subgroups. Thus the above mentioned relevant differences in patient selection and accrual between the pure chemoradiation trials and the randomized trials including surgical arms cannot be overcome by comparing TN-data from these studies. All three definitive chemoradiation trials did only give IIIA and IIIB subset numbers of their patient population. However, patient accrual was much faster in all three definitive chemoradiation studies, pointing to a less selective patient inclusion into these trials. Some of the differences in the observed OS and PFS results noted could in fact be based on these different patient selection procedures rather than on differences between the individual treatment strategies. Conclusion: Based on a differential analysis of the recent five largest randomized phase-III trials with multimodality treatment of stage III NSCLC, we cannot readily compare the patient selection for "pure" concurrent chemoradiotherapy trials on one hand, to that within multimodality trials including surgery in at least one trial arm on the other side. This strongly points to the fact, that we cannot currently widen up any indication for an inclusion of immunotherapy for subsets of patients with potentiallly resectable stage III NSCLC. Patient with resectable stage III (mostly IIIA) should either be treated within multimodality protocols including surgery (based on the local expertise) or should be offered to participate within clinical trials that try to implement immunotherapy with PD-1 or PD-L1 antibodies into this multimodality setting including surgery. Several clinical studies wirth induction chemoimmunotherapy followed by surgery or induction chemoimmunotherapy/chemoradiationimmunotherapy followed by surgery are currenlty being performed by different multimodality treatment groups. The practice-changing results of the PACIFIC trial for unresectable stage III disease leave us very enthusiastic, that this new approach could also improve the results for potentially resectable stage III patients groups in NSCLC. [1]Antonia, NEJM 2017 [2] Antonia, NEJM 2018 [3] Gray, ASCO 2019 [4]Goldstraw, J Thorac Oncol 2016 [5]Eberhardt, Ann Oncol 2015 [6]Pless, Lancet 2015 [7]Albain, Lancet 2009 [8]Eberhardt, J Clin Oncol 2015 [9]Senan, J Clin Oncol 2016 [10] Bradley, Lancet Oncol 2015

Keywords: Stage III, combined modality therapy, Lung cancer

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ES23.04 OPTIMAL SUPPORTIVE CARE DURING AND AFTER CONCURRENT CHEMORADIOTHERAPY AND I/O

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Concurrent chemotherapy and radiotherapy (CCRT) is the treatment of choice for most fit patients with locally advanced NSCLC. Recently, adjuvant durvalumab has improved the overall survival further. However, CCRT is a toxic treatment. Treatment-related deaths occur in a few percent of patients and many suffer severe side effects that require medical interventions and even in-patient care. In contrast to extensive research on infections and emesis, most data on other important side effects are scant. Two examples of this are acute esophagitis and cough and dyspnea. *Correlation between dysphagia and endoscopic findings* In a prospective trial with 38 patients receiving radiotherapy alone for lung cancer, an endoscopy was done during radiotherapy when patients had received a dose of 30-40 Gy on the esophagus. Eighteen patients (47 %) had dysphagia of any grade, but only in 12 of them (67 %) endoscopy showed esophagitis. Of the remaining 20 patients without complaints, 5 (25 %) had endoscopic signs of esophagitis. Gastritis was found in 18 patients (47 %), with or without esophagitis. In another study, 82 NSCLC patients were evaluated by endoscopy. There was a good correlation between the RTOG clinical score for dysphagia and the endoscopic findings (Spearman rank correlation coefficient 0.428; p< 0.0001). All patients with clinical grade 3 dysphagia had endoscopic grade 2 or 3 esophagitis. Also in case of RTOG grade 2 dysphagia, all patients had endoscopic esophagitis, although 40 % had endoscopic grade 1 and 27 % had endoscopic grade 3 esophagitis. Of patients with or without only mild (grade 1) dysphagia, 11 % showed grade 3 endoscopic esophagitis. Sixteen percent of patients has esophageal candidiasis, but its relation with dysphagia or endoscopic grade of esophagitis was not reported. No data on the incidence of gastritis were given. *Effect of radiotherapy on esophageal motility* An impaired esophageal motility may also lead to dysphagia. The esophageal transit time (ETT) before and during (10 Gy and 30 Gy) radiotherapy alone was evaluated in 11 patients. An increase in the ETT was seen in 9 of 11 patients (82%) (p<0.05). The ETT was also investigated in 18 breast cancer patients receiving radiotherapy to the inner quadrants of the breast using a dose of 50 Gy/ 25 fractions. The cranial part of the esophagus received a mean dose of 6 Gy/ 25 fractions, and the distal two-thirds a mean dose of 15.3 Gy/ 25 fractions. Comparing the ETT before and after radiotherapy, for the upper third and the distal two-thirds of the esophagus, the ETT increased from 4.77 ± 1.08 sec. to 6.92 ± 2.15 sec., from 11.22 ± 2.85 sec to 23.30 ± 5.65 sec. and from 11.61 ± 2.97 sec. to 23.74 ± 5.70 sec., respectively (p<0.001). Because of the motility impairment even at very low radiotherapy doses, the use of proton pump inhibitors is logical. *Prevention and treatment of acute esophagitis* In a randomized study with advanced NSCLC patients, treated with radiotherapy alone or radiotherapy plus amifostine, amifostine reduced the incidence of esophagitis in week 4 during radiotherapy from 42 % (31/73) to 4 % (3/73) (p<0.001), without decreasing the tumor response 2 months after treatment. In a larger randomized series of the RTOG, 243 stage II-III NSCLC patients were enrolled and randomized between carboplatin-paclitaxel concurrent chemo-radiotherapy with or without amifostine. No significant differences between the arms regarding overall survival, disease-free survival or long-term toxicity were observed. In another study, 60 stage III NSCLC patients were randomized between concurrent carboplatin-paclitaxel and radiotherapy with or without amifostine. No significant difference in esophagitis was observed. Therefore, amifostine has no consistently proven effect of preventing acute radiation-induced esophagitis. In a small double-blind study, 14 stage III NSCLC patients were randomized between placebo or prophylactic indomethacin. Endoscopically-assessed esophagitis seemed to be milder, but no firm conclusions could be drawn. Another small, placebo-controlled randomized trial, investigated naproxen in 28 stage III NSCLC patients receiving radiotherapy alone. There were no differences in clinical or endoscopic esophagitis rates. Eight patients (29 %) developed esophageal candidiasis, with no difference between the groups. A placebo-controlled randomized trial could not demonstrate a beneficial effect of sucralfate on dysphagia. In NRG/ RTOG 1012, patients were randomized between prophylactic Manuka honey, either in liquid or in lozenge form, and standard supportive care during concurrent chemo-radiotherapy for NSCLC. Standard supportive care consisted of a compound containing viscous lidocaine, an antacid such as magnesium aluminum oxide, and liquid or solid oxycodone, 5–10 mg, every 3 hours as needed. The primary endpoint was patient-reported pain on swallowing utilizing an eleven point (0–10) scale at 4 weeks (Numerical Rating Pain Scale, NRPS). Fifty-three patients were randomized to supportive care, 54 randomized to liquid honey and 56 to lozenge honey. There was no significant difference in the primary endpoint of change in the NRPS at 4 weeks between arms. There were no differences in any of the secondary endpoints except for opioid use at 4 weeks during treatment between the supportive care and liquid honey arms (p=0.03), with 52 % vs. 67 % of patients experiencing no pain with liquid honey. No difference was observed with lozenge honey. with more patients on the supportive care arm taking opioids. However, the differences were only observed at 4 weeks and not at the end of radiotherapy. From this example, already, it is clear that more in-depth knowledge of the physiopathology of radiation injury is needed. A joint task force between ESTRO and ESMO members will address a spectrum of supportive care interventions in patients receiving concurrent chemotherapy and radiotherapy for lung cancer.

Keywords: Non-Small Cell Lung Cancer, supportive care, esophagitis

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ES23.05 THE FUTURE OF SYSTEMIC THERAPY IN STAGE III

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Stage III NSCLC comprises a very heterogeneous group of patients with regard to tumor extent, prognosis, and treatment options. It represents between 25-30% of NSCLCs and the majority of them are unresectable. Potentially curative treatment of unresectable stage III necessitates adequate locoregional control as well as control of the micrometastatic disease that is likely to be present in most patients. Several randomized clinical trials dating back

as far as 20 years and metanalysis have shown the superiority of cisplatin-based chemotherapy and radiotherapy over radiotherapy alone. Sequential versus concomitant approach has been directly compared in several trials; almost all of them showed a trend in favor of concomitant treatment. These results clearly supported the use of concomitant chemoradiotherapy as standard of care for these patients[1] fit enough to tolerate the risk of severe toxicity, particularly grade 3-4 esophagitis that is the most common adverse effect of the concomitant approach. Attempts to improve outcomes have included studies of radiotherapy dose escalation and new chemotherapy combinations, as well as adding biological agents and cancer vaccines to existing regimens. Technical radiotherapy modifications, including intensity-modulated radiotherapy and particle beam therapy, have also been investigated. In spite of it, the long-term survival has remained largely unchanged for many years, with only 15% of patients are alive at 5 years. In the last years, immune-checkpoints blockade revolutionized the standard of care of metastatic NSCLC. The PACIFIC study is an randomized, double-blind, placebo-controlled, multi-centre, phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in patients with locally advanced, unresectable stage III NSCLC who have not progressed following definitive, concurrent platinum-based chemotherapy and thoracic RT. The study was positive for both primary endpoints progression- free survival (HR=0.51; 95%CI: 0.41-0.63)) and overall survival (HR=0.68; 95%CI: 0.49-0.99; p=0.00251)[2]. This benefit was observed in both non-squamous and squamous histology as well as in both stages IIIA and IIIB NSCLC. Based on this study, there is a new standard of care for unresectable stage III NSCLC patients. Nevertheless, improving outcomes for patients with stage III disease remains a challenge and many questions have to address in well-designed clinical trials. 1.- Postmus PE, Kerr KM, Oudkerk M et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 Suppl 4: iv1-iv21. 2.-Antonia SJ, Villegas A, Daniel D et al. Overall survival with Durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018; 379: 2342-50

Keywords: durvalumab, stage III, chemoradiation

ES25 LIQUID BIOPSY
TUESDAY, SEPTEMBER 10 14:30–16:00

ES25.01 LIQUID BIOPSY: STATE OF THE SCIENCE

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I. The present. Molecular diagnosis in cancer certainly requires the analysis of a tumor biopsy. However, in lung cancer, there is still a 20- 30% of tissue failure rates for tumor genotyping in routine pathological samples. As a consequence, liquid biopsy (LB) has emerged as a valid alternative source of information for the analysis of tumor specific alterations. LB refers to specimens obtained from body fluid such as blood, urine, saliva, cerebrospinal fluid, among others. In the complex matrix represented by blood, the main clinical developments have focused on the analysis of: i) circulating tumor DNA (ctDNA), which represents a small part of cell free circulating DNA released from tumor cells and, ii) circulating tumor cells (CTCs), defined as disseminated cancer cells in the bloodstream. Each of these materials offers unique opportunities to test different biomarkers and to analyze characteristics of the tumors. The advantages of the use of blood samples are clear: i) it is a minimally invasive way to get relevant tumor information, ii) serial samples can be obtained capturing tumor evolution in real time, iii) LB abrogates the limitations associated with tumor heterogeneity, since nucleic acids or tumor cells present in circulation recapitulate the information belonging from different tumor locations (primary tumor and metastases), iv) the development of new sensitive assays for analyses of ctDNA and CTCs allow the assessment of minimal residual disease and v) the costs of LB analysis are comparable with other molecular biology techniques already used in the clinical setting in addition to the reduced risks of complications associated with tissue biopsy. All these factors accelerated the implantation of LB in the clinical practice in oncology in several scenarios, especially in lung cancer. I.1.Lung Cancer. Clinical applications of liquid biopsies. At present, LB is no longer a promise but a reality allowing better treatment selection, real-time monitoring of lung cancer patients and early detection of acquired resistances. Figure 1 highlights the biological basis of LB as a source for biomarkers analysis and key clinical applications in lung cancer. •Personalized therapeutics/ Resistance detection: regarding the detection of tumor-associated genetic alterations in LB samples, there are a lot of scientific data demonstrating similar response rates to targeted therapies than the obtained in tissue biopsies. In particular, in the context of NSCLC patients with progressive or recurrent disease during treatment with TKIs, the IASLC guidelines suggest the use of LB-first algorithm to detect resistance mechanism. For those lung cancer patients receiving immune-based therapeutic treatments, recent data show that assessment of tumor mutational burden in plasma (bTMB) correlated with the values found in tissue and predicts efficacy of immune-checkpoint inhibitors. •Detection of minimal residual disease: Persistent detection of ctDNA or CTCs after local therapy or after adjuvant treatments was found associated with poor clinical outcome. In this particular clinical setting it is important to highlight that sensitivity of the methods used for ctDNA or CTCs evaluation really matters. •Real-time monitoring of disease: this is one of the most interesting application of LB, since tissue biopsies are intrinsically unable to capture tumor heterogeneity while ctDNA can comprehensively recapitulates clonal evolution over time, allowing to early detect and track the emergency of resistance mutations. II. The future. Current assays for LB analysis do not meet all the needs required for the fully implementation of the Precision Oncology. There is still room for improvement to reach its maximum informative potential. Hopefully, studies on exosomes, platelets, cfRNAs, metabolites, will help to have a more integrative picture of tumor status at each time it is evaluated. One of the clinical applications in which LB is called to play a key role is in the screening and early detection of lung cancer. In this regard, there are some interesting data coming from multiparametric (DNA and protein) plasma analysis. However, caution is required since there are still some important issues, such as clonal hematopoiesis, that need to be further considered. Another important challenge for LB is standardization. It is necessary to cross-validate platforms, standardize pre-analytical issues, compare sensitivity of different methodological approaches and also to work in the harmonization of bioinformatic tools for data analysis. It is clear that in the near future, tests based on the analysis of "liquid biopsies" will be more generalized, offering complementary information to tissue biopsies and providing valuable information to early diagnose lung cancer, to detect molecular progressions even prior to radiographic or clinical progression and as a source for real-time treatment monitoring. References Alix-Panabières C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. Cancer Discov. 2016;6(5): 479-91. Bardelli A, Pantel K. Liquid Biopsies, What We Do Not Know (Yet). Cancer Cell. 2017; 31(2):172-179. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. 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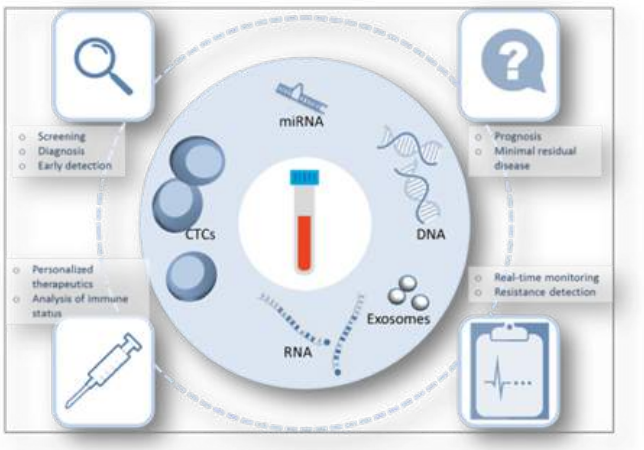

Keywords: liquid biopsy, ctDNA, circulating tumor cells

ES25 LIQUID BIOPSY
TUESDAY, SEPTEMBER 10 14:30–16:00

ES25.03 LEVERAGING THE QUANTITATIVE NATURE OF CFDNA GENOTYPING FOR LUNG CANCER CARE

C. Paweletz

Dana-Farber Cancer Institute, Boston/United States of America

Nearly 70 years after the discovery of free-floating DNA in the blood, also known as cell free DNA (cfDNA) (1), plasma genotyping of cfDNA is transforming cancer care with promise in non-invasive genotyping, early diagnosis, and disease prognostication by detection of minimal residual disease (MRD). At present the most widespread use of cfDNA in lung cancer is detection of mutations in *EGFR* and *KRAS* or re-arrangements in *ALK*and *ROS1* in the metastatic setting. In fact, the only FDA approved liquid biopsy test among all cancers is Roche's Cobas plasma EGFR mutation test for non-small cell lung cancer. (NSCLC) (2), while many diagnostic companies have developed PCR or next generation sequencing (NGS) laboratory developed tests that are commonly reimbursed by payors in house. Next-generation sequencing (NGS) permits broader inquiries, allowing assessment of the mutation status of thousands to millions of bases. The use of cfDNA in early cancers is confounded by the fact that early detection demands ultra-sensitive assays of low abundant biological markers. As proof of concept Bettegowda et al. performed digital PCR on cfDNA of 640 cancer patients of varying cancer type and stage. Intriguingly they found that rates of tumor DNA differed by tissue of origin, and 47% of stage I cancers and 55% of stage II cancers had detectable circulating tumor DNA (ctDNA) (3). An observation that as we and others have confirmed is a main source for false negatives (4). At present, NGS efforts are focused either on targeted approaches using either barcoded targeted amplicon (TAmSeq) or hybrid capture approaches (CAPP-Seq) covering 10Mb to 50Mb at reported sensitivities of 0.01% to 0.50% for fit for purpose build NGS assays. However, pushing assay sensitivity increases false positives. Recently, we and other have found that false positives are reported in many commercial assays and are routinely attributed to 'tumor heterogeneity'. These can be attributed to DNA shed from normal cells, including germline variants or non-cancerous somatic variants from clonal hematopoiesis (CH) (5-8). The latter is particularly challenging because CH can involve cancer-associated genes (e.g. TP53, JAK2, KRAS). To limit false positives and to investigate the common link between cancer-related mutations within the blood and underlying malignancies broad sequencing of cfDNA should also detect other cancer-related mutations, such as inactivating mutations in tumor suppressors and include assaying of the patients blood cells to filterout germlines. Thus, deep and broad sequencing could provide sensitivity needed to detect low levels of cfDNA alterations in early stage patients. Indeed, Abbosh et al. perform multi region whole-exome sequencing of early-stage NSCLC tumors to show an abundance of clonal mutations in these tumors (9). Abbosh and colleagues provide an intriguing solution to this issue by requiring the detection of two or more SNVs for the determination of the presence of cancer.In this presentation we present factors affecting ultras sensitive assays with particular emphasis on interpretation of commercial tests and future use of cfDNA assays in early cancers.
1. Mandel P and Metais P. Les acides nucleiques du plasma sanguin chez l'homme [in French]. C R Seances Soc Biol Fil 1948;142:241-243. 2.Center for Drug Evaluation and Research. Approved Drugs - cobas EGFR Mutation Test v2 [Internet]. U S Food and Drug Administration Home Page. Center for Drug Evaluation and Research; Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm504540.htm 3.Bettegowda C, Sausen M, Leary R, Kinde I, Agrawal N, Bartlett B, et al. Detection of Circulating Tumor DNA in Early and Late Stage Human Malignancies. Science Translational Medicine 2014;16:224ra24. 4. Oxnard GR, Thress KS, Alden RS, et al: Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 34:3375–3382, 2016 5.Hu Y, Ulrich BC, Supplee J, et al: False-Positive Plasma Genotyping Due to Clonal Hematopoiesis. Clin Cancer Res 24:4437-4443, 2018 6.Hu Y, Alden RS, Odegaard JI, et al: Discrimination of Germline EGFR T790M Mutations in Plasma Cell-Free DNA Allows Study of Prevalence Across 31,414 Cancer Patients. Clin Cancer Res 23:7351-7359, 2017 7.Slavin TP, Banks KC, Chudova D, et al: Identification of Incidental Germline Mutations in Patients with Advanced Solid Tumors Who Underwent Cell-Free Circulating Tumor DNA Sequencing. Journal of Clinical Oncology 36:3459-3465, 2018 8.Oxnard GR, Tara M, Earl H, et al. Genome-wide sequencing for early stage lung cancer detection from plasma cell-free DNA (cfDNA): The Circulating Cancer Genome Atlas (CCGA) study. Journal of Clinical Oncology:LBA8501-LBA8501, 2018 9.Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA Analysis Depicts Early Stage Lung Cancer Evolution. Nature 2017;545:446-451.

Keywords: cell free DNA, ultra sensitive assays, false positives

ES25 LIQUID BIOPSY
TUESDAY, SEPTEMBER 10 14:30–16:00

ES25.04 LIQUID BIOPSY: UTILITY FOR EARLY DETECTION

A. Vivancos

Vall d´Hebron University Hospital and Institute of Oncology (VHIO), Barcelona/Spain

Personalized treatment according to molecular profile is standard of care in advanced NSCLC patients. Epidermal Growth Factor Receptor (*EGFR*) activating mutations predict sensitivity to first- and second-generation anti-EGFR tyrosine kinase inhibitors (TKIs) in patients with non-small cell lung cancer (NSCLC). However, obtaining a tissue biopsy remains a limitation in NSCLC patients. Liquid biopsy is a non-invasive method that allows the detection and quantification of tumor somatic mutations in plasma, although around 20% of all tumors don't appear to shed DNA into the bloodstream. Here, we aimed to correlate the presence and amounts of ctDNA in plasma of NSCLC patients with several clinical parameters, as well as obtaining serial data on non-shedding patients throughout their course of illness. We collected 280 serial blood samples of 40 patients with NSCLC diagnosis harboring *EGFR* sensitizing mutations in their tumor biopsy. Extracted ctDNA was tested for five common *EGFR* mutations (exon 19 deletion, L858R, L861Q, T790M and C797S) by highly sensitive and quantitative Droplet Digital PCR (ddPCRTM; Bio-Rad), at a limit of detection between 0.1-0.5% and quantified the percentage of mutant alleles of EGFR. Of these patients, 16 provided one plasma sample (32%) and the other 34 (68%) provided multiple blood collections with an average of 5 follow-up plasma samples. All patients received targeted TKI therapy before or during the study. Lines of treatment, Progression free survival (PFS) and overall survival (OS) were annotated for each patient in the cohort. Out of the 40 patients evaluated, we detected presence of baseline ctDNA in 32 patients (80%). Such parameter was independent of the sensitizing mutation; tumors harboring exon 19 or exon 21 mutation tend to equally shed DNA into the bloodstream (78% and 80%, respectively). After a median follow up of 36.1 months, and immature survival data, the PFS and OS are higher among patients with baseline ctDNA positive compared to patients without ctDNA detected: 22 months vs. 13.6 months and 35 vs. 24 months, respectively. T790M and C797S resistance mutations were detected at different prevalences, depending on the TKI treatment regimen, and were always subclonal in plasma as compared to the clonal EGFR mutation (indel 19/L858R). We observed that, for the whole period analyzed in non-shedding patients, ctDNA was never detected. In our series, sensitizing *EGFR* mutations in plasma were identified in 80% of the patients by ddPCR. Acquired resistance mutations in *EGFR* appeared to be subclonal, which might impact detection in liquid biopsy. Shedding is a complex biological entity that warrants further research in order to improve our understanding on its impact in prognosis.

Keywords: ctDNA, EGFR, ctDNA shedding

ES26 THE IMPACT OF SPECIALIST NURSING AND ALLIED HEALTH PROFESSIONALS IN THE CARE OF THORACIC ONCOLOGY PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

ES26.01 THE IMPACT OF SPECIALIST NURSING INTERVENTION IN LUNG CANCER

A. Leary[1,2]

[1]*London South Bank University, London/United Kingdom,* [2]*University of South Eastern Norway, Oslo/Norway*

The Impact of Specialist Nursing Intervention in Lung Cancer Alison Leary on behalf of Iain Stewarta, Aamir Khakwania, Richard B. Hubbarda, Paul Beckettb, Diana Borthwickc, Angela Toddd, Alison Learye, Laila J. Tataa A Division of Epidemiology and Public Health, University of Nottingham, NG5 1PB, UK B Derby Teaching

Hospitals NHS Foundation Trust, DE22 3NE, UK c Edinburgh Cancer Centre, Western General Hospital, EH4 2JT, UK d School of Nursing and Midwifery, University of Sheffield, S10 2LA, UK e School of Primary & Social Care, London South Bank University, SE1 0AA, UK Introduction In the UK the role of the Clinical Nurse Specialist is well established. Lung Cancer Clinical Nurse Specialists (LCNS) often start a therapeutic relationship with patients and families before formal diagnosis has been made. LCNS often manage the care of people with lung cancer but in an environment of austerity their worth to employers is still questioned. This series of studies examined the impact of the LCNS on outcomes for lung cancer patients. The focus of this abstract is one of the studies which looks at receipt of treatment for lung cancer. Treatment choices for people with lung cancer may be influenced by contact and engagement with lung cancer nurse specialists (LCNSs). We investigated how service factors, LCNS workload, and LCNS working practices may influence the receipt of anticancer treatment. Materials and methods English National Lung Cancer Audit data and inpatient Hospital Episode Statistics for 109,079 people with lung cancer surviving 30 days from diagnosis were linked along with LCNS workforce census data and a bespoke nationwide LCNS survey. Multinomial logistic regression was used to determine adjusted relative risk ratios (RRRs) for receipt of anticancer therapies associated with LCNS assessment, LCNS workforce composition, caseload, LCNS reported working practices, treatment facilities at the patients' attending hospitals, and the size of the lung cancer service. Results Assessment by an LCNS was the strongest independent predictor for receipt of anticancer therapy, with early LCNS assessments being particularly associated with greater receipt of surgery (RRR 1.85, 95%CI 1.63–2.11). For people we considered clinically suitable for surgery, receipt was 55%. Large LCNS caseloads were associated with decreased receipt of surgery among suitable patients (RRR 0.71, 95%CI 0.51–0.97) for caseloads >250 compared to ≤150. Reported LCNS working practices were associated with receipt of surgery, particularly provision of psychological support (RRR 1.60, 95%CI 1.02–2.51) and social support (RRR 1.56, 95%CI 1.07–2.28).

Table 1
Lung cancer nurse specialist (LCNS) workload factors and their associations with receipt of anticancer therapy.

	Total		No therapy	Receipt of surgery			Receipt of chemotherapy			Receipt of radiotherapy		
	n = 109,079		n = 34,729	n = 17,459			n = 36,951			n = 19,940		
	Freq	%	%	%	RRR*	(95% CI)	%	RRR*	(95% CI)	%	RRR*	(95% CI)
Assessed by LCNS												
No	4,730	4.3	8.0	3.3	1		2.0	1		3.3	1	
Yes	70,904	65.0	57.3	65.4	1.98	(1.11–3.53)	70.7	2.18	(1.24–3.82)	68.9	1.84	(1.17–2.87)
Missing	33,445	30.7	36.0	31.3	1.73	(1.32–2.26)	27.3	2.14	(1.67–2.75)	27.8	1.72	(1.41–2.10)
First LCNS assessment												
After diagnosis	30,578	28.0	28.4	20.2	1		30.1	1		31.1	1	
Before/at diagnosis	36,995	33.9	25.7	41.5	1.85	(1.63–2.11)	37.8	1.27	(1.14–1.42)	34.9	1.16	(1.05–1.28)
Missing	41,506	38.1	47.2	38.3	1.41	(0.93–2.14)	32.1	0.74	(0.52–1.07)	34.0	0.81	(0.56–1.18)
LCNS workforce												
Band 7 only	47,244	43.3	43.7	44.0	1		44.4	1		40.9	1	
Bands 6–7	46,677	42.8	42.7	41.6	0.94	(0.76–1.16)	42.5	0.97	(0.78–1.20)	45.5	1.15	(0.97–1.35)
Band 8 included	15,158	13.9	14.9	14.4	0.81	(0.57–1.14)	13.0	0.73	(0.54–0.97)	13.7	0.96	(0.73–1.25)
Total LCNS caseload												
≤150 patients	22,673	20.8	21.7	21.1	1		20.9	1		37.3	1	
151–250	61,218	56.1	56.4	56.3	0.97	(0.82–1.14)	56.8	1.08	(0.87–1.33)	96.9	1.09	(0.91–1.30)
> 250	25,188	23.1	23.2	22.5	0.96	(0.73–1.25)	22.2	1.00	(0.78–1.28)	40.0	1.26	(1.00–1.59)
Treatment facilities												
No specialty	27,499	25.2	29.4	23.7	1		22.8	1		24.3	1	
Surgical	29,646	27.2	24.0	31.9	1.80	(1.42–2.28)	28.4	1.81	(1.45–2.26)	26.8	1.47	(1.20–1.80)
Chemotherapy	51,934	47.6	47.8	44.4	1.22	(0.95–1.56)	48.8	1.39	(1.10–1.75)	48.9	1.27	(1.05–1.53)
Annual service size												
< 175 new LC patients	39,797	36.5	37.5	37.6	1		36.7	1		34.1	1	
175–264	32,959	30.2	30.5	28.4	0.83	(0.63–1.09)	29.8	0.87	(0.67–1.15)	32.8	1.05	(0.89–1.24)
≥265	36,323	33.3	33.3	34.0	0.89	(0.73–1.08)	33.5	0.95	(0.79–1.15)	33.1	1.03	(0.86–1.23)

LC, lung cancer.
* Relative risk ratio adjusted for LCNS assessment and timing, workforce banding, average caseload size per LCNS, therapy availability and service size, as well as patient's age, sex, performance status, stage, comorbidity, and socioeconomic deprivation. Clustered by English Regional Cancer Network.

Conclusion LCNS assessment, workload, and working practices are associated with the likelihood of patients receiving anticancer therapy. Enabling and supporting LCNSs to undertake key case management interventions offers an opportunity to improve treatment uptake and reduce the apparent gap in receipt of surgery for those suitable Early nurse specialist contact is associated with greater receipt of therapy. •Receipt of surgery is less likely where nurse specialists have large caseloads. •Therapy receipt is more likely if key nursing interventions are routinely provided. •Managing nurse specialists' workload could address disparities in therapy uptake. Are working practices of lung cancer nurse specialists associated with variation in peoples' receipt of anticancer therapy? (2018) Stewart, Iain et al. Lung Cancer, Volume 123, 160 – 165 https://www.lungcancerjournal.info/article/S0169-5002(18)30482-3/pdf

Keywords: Nursing, Advanced practice, treatment

ES26 THE IMPACT OF SPECIALIST NURSING AND ALLIED HEALTH PROFESSIONALS IN THE CARE OF THORACIC ONCOLOGY PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

ES26.02 REHABILITATION AFTER TREATMENT OF THORACIC MALIGNANCIES

C. Wells

University of Maryland Medical Center, Baltimore/United States of America

In this presentation the speaker will focus the talk on the collaborative model between the Departments of Nursing and Rehabilitation Services in the promotion of functional recovery of hospitalized adults. The speaker will incorporate the current literature regarding early mobilization and rehabilitation and the program's effects on outcomes. The talk will also examine the physical impairments and functional limitations associated with cancer associated frailty. Finally, the speaker will share some priminary data from the efforts at the University of Maryland Medical Center on the implementation of a collaborative mobilization and rehabilitation program to address barriers to recovery and hospital discharge.

Keywords: Rehabilitation, Functional Recovery, Early Mobilization Program

ES26.03 ACHIEVING HOLISTIC CARE IN HARD TO REACH PATIENT COHORTS

P. Magabanyane[1], J. Tewaternaude[2]

[1]*Asbestos Relief Trust, Kuruman/South Africa,* [2]*Asbestos Relief Trust, Cape Town/South Africa*

Achieving Holistic Care in Hard to Reach Patient Cohorts Against the odds - Achieving Holistic Care in Hard to Reach Patient Cohorts Phemelo Magabanyane (Author presenter) Registered Nurse, Midwife, Community health Nurse, Primary Health Care & Palliative Care Nurse Background:This abstract outlines the functionality of a holistic palliative care service under the unique circumstances of Kuruman, South Africa. This district comprises 186 villages with a total population of 241 836 people with only 39 clinics, three community health centres, two district hospitals, one oncology unit and no intensive care unit, the closest being 250 km away in the nearest city, Kimberley. The Kuruman Oncology unit is one of three specialist outreach programs, developed with the aim of improving accessibility to quality healthcare in rural areas. The need for the oncology and palliative care outreach program in Kuruman stems from the town's proximity to the crocidolite asbestos hills. Although mining stopped in 1998 and asbestos was banned officially in 2008, the legacy of asbestos – both occupational and environmental – lives on in the form of mesothelioma, and - in a situation of low smoking rates - lung cancer. The suffering of those affected by mesothelioma and lung cancer was worsened by the absence of palliative care and in-patient hospice services. 12 years ago, two asbestos trusts decided to initiate Kuruman's first and only fully functional palliative care service: a nurse. Discussion: Kuruman's semi-arid and under-resourced setting requires innovation, specialised training and good management to address palliative care needs. Although inadequate infrastructure lessens accessibility, cultural attitudes and beliefs hinders biomedical treatment, favouring traditional methods or simply keeping dread illnesses private. Resistance is further influenced by low literacy levels and a fear of attending tertiary institutions where people are perceived to die. Although these areas are the prime focus of our educational seminars, patients remain rooted in their beliefs and practices, hence often die from asbestos related diseases sooner than if they'd sought treatment from appropriate facilities. Despite this, our program has, since 2007, cared for 1987 asbestos affected patients. Our palliative care service was envisioned and enacted to facilitate the best feasible services to thoracic malignancy patients. With the hospital's oncology service, the Cancer Charity Workers (CCW), and patients' families, a collective evolved to effect holistic support – in health, psychologically, spiritually, and financially - including those everyday grinding tasks of end-of-life care. Financial support of the CCW from the Relief Trusts, CCW becoming an NGO, more formalised use of Community Health Care givers, becoming a grantee of a major Foundation, and the appointment of a second palliative care professional nurse by the Trusts have been recent developments in our functionality. Through community meetings, educational seminars, and free lung screenings, the collective has been able to identify greater numbers of cancer sufferers residing in remote areas and to encourage and channel palliative care services to them. Summary: Palliative care's principle of holistic care built on creating compassionate relationships between carer and patient produces better outcomes for the patient, their family, and the healthcare professionals involved. This service relies on a dedicated team of poly-organisational multidisciplinary professionals who are committed to realising and meeting the needs of the community. It is devoted to education, patient care, and furthering research on the optimization of the palliative healthcare system. Co- Authors: Dr Jim teWaterNaude, Fatimah Patel, Amira Wallace

Keywords: Achieving Holistic Care in Hard to Reach Patient Cohorts, Against all odds, IASLC

ES26 THE IMPACT OF SPECIALIST NURSING AND ALLIED HEALTH PROFESSIONALS IN THE CARE OF THORACIC ONCOLOGY PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

ES26.04 THE IMPACT OF EARLY NURSING INTERVENTION ON OUTCOMES FOR THORACIC ONCOLOGY PATIENTS

I. Nohavova

Charles University in Prague, Prague/Czech Republic

Introduction: The roles of nurses vary from cancer screening, detection, and prevention, to active clinical assessment, treatment administration or symptom management. These various aspects play part when raising public awareness of important role of prevention. One of the very effective examples of an early health intervention is prevention of no tobacco use uptake or quitting using tobacco products in order to enhance health outcomes. The latest WHO/Europe report[1] "European tobacco use – trends report 2019" shows tobacco use continues to be a paramount public health issue. At the same time, it is estimated 90% of lung cancers (incl. tracheal or bronchal) could be avoided if tobacco use is eliminated. Sadly, the WHO European Region has the highest proportion of tobacco use in the world, with an estimated 29% of population using tobacco. Nurses can help. Methods: A review of guidelines and recommendations for nurses to use in daily practice will be presented. Results: Not applicable Conclusions: With prevention must be the key priority action, such focused early nurses interventions can contribute to timely diagnosis of the cancer positively impacting outcomes of thoracic oncology patients, including quality of life and care experience. Nurses are ideally positioned to assume this role. This presentation will explore current evidence related to the role of cancer nurse in early interventions to thoracic cancer patients' outcomes. The session will include discussion and recommendations to increase role of nurses in prevention of tobacco use. References: 1. WHO (2019). European Tobacco Use: Trends Report 2019. Retrieved from http://www.euro.who.int/__data/assets/pdf_file/0009/402777/Tobacco-Trends-Report-ENG-WEB.pdf

Keywords: Nurses, Lung cancer, prevention

ES26 THE IMPACT OF SPECIALIST NURSING AND ALLIED HEALTH PROFESSIONALS IN THE CARE OF THORACIC ONCOLOGY PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

ES26.05 EARLY INTERVENTION AND REHABILITATION FOR PATIENTS NEWLY DIAGNOSED WITH THORACIC MALIGNANCIES

M. Quist

Copenhagen University hospital, Copenhagen/Denmark

This presentation will outline the rationale, role and evidence supporting early Intervention and rehabilitation for patients newly diagnosed with thoracic malignancies. Thoracic malignancies are associated with high disease burden and increased inactivity. Newly diagnosed Individuals with thoracic malignancies experience complex symptoms, which can include dyspnoea, fatigue and pain. These frequently lead to a cycle of inactivity and functional decline. Individuals with thoracic malignancies are less physically active than similar aged healthy peers at time of diagnosis, with less than 40% meeting the physical activity guidelines (1). Following diagnosis, physical activity levels are lowest whilst patients undergo treatment and do not recover back to pretreatment levels within six months. Progressive functional decline occurs over time, with reduction in exercise capacity and muscle strength (1). In thoracic malignancies, reduced exercise performance is associated with poorer functional independence, worse cancer treatment tolerability and higher all-cause mortality (2). People with thoracic malignancies, who are less physically active, have worse symptoms, and poorer exercise capacity and health-related quality of life (HRQoL) compared to those who are more active (1). This is supported and linked with the research by Gralla et al in 2014 (3) who identified key issues that patients with thoracic malignancies mainly fear. Gralla el al described the five rated issues which were: maintaining independence, ability to perform normal daily activities, ability to sleep, not being a burden for caregivers and not being fatigued, in a survey among 660 patients with lung cancer. Moreover, up to 44% of patients

with thoracic malignancies experience depression and anxiety symptoms, which is consistently higher than other cancers types, and psychological distress has also been proven to affect anti-cancer treatment and mortality (4). Supervised high-intensity exercise training is associated with improved exercise capacity and QOL in most cancer patients (5). Systematic reviews have reported that both pre- and postoperative exercise interventions are safe and feasible for patients with operable thoracic malignancies, and suggest benefits on exercise capacity, symptoms as fatigue and some domains of QOL (6). However, this evidence does not include patients with advanced inoperable thoracic malignancies. Although research groups have previously shown that exercise in these patients is safe, feasible, and beneficial (7), conclusive randomized controlled trials (RCT) still remain to be carried out to determine the effect of exercise for patients with advanced inoperable thoracic malignancies. But larger RCT within this group of patients is currently finished and ongoing and within the next few years the evidence will increase. Next step though is to implement evidence into daily practice. 1. Granger CL, McDonald CF, Irving L, Clark RA, Gough K, Murnane A, et al. Low physical activity levels and functional decline in individuals with lung cancer. Lung Cancer. 2014;83(2):292-9. 2. Jones LW, Hornsby WE, Goetzinger A, Forbes LM, Sherrard EL, Quist M, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. Lung Cancer. 2012;76(2):248-52. 3. Gralla RJ, Hollen PJ, Msaouel P, Davis BV, Petersen J. An evidence-based determination of issues affecting quality of life and patient-reported outcomes in lung cancer: results of a survey of 660 patients. Journal of thoracic oncology:official publication of the International Association for the Study of Lung Cancer. 2014;9(9):1243-8. 4. Sullivan DR, Ganzini L, Duckart JP, Lopez-Chavez A, Deffebach ME, Thielke SM, et al. Treatment receipt and outcomes among lung cancer patients with depression. Clinical oncology (Royal College of Radiologists (Great Britain)). 2014;26(1):25-31. 5. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer treatment reviews. 2017;52:91-104. 6. Ni HJ, Pudasaini B, Yuan XT, Li HF, Shi L, Yuan P. Exercise Training for Patients Pre- and Postsurgically Treated for Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis. Integr Cancer Ther. 2016. 7. Quist M, Adamsen L, Rorth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther. 2015;14(4):341-9.

Keywords: Rehabilitation, physical activity, quality of life

Interactive Breakfast Sessions

IBS01 MY OLIGOMETASTATIC ONCOGENE DRIVEN PATIENT
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS01.01 SYSTEMIC OR LOCAL TREATMENT: WHAT TO DO FIRST?

B. Solomon

Peter MacCallum Cancer Center, Melbourne/Australia

In the era of increasingly effective systemic treatments including EGFR and ALK tyrosine kinase inhibitors we will review the rationale for aggressive treatment of oligometastatic or oligopersistent disease in order to improve long term treatment outcomes. In the setting of oligometastatic disease to the brain, treatment of one or more sites of brain metastases with effective systemic treatment with stereotactic radiotherapy may allow whole brain radiation to be avoided or delayed. For extracranial disease, locally ablative therapies to solitary sites of metastases may enable potentially curative approaches to primary tumours. Further, benefit for treatment of oligo-persistent sites of disease after intial systemic treatment with local consolidative therapy has been demonstrated. Central to aggressive local approaches are appropriate staging investigations including MRI Brain and FDG-PET scan to determine the extent of metastatic disease.

Keywords: oligometastatic, EGFR, ALK, local consolidation therapy

IBS01 MY OLIGOMETASTATIC ONCOGENE DRIVEN PATIENT
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS01.02 STRATEGIES TREATMENT AFTER OLIGOPROGRESSION

F. Cappuzzo[1,2], L. Landi[2]

[1]*Medical Oncology Unit Ravenna, Ravenna/Italy,* [2]*AUSL Romagna-Ravenna, Ravenna/Italy*

Lung cancer remains the leading cause of cancer-related mortality with more than 50% of the cases diagnosed at advanced stage. For decades, metastatic Non-Small-Cell Lung Cancer (NSCLC) has been considered as incurable disease with limited therapeutic opportunities. In such context, local ablative therapies (LAT), mainly represented by surgical metastasectomy, was the sole treatment with curative intent for selected patients with single brain or adrenal lesion. However, improvements in the knowledge of cancer biology coupled with progresses in systemic therapy positively impacted the duration and quality of life. This is the case of NSCLC carrying epidermal growth factor receptor (*EGFR*) activating mutations or anaplastic lymphoma kinase (*ALK*) rearrangement, where targeted therapies have changed the natural history of the disease, with median survival exceeding 4 years. Beyond *EGFR*mutations and *ALK*rearrangement, additional actionable alterations have been identified, including*BRAF*mutations or *ROS1*rearrangements as the latest entered in clinical practice. Specific therapies are now available in clinic for all of these aberrations, with osimertinib, alectinib, crizotinib or the combination of dabrafenib and trametinib as the best first-line option for individuals harboring alterations respectively in the *EGFR*, *ALK*, *ROS1*or *BRAF*. Unfortunately, after an initial response all patients eventually progress. From a clinical point of view, there are two main patterns of progression including rapid and systemic progression or slow, limited and often indolent progression. In the first scenario, shift to a second line therapy is recommended. In the other case (oligoprogressive disease), LAT plus continuation of front-line inhibitor given beyond progression seems the best option. The oligoprogressive state is characterized by a limited number of sites in progression, implying that the other sites remain controlled and therefore sensitive to systemic treatments. The advent of non-invasive techniques such as stereotactic radiotherapy, radiofrequency, and mini-invasive surgery has led to a precise re-evaluation of LATs in this situation. Local treatment of the oligoprogressive lesions may allow modification of the natural history of the disease, maintenance of effective systemic targeted treatment and, ultimately, to improved survival. In addition, some LATs have the advantage that can be repeated over time in difficult-to-treat organs as brain. Data validating an aggressive local therapeutic approach in oligoprogressive NSCLC patients are currently limited and essentially retrospective. Several international trials are ongoing and their results could contributing in better defining the role of radical local treatment in oligoprogressive advanced NSCLC patients. Unfortunately, even if the addition of a LAT contributes in disease control, majority of patients finally relapse and die for additional metastatic spread. Therapy options at the time of oligometastatic progression are largely influenced by previous therapies, site of progression and molecular portrait of the disease. Molecular characteristics are of particular relevance for defining the possibility of sequential use of additional target agents. This is the case of T790M EGFR mutation occurring in the vast majority of patients progressing after old generation EGFR TKIs for which osimertinib is superior to standard platinum-doublet chemotherapy. Viceversa, in absence of the acquired mutation (T790M negative), chemotherapy or combinations of chemotherapy and immunotherapy should be the preferred choice. In conclusion, molecular target therapies and more recently immunotherapy significantly improved survival of patients presenting with metastatic disease at diagnosis. However, acquired resistance inevitably occurs, limiting patient survival. A subset of patients presenting oligometastic disease represent a unique subgroup of patients who can benefit from LAT followed by continuation of systemic therapy. Randomized clinical trials are needed the role of LAT in this context.

Keywords: oligoprogression, local ablative therapy, oncogene driven NSCLC

IBS02 MAKING SENSE OF TREATMENT WITH SO MANY OPTIONS: MY ALGORITM
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS02.01 MAKING SENSE OF TREATMENT WITH SO MANY OPTIONS: MY ALGORITM - A EUROPEAN VIEW

N. Reguart

Hospital Clínic Barcelona, Barcelona/Spain

The treatment paradigm for metastatic non-small cell lung cancer (NSCLC) continues to evolve quickly due to the introduction of immunotherapy and new targeted therapies as well as our increasing knowledge of molecular signaling pathways. As a result of treatments becoming more efficacious and more personalized, outcomes for selected patients with NSCLC are increasing. Algorithms change rapidly and those published one year ago are already outdated today. In this interactive session, we will discuss current treatment algorithm / recommendations for advanced NSCLC patients, those whose tumors have driver oncogenes as well as wild-type lung tumors. We will describe the decision-making process to arrive at a treatment recommendation for a particular patient from the perspective of three different areas of the world: Europe, North-America and Australia. Recommendations for the best standards of care, based on evidence-based medicine and local clinical practice guidelines will be covered and applied in this case to the European local-practice context.

Keywords: Algorithms, NSCLC, treatment

IBS02 MAKING SENSE OF TREATMENT WITH SO MANY OPTIONS: MY ALGORITM
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS02.02 MAKING SENSE OF TREATMENT WITH SO MANY OPTIONS: MY ALGORITM - A NORTH AMERICAN VIEW

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The Treatment of Lung Cancer: Can it be logical? The treatment of lung cancer has evolved dramatically in the past decade. Targeted therapy, and more recently immunotherapy have provided not only new and better treatment options, but have radically transformed the understanding of the biology of the disease. For the individual

practitioner, and even for the thoracic oncologist expert, it can be challenging to keep up with the new advances and apply the data to clinical practice. Consensus guidelines have become a popular vehicle to educate and support decision making at the individual level. Oncologists often rely on recommendations from professional societies, such as ASCO, IASLC, ESMO, and NCCN, to refresh their knowledge and to identify a treatment algorithm that is appropriate for a specific patient. There is however significant heterogeneity among the guidelines in terms of methodology and strength of recommendations. Guidelines are based on systematic reviews of the literature, and interpreted by a recognized panel of experts. The recommendations should be rated based on the quality of the evidence. Translating the recommendation into a treatment decision requires consideration of additional factors, clinical and non-clinical, that balance the weight of the evidence with the uniqueness of the patient's circumstances. In general, when the evidence is strong, and the patient falls into the subset for whom the recommendation is intended, the intervention should be offered. Conversely, if the recommendation is weak, or the patient has factors that cofound the clinical context, clinicians need to be more discretionary and consider alternative options. Just as important, guidelines can discourage the use of ineffective, unproven, or even harmful therapies. They also serve as a platform for discussions among clinicians, or between clinicians and patients when controversies about treatment arise. Another level of decision tool is a clinical pathway, which provides an evidence-based, step by step protocol for delivering care to patients with specific diseases and stages. Studies have documented that use of pathways is associated with improved outcomes and often lower costs. Several health care systems across the US have implemented pathways for cancer care, with varying degrees of adherence. One type of pathway often used in oncology focuses on chemotherapy regimens. Committees of national experts provide recommendations as to the most appropriate regimens for a specific stage and disease, such as advanced non-small cell lung cancer, with and without a molecular target. The options are ranked based on efficacy; toxicity; and costs, usually in this order. Institutions may acquire the pathway from a vendor, or decide to rely on their own experts to develop recommendations. These guidelines should be updated frequently. Financial aspects become more relevant in chemotherapy pathways. In cases where efficacy and toxicity do not differ significantly among the regimens, differences in cost ultimately determine the order of prioritization. Because drug costs account for a large component of the financial well being of a cancer hospital, Pharmacy Committees are often asked to develop guidelines for selection of the more cost-effective therapies, and pathways can assist in this process. Other potential benefits of clinical pathways include the ability to collect information on providers' practices; identify outliers with respect to priority regimens; and flag regimens that have limited efficacy data in a particular setting. Above all, pathways promote standardization of care within institutions, particularly when oncologists are spread across multiple sites. Guidelines and pathways are designed primarily to improve quality and consistency of care, and are not meant to replace clinical judgement. At a time when advances in cancer treatment outpace any one individual's ability to keep up with the new information, they serve as a valuable resource for physicians and patients alike.

IBS03 PERSONALIZED MANAGEMENT OF ELDERLY PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS03.01 MANAGING LOCALLY ADVANCED NSCLC IN THE ELDERLY IN 2019

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In the management of locally advanced (LA) non-small cell lung cancer (NSCLC), at least 10 studies over the past 25 years have shown superiority for chemoradiation over radiation (XRT) alone; more recently, concurrent chemoradiation has proven superior to sequential or asynchronous chemotherapy followed by XRT. Retrospective analyses evaluating outcomes in the elderly receiving these regimens have generally demonstrated similar progression-free (PFS) and overall survival (OS) compared to their younger counterparts on study, albeit with increased toxicity.[1,2,3] Generally, those over 70 years of age were under-represented on these trials compared to the NSCLC population at large - while more than 40% of those diagnosed with LA-NSCLC were 70 years of age or older, fewer than 20% of those enrolled on relevant clinical trials were elderly.[4] Virtually all of the earlier efforts were cisplatin-based, which made the routine use of this approach in elderly patients outside of clinical trials somewhat problematic, particularly in the face of age-associated co-morbidities that might preclude or limit the application of platinating agents. Since the beginning of the new millenia, non-cisplatin regimens, generally using weekly carboplatin in combination with a taxane or other partner agents active in NSCLC have been shown to yield "equivalent" efficacy with less toxicity. For elderly patients treated outside of a clinical trial, I generally favor weekly carboplatin (AUC 2) coupled with weekly solvent-based paclitaxel (45-50 mg/m2) in conjunction with a minimum dose of 60 Gy administered over a 6-7 week period. At least one trial from Japan conducted exclusively in the elderly with LA-NSCLC showed superior OS for concurrent XRT and low dose daily carboplatin vs XRT alone with median survival of 22.4 mos compared to 16.5 mos in the control group (HR 0.64).[5] However, monotherapy with carboplatin during XRT is not considered the standard approach in LA-NSCLC. The only randomized trial to compare cisplatin- to carboplatin-based combinations in LA-NSCLC was a Japanese study which randomized patients to either MVP during thoracic XRT or to weekly carbo and either irinotecan or paclitaxel; this study showed virtually no difference in long term outcome (18 to 20% 5 year survival), with pacitaxel/carboplatin proving better tolerated.[6] These results are dissatisfying, but clearly better than historic controls with XRT alone (5-7% 5 year OS). To date, unfortunately, in North American, we have no prospective, randomized, head-to-head comparisons of cisplatin based treatment vs. paclitaxel/carboplatin or other carboplatin-based regimens in stage IIIA/B NSCLC. Retrospective data from the VA and the SEER database, however, suggest little difference in long term OS.[7] The results of RTOG 0617 would tend to validate paclitaxel/carboplaitn as a "viable" regimen in "good prognosis" LA-NSCLC pts with median survival in the 23 to 29 month range for weekly paclitaxel/carboplatin during radical XRT, with no advantage for 74 Gy over 60 Gy or the addition of cetuximab.[8] More recently, the PACIFIC trial showed that patients with LA-NSCLC who received "consolidative" durvalumab, a PDL1 inhibitor, for up to a year, after responding to or stabilizing on concurrent chemoradiation, could enjoy a three-fold increase in PFS (16.8 vs 5.6 mos) and a 10% absolute improvement in OS (66.3% vs 55.6%).[9] These benefits were both statistically significant (HR 0.68) and clinically meaningful; and the PACIFIC regimen featuring concurrent chemo-radiation followed by durvalumab has emerged as the "standard of comparison" if not the "standard of care" in fit individuals with LA-NSCLC, regardless of age. Of note, the HR for OS benefit in PACIFIC in those 65 years of age and older was 0.76 (95% CI: 0.55 - 1.05) vs 0.62 (95% CI: 0.44-0.88) for patients under 65. Whether this approach should be applied to patients whose tumors do not harbor PDL1 expression or whose tumors have an oncogenic driver such as EGFR mutations remains controversial. References: 1. Rocha-Lima, C et al, Cancer 2002 2. Langer, C et al, ASCO 2002 3. Schild, S et al, JCO 2002 4. Auperin et al, JCO 2010 5. Atagi et al, Lancet Oncology, 2012 6. Yamamoto et al, JCO 2010 7. Santana-Davila, R et al, JCO 2015 8. Bradley, J et al, Lancet Oncology 2015 9. Antonia, S et al, NEJM 2018

Keywords: locally advanced NSCLC, elderly

IBS03 PERSONALIZED MANAGEMENT OF ELDERLY PATIENTS WITH STAGE III NSCLC
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS03.02 SURGERY FOR ELDERLY PATIENTS WITH STAGE III NON-SMALL-CELL LUNG CANCER (NSCLC)?

B. Passlick

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About 40 % of the patients with newly diagnosed Non-small-Cell Lung cancer are between 65 to 75 years old and more than 15 % are older than 75 years at the time of diagnosis. Elderly patients have in general a reduced cardiopulmonary performance status, including a higher risk for ischemic heart disease and COPD. Furthermore higher co-morbidity can be expected (renal, metabolic, and cerebral). The major question whether surgery should be offered to patients of more than 70 years are whether there is a higher morbidity and mortality in elderly patients and the second question is, whether curative surgery approach is worthwhile in patients over 75 years. The question whether a higher age is associated with a higher morbidity in elderly patients has been investigated by different studies, most of them with a retrospective design. While in older studies from

the 80-ies of last century (i.e. lung cancer study group) there was an elevated mortality in patients over 70 years, this was not true anymore in publications from the late 90th of last century and current publications: For example in a recent publication from the Japanese association of chest surgeons the postoperative mortality was 2 % in patients between 70 - 79 years old and it was 2.2 % in patients over 80 years old. Furthermore, there is only a little influence of the age with respect to the postoperative lung function parameters. If we try to analyze whether surgery is worthwhile in elderly patients, we have to realize that men who are now 85 years old have a mean life expectancy of 5.3 years and women of 6.3 years. Furthermore, there is no survival difference in surgically treated patients for stage III lung cancer which are younger or older than 70 years old. In a Japanese study patients over 80 years have achieved a long term survival of more than 50 % after surgery for lung cancer. Limited resections can be successfully performed in patients with limited cardio pulmonary function parameters. In summary, the morbidity and mortality in elderly patients is not elevated after surgery and the median cancer specific long term survival is not different as compared to younger patients. References: 1. Castillo MD et al., Curr Opin. Anaesthesiol. 2007; 20, 4 2. Okami J et al. JThorac Oncol. 2009, 4, 12 47 3. Cerfolio RJ et al. Ann. Thorac. Surg. 2006; 82, 424 4. Sullivan V et al. Chest 2005: 128, 2671

Keywords: surgery, Elderly patients, NSCLC

IBS04 HYPERPROGRESSIVE DISEASE
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS04.01 BIOLOGICAL MECHANISMS

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Inhibitors of programmed cell death 1 (PD-1) and one of its ligands, PD-L1, have rapidly been incorporated into the treatment of patients with lung cancer and other malignancies. In lung cancer, when used as single agents, a minority of patients respond to PD-1 or PD-1 inhibitors. Although some patients now receive these agents along with chemotherapy, many patients still receive single agent inhibitors of immune checkpoints such as PD-1 or PD-L1. A phenomenon of hyperprogression has been described among patients undergoing therapy with immune checkpoint inhibitors. There is a great deal of literature describing the radiographic criteria associated with hyperporgression. Although there is wide agreement that a portion of patients do meet these radiographic criteria, the extent to which inhibitors of PD-1 and PD-L1 can induce the growth of lung cancer is a topic generating a great deal of interest. Studies are beginning to assess potential mechanisms underlying this pnenomenon. Assessment is complicated by the fact that some patients are likely to rapidly progress based solely on lack of effective therapy, and therefore, the group of patients meeting the described radiographic criteria for hyperprogression may be heterogeneous.

Keywords: pd-1, PD-L1

IBS05 LUNG CANCER GENETICS TO BEAT LUNG CANCER
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS05.01 KRAS MUTANT LUNG CANCER

P. Jänne

Dana Farber Cancer Institute, USA/United States of America

*KRAS*mutations are the most common oncogenic alteration in Caucasian patients with advanced non-small cell lung cancer (NSCLC), detected in approximately 25% of patients with adenocarcinoma. Although *KRAS*mutations were discovered over 30 years ago, no approved targeted therapies exist for *KRAS*mutant NSCLC. *KRAS*mutations occur most commonly in codon 12 and less frequently in codons 13 and 61. The development of KRAS mutant lung cancer is most closely associated with a history of current or former smoking although *KRAS*mutations can also occur in up to 15% of never smokers who develop lung cancer (1). While *KRAS* G12C mutations are the predominant mutation subtype in smokers, G12D mutations are the most common subtype of KRAS mutations in never smokers. Until recently, no direct targeted therapies existed for KRASmutant lung cancers and the therapeutic efforts have mostly focused on targeting downstream effector pathways including the MAPK and PI3K/AKT pathways. MEK inhibitors have limited single agent activity (response rates 10-20%) and initial enthusiasm from a randomized phase II trial of selumetinib/docetaxel vs. docetaxel suggested a potential benefit of adding chemotherapy to a MEK inhibitor (2). However, the initial findings could not be reproduced in a larger randomized phase III trial (3). The CDK4/6 inhibitor abemaciclib has also been evaluated as a single agent in KRASmutant lung cancer based on both preclinical data and as a result of the phase I trial which demonstrated a differential benefit in patients with KRASmutant NSCLC (4). However, a phase III trial, randomizing previously treated KRASmutant NSCLC to either abemaciclib or erlotinib failed to demonstrate an improvement in overall survival. It has increasingly been recognized that not all KRASmutant cancers are the same. Not only are there a variety of allelic variants of KRAS, there several subtypes of co-mutations within KRAS mutant cancers (5). Approximately 30% of KRASmutant tumors harbor a concomitant alteration in TP53 which another 30% harbor concomitant mutations in LKB1/STK11. Mutations in LKB1/STK11most commonly result in loss of function of the LKB1/STK11protein(5,6). Immune checkpoint blockade (ICB), administered as a single agent or in combination with chemotherapy, is an effective therapy in lung cancer (7). While strategies to identify biomarker to predict optimal response to ICB are diverse, LKB1/STK11mutations are associated with lack of response to both single agent ICB or when administered together with combination chemotherapy. Ongoing efforts are focusing on understanding the mechanistic basis for the lack of response to ICB in LKB1/STK11mutant tumors and levering this understanding to develop new strategies to enhance responsiveness of this subset of NSCLC to ICB. New therapeutic approaches to target KRAS are rapidly entering the clinic. These include inhibitors or SHP2, SOS1 and the direct inhibitors of KRAS G12C. Novel structural insights into into the KRAS protein helped identify a unique allosteric site formed in the presence of the G12C mutation. These insights led to the identification of potential drugs that could occupy this pocket and covalently bind KRAS G12C (8). Multiple companies are now developing KRAS G12C inhibitors including Mirati Therapeutics (MRTX849) and Amgen (AMG510). Encouraging early clinical signs of efficacy have been observed. Over the next few years, clinical data will emerge on the efficacy of direct KRAS G12C inhibitors, the impact of concomitant genomic alterations, the mechanisms of acquired resistance as well as combination treatment strategies. In addition, continued studies of KRAS biology and new therapeutic studies will also hopefully lead to new treatments for patients with non-G12C KRASmutations. References 1. 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Keywords: KRAS, mutation, Targeted therapy

IBS05 LUNG CANCER GENETICS TO BEAT LUNG CANCER
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS05.02 FUNCTIONAL GENOMIC APPROACHES TO IDENTIFY NOVEL THERAPEUTIC TARGETS IN LUNG CANCER

T. Zou, M. Meyerson

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Despite the discovery and availability of targeted therapies and immunotherapies, lung cancer remains the leading cause of cancer death worldwide. Importantly, most lung cancer patients are not eligible for targeted therapies because their tumors lack an actionable genomic alteration. Moreover, immunotherapy-based regimens fail to induce treatment responses in a substantial proportion of lung cancer patients (1-3). Therefore, the identification of novel therapeutic modalities remains critical to improving outcomes in lung cancer care. Lung cancer cells may harbor specific genomic or functional alterations that render them vulnerable to particular genetic perturbations (4,5). Discovery of these synthetic lethal interactions may provide opportunities to develop novel classes of therapeutics for this disease. Through systematic analysis of genome-scale loss-of-function datasets (6,7), we identify adenosine deaminase acting on RNA (ADAR or ADAR1) as an essential gene for the survival of a subset of lung cancer cell lines (8). ADAR1-dependent cell lines display increased expression of interferon-stimulated genes. Moreover, activation of type I interferon signaling in the context of ADAR1 deficiency can induce cell lethality in non-ADAR1-dependent cell lines. ADAR deletion causes activation of the cytoplasmic double-stranded RNA sensor, protein kinase R (PKR). Disruption of PKR signaling, through inactivation of PKR or overexpression of either a wild-type or catalytically inactive mutant version of ADAR1, partially rescues cell lethality after ADAR1 loss, suggesting that both catalytic and non-enzymatic functions of ADAR1 may contribute to preventing PKR-mediated cell lethality. Taken together, these data nominate ADAR1 as a potential therapeutic target in lung cancers displaying elevated interferon-stimulated gene expression and underscore the ability of functional genomic approaches to uncover novel genetic vulnerabilities in lung cancer. References 1. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92 2. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51 3. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33 4. Oike T, Ogiwara H, Tominaga Y, Ito K, Ando O, Tsuta K, et al. A synthetic lethality-based strategy to treat cancers harboring a genetic deficiency in the chromatin remodeling factor BRG1. Cancer Res 2013;73:5508-18 5. Zhou Z, Patel M, Ng N, Hsieh MH, Orth AP, Walker JR, et al. Identification of synthetic lethality of PRKDC in MYC-dependent human cancers by pooled shRNA screening. BMC Cancer 2014;14:944 6. Tsherniak A, Vazquez F, Montgomery PG, Weir BA, Kryukov G, Cowley GS, et al. Defining a Cancer Dependency Map. Cell 2017;170:564-76 e16 7. Aguirre AJ, Meyers RM, Weir BA, Vazquez F, Zhang CZ, Ben-David U, et al. Genomic Copy Number Dictates a Gene-Independent Cell Response to CRISPR/Cas9 Targeting. Cancer Discov 2016;6:914-29 8. Gannon HS, Zou T, Kiessling MK, Gao GF, Cai D, Choi PS, et al. Identification of ADAR1 adenosine deaminase dependency in a subset of cancer cells. Nat Commun 2018;9:5450

Keywords: Functional genomics, Target discovery, Innate immune signaling

IBS06 MULTIMODALITY TREATMENT - REALTIME DATA FROM NATIONAL REGISTRIES
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS06.01 REAL TIME DATA FROM EUROPE ETOP / ESTS DATABASE

I. Schmitt-Opitz[1], A. Bille[2], Z. Tsourti[3], K. Nakaerts[4], L. Ampollini[5], M. De Perrot[6], L. Brcic[7], E. Nadal[8], S. Gray[9], J. Aerts[10], E. Verbeken[11], E. Silini[5], F. Zaeimi[6], M. Samarzija[12], R. Llatjos[8], S. Tsimpoukis[13], J.H. Van Der Thüsen[10], S. Finn[14], N. Marti[15], G. Dimopoulou[3], K. Monkhorst[16], A. Brunello[17], R. Kammler[15], A. Soltermann[18], P.-E. Falcoz[19], P. Baas[16], R. Stahel[18], F. Etop Mesoscape[20], F. Ests Consortia[21]

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Malignant pleural mesothelioma (MPM) is an aggressive malignancy with increasing prevalence and poor prognosis. Despite a still increase in incidence, it remains an orphan disease and studying limited numbers of MPM cases hampers the derivation of solid conclusions. The combination of two databases including clinical as well as pathological information will allow researchers to improve the knowledge and facilitate decision-making in patients with MPM. The European Thoracic Oncology Platform (ETOP) Mesoscape project and the European Society of Thoracic Surgeons' (ESTS) database are designed to address clinical, pathological, and molecular characteristics of mesothelioma patients and their impact on outcome. The joined analysis of both databases is a unique approach to real-time data reflecting the reality of mesothelioma characteristics, treatment and prognosis in Europe. Materials and Methods: A decentralized biobank with fully annotated tissue samples is established for ETOP Mesoscape. Selection criteria for participating centers included sufficient number of cases, and documented ethical approval. Patient selection is based on availability of comprehensive clinical data with adequate follow-up, and adequate quantity and quality of formalin-fixed tissue.The ESTS database is a clinical database with pre-operative, intra-operative and post-operative data. A minimum set of data is captured, including demographic, histology, treatment, staging and follow up data. The characteristics between the two databases are compared using the Fisher's exact test (for categorical variables) and Mann-Whitney test (for continuous variables), while Kaplan-Meier method (with log-rank test). Results: Up to 29 May 2019, the ETOP Mesoscape included information on 497 patients from 10 centers, diagnosed between 1999-2018. In the ESTS database, as of April 2019, 2269 patients are included, diagnosed between 1989-2019. Patients in both databases are primarily men (84% in the ETOP, 71% in the ESTS), of 0/1 ECOG Performance status (46/46% and 59/29% in ETOP and ESTS respectively), with known previous exposure to asbestos (75% and 93%) and median ages 64 and 67 years old. Significant differences are detected between the two data sources with respect to gender, exposure to asbestos and age (p-value <0.001). The primary histology of patients is epithelioid (72% in ETOP and 70% in ESTS), followed by biphasic (22%; 17%) and sarcomatoid (6%; 9%) (not significantly different between the two databases). Clinical staging is available for 77% of the patients in ETOP, but only for the 28% in the ESTS database. The stage distribution (I/II/III/IV) is 14/29/42/15% in the ETOP and 23/21/41/16% in the ESTS (significantly difference p<0.001). Among the biomarkers common in both data sources, Calretinin and WT1 are detected in the vast majority of patients tested (Calretinin: 97% in both cases; WT1: 89% and 87% in the ETOP and ESTS database respectively). For the ETOP cases 90% (of those tested) are CK5/6 positive, 91% D2-40 positive and 97% Pan-CK positive. Palliative treatment has been administered in 41% of the ETOP cases. Among them, 84% received palliative chemotherapy (with the vast majority 92%, using multiple agents). Palliative surgery was undertaken in 32% (62 of 194 patients with available information) and palliative

radiotherapy for 13% of the patients. Complete resection has been performed in 59% of the ETOP Mesoscape patients. This was combined with induction chemotherapy (81%), while adjuvant chemotherapy and radiotherapy was administered in 4% and 37% respectively. The surgical approach adopted for the ESTS patients was either video-assisted thoracoscopic surgery (VATS) (59%) or thoracotomy (41%) based on a subset of 887 patients with available information. Post-operation treatment information is available for 620 ESTS patients. Among them, 71% received chemotherapy, 54% underwent surgery and 15% radiotherapy. Conclusion: We present the combined results from the ETOP Mesoscape and the ESTS database, one of the largest databases. These two series allow us to report on mesothelioma epidemiology and treatment. Up to now, the comparison of the baseline characteristics of the patients of the two data sources revealed some statistically significant differences with respect to gender, age, exposure to asbestos and clinical stage. As tissue from all ETOP Mesoscape patients is preserved locally and is available for detailed molecular investigations, Mesoscape provides an excellent basis to evaluate the influence of molecular parameters on the disease outcome, besides providing an overview of the molecular landscape.

Keywords: Mesothelioma, European registries, biomarker, clinical, pathological, molecular characteristics

IBS06 MULTIMODALITY TREATMENT - REALTIME DATA FROM NATIONAL REGISTRIES
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS06.02 REAL TIME DATA FROM US (SEERS)

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The association between asbestos exposure and malignant mesothelioma has been well established. Exposure to asbestos mainly occurs through work although environmental exposure has been documented. Several countries have put in place an active epidemiologic surveillance of mesothelioma cases. Through a PubMed and Google Scholar search using the key words "*mesothelioma*" and "*registry*", and by reviewing data sources of studies described in a review of environmental exposure and malignant mesothelioma, we identified existing mesothelioma registries. Countries with mesothelioma specific registries are Australia, Belgium, France, Germany, Italy, Japan, South Korea, South Africa, Turkey, and the UK. Nation-wide coverage is obtained in Italy, Australia and South Korea. Registries in Australia, France, Italy, and South Korea use interviews to obtain exposure data from the patient or a close relative, although none of these countries has a tissue bank. The UK has a mesothelioma tissue bank although it is not linked with the National Mesothelioma Audit registry. All registries have or will develop linkage with death index registries to monitor survival outcomes. (Table 1) The Scandinavian countries including Norway, Sweden, Finland and Denmark, have a population based cancer registry that includes mesothelioma and is linked to other databases, such as an occupational database, thus has more comprehensive information on each case. Mesothelioma surveillance in the US to date Currently, no nation-wide, mesothelioma specific registry exists in the US. Various existing databases are used to investigate mesothelioma, for instance the National Cancer Database has been used to look at prognostic factors; gender and race differences in mesothelioma survival have been studied using the Surveillance, Epidemiology, and End Results (SEER) database. All these datasets suffer of a time-lag between case occurrence, reporting, registration and eventually data availability for research purposes; these are serious limiting factors in the case of mesothelioma. Because of the rarity and lethality of the disease, a real-time capture registry is needed to thoroughly collect exposure data, complete data on treatments, quality of life before and after treatment, symptoms and pain management. All these elements are lacking in the existing databases. Because the US mesothelioma incidence is not decreasing as quickly as predicted and new cases still occur as well the fact that mortality rates are steady overtime, the overall health burden due to mesothelioma in the US still remains. Although the use of asbestos has been restricted or banned since 1980, several scientific questions remain open due to the long latency period between exposure and mesothelioma clinical occurrence, and to gaps in knowledge of the carcinogenesis process. Data on occupational and environmental asbestos exposure and co-exposure to other carcinogens are needed. Certain patterns, such as differences in outcomes by gender, differences in incidence rates by race, as well as geographic clusters of increased number of cases, are hard to explain with the existing data. Possible next steps towards a US mesothelioma registry "Real time" enrollment is important in order to systematically collect information on asbestos and other exposures through interviews with mesothelioma patients or a close relative. Furthermore, optimal coverage, preferably population based and nation-wide, and a simplified consent process are needed in order to capture a maximum number of cases. A centralized quality control system, standardized data collection methods, and the ability to link to relevant other existing registries are important in order to integrate the registry with clinical and prognostic information. Additionally, consistency in the design and questionnaire content with other countries would be ideal, in order to conduct comparisons and possibly pool the data. The flexibility to add or modify modules to tailor to future research questions are other preferable features for a US mesothelioma registry. (Figure 1) A discrete amount of work has been devoted to molecular markers such as mesothelin and certain germline mutations as prognostic factors. The role of these biomarkers could be validated on larger populations of patients if a comprehensive registry that includes tissue is implemented. Summary and conclusions In conclusion, with the remaining health burden due to mesothelioma, the changing landscape of asbestos exposure, and the many unanswered scientific questions, a nation-wide, real-time US mesothelioma registry is urgently needed. Methods for data sharing, linkage to existing tissue banks, and data access should be implemented and tested on a small scale before being implemented nationwide. One of the most practical outputs of these efforts would be the ability to conduct pragmatic trials that could be built out of a "real time" case capture system.

Table 1: Overview of mesothelioma registries

	Country	Treatment information	Tissue bank	Patient interview	Family interview (for all or deceased cases)	Exposure information	Nationwide coverage	Linkage with death information	Active monitoring system	Only pathologically confirmed cases and/or pathology information available	Mandated reporting	Outcomes
Italian National Mesothelioma Registry (ReNaM)	Italy			✓	✓	✓	✓	✓	✓	✓		-Incidence -Etiology -Survival -Trends over time
National Program for Mesothelioma Surveillance (PNSM)	France			✓	✓	✓		✓	✓	✓		-Incidence -Etiology -Survival -Trends over time
National Mesothelioma audit (UK)	UK	✓	✓*			✓		✓		Pathological confirmation in 81%-91%		-Treatment outcomes -Survival
Australian mesothelioma registry (AMR)	Australia			✓		✓	✓	✓	✓	Information about best basis of diagnosis	✓	-Incidence -Etiology -Survival -Trends over time
Korean Mesothelioma Surveillance System	South Korea			✓	✓	✓	All general hospitals included	Possible in the future	✓	✓	✓	-Incidence -Etiology -Trends over time

*MesobanK UK: Malignant Pleural Mesothelioma Tissue Bank separately created from the National Mesothelioma Audit.

Keywords: Mesothelioma, epidemiology

IBS06 MULTIMODALITY TREATMENT - REALTIME DATA FROM NATIONAL REGISTRIES
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS06.03 JAPANESE DATA

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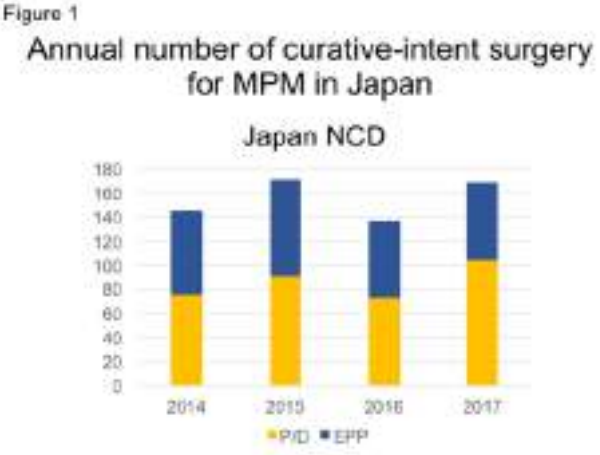
Annual surveys of cardiothoracic surgery throughout Japan has been conducted by the Japanese Association for Thoracic Surgery (JATS) since 1986 in order to establish the statistics for the number of procedures by operative category[1]. Regarding malignant pleural mesothelioma (MPM), however, only annual case numbers of both diffuse and localized MPM have been registered since 1996. From 2009 onward, surgical technique, 30-day mortality, and in-hospital mortality have been also described. According to the JATS survey, all-kind of surgery for MPM increased 76% during 1996 and 2016: 164 cases in 1996 and 289 cases in 2016. JATS survey also revealed dramatic increase of pleurectomy/decortication (P/D) cases during 2009 to 2016: proportion of P/D surgery in all curative-intent surgery was 1.4% (2/142) in 2009 and 53.3% (73/137) in 2016. Methods In 2011, the National Clinical Database (NCD) of Japan adopted an annual web-based nationwide data collection system[2]. Since NCD is associated with the Japanese Surgical Board Certification System, it contains detailed perioperative clinical information such as preoperative patient characteristics, operation time, blood loss, intraoperative accidents, pathological TNM stages, postoperative adverse events, redo-surgery, 30-day and in-hospital mortality, cause of death, and so on. Approximately 10 million surgical procedures from >5000 hospitals have been collected by 2017. An NCD specifically for general thoracic surgery was launched in 2014[3]. This time, we conducted an analysis on MPM surgery in Japan using the Japan NCD. Results (Table 1) In the period of 4 years between 2014 and 2017, a total of 622 curative-intent surgery was performed in Japan. Median age was 66 years (IQR, 61-71), and 87.6% were male. A median BMI was 22.6 (20.3-24.8), and 77.3% was ECOG PS0. Induction therapy was given in 40.8% of patients. Extrapleural pneumonectomy was performed in 279 patients (44.9%) and P/D in 343 (55.1%). Blood transfusion was required in 320 (51.4%) patients (Figure 1). Injury of major intrathoracic organ occurred in 22 (3.5%) patients. Morbidity rate was 40.0% (249/622). Thirty-day mortality and in-hospital mortality were 1.1% and 3.2%, respectively (Table 1). Conclusion In addition to the above JATS survey and Japan NCD, a nationwide, prospective, observational study of patients with MPM has just completed 2-year's patient accrual[4]. It is promising that these Japanese data will substantially contribute to understanding MPM in near future. 1 Thoracic and cardiovascular surgery in Japan in 2016. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Shimizu S, Endo S, Natsugoe S, et al. Gen Thorac Cardiovasc Surg 2019; 67: 377-411. 2 http://www.ncd.or.jp/ 3 Development of an annually updated Japanese national clinical database for chest surgery in 2014. Endo S, Ikeda N, Kondo T, et al. Gen Thorac Cardiovasc Surg 2016; 64: 569-576. 4 Shintani Y, Hasegawa S, Takuwa T, et al. Prospective registry database of patients with malignant mesothelioma: Directions for a future Japanese registry-based lung cancer study. J Thorac Dis 2018; 10: 1968-71

Table 1

		EPP (n=279)	P/D (n=343)	Total (n=622)
age (median, IQR)		65 (59-69)	67 (63-73)	66 (61-71)
male sex		250 (89.6%)	295 (86.0%)	545 (87.6%)
BMI (median, IQR)		22.3 (20.2-24.2)	23 (20.4-25.1)	22.6 (20.3-24.75)
PS	0	215 (77.1%)	266 (77.6%)	481 (77.3%)
	1	57 (20.4%)	65 (19.0%)	122 (19.6%)
	2-4	5 (1.8%)	10 (2.9%)	15 (2.4%)
	unknown	2 (0.7%)	2 (0.6%)	4 (0.6%)
Induction therapy		103 (36.9%)	151 (44.0%)	254 (40.8%)
Blood transfusion		159 (57.0%)	161 (46.9%)	320 (51.4%)
Major organ injury		12 (4.3%)	10 (2.9%)	22 (3.5%)
Morbidity		126 (45.2%)	123 (35.9%)	249 (40.0%)
30-day mortality		3 (1.1%)	4 (1.2%)	7 (1.1%)
in-hospital mortality		9 (3.2%)	11 (3.2%)	20 (3.2%)

Figure 1



Keywords: national database, malignant pleural mesothelioma

IBS07 ENHANCING RECOVERY IN THE TREATMENT OF THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS07.01 ENHANCED RECOVERY FOR THORACIC SURGERY

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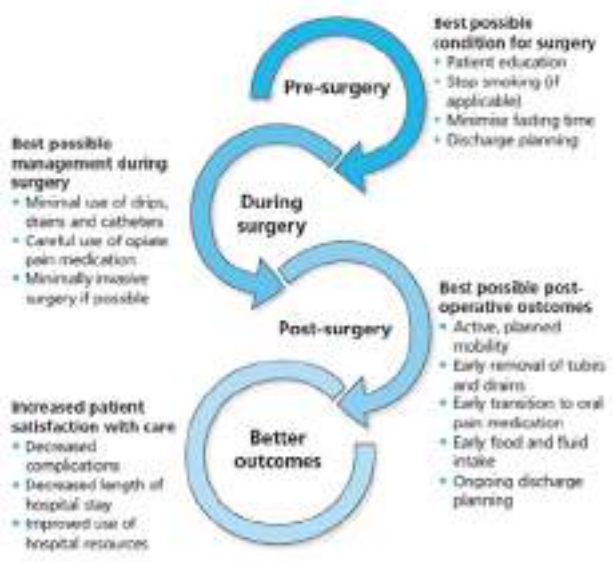
Background Enhanced Recovery After Surgery (ERAS) also known as "fast track surgery", was pioneered back in the 1990s by Henrik Kehlet in colorectal surgery. It has developed as a multimodal evidenced based approach which has been designed and tested to enable patients to recover more quickly after major surgery thus reducing the length of hospital stay and the associated costs, Its aim is to minimise the physical and psychological stress response to surgery and has been proven effective in many different areas, by delivering multiple interventions throughout the entire patient journey from referral to discharge and beyond. Over the years the evidence modified this approach and now ERAS programmes are growing in popularity and are becoming more established across a range of surgical specialities, but there is still a little way to go

in thoracic surgery to build evidence and recommendations on the elements of the ERAS programme. Methods The main principles for ERAS programmes are; to enable the patients to be as healthy as possible before surgical treatment, receive the best possible care during their operation and have the best possible care while recovering (picture 1). There are as many as 45 enhanced recovery items throughout the entire pathway. The ideal start to the ERAS pathway is to optimise the pre-operative health which should commence when the referral from primary care is made. Interventions for smoking cessation and managing pre-existing comorbidities such as diabetes and hypertension are key elements in getting the patients in the best possible condition for surgery. Other pre surgery interventions are prehabilitation, nutritional screening, and patient information to manage expectations and discharge planning. Key recommendations for the admission on the day of surgery are to give patients pre surgery carbohydrate loading drinks and minimise their fasting period. In terms of intraoperative items, minimally invasive surgery, less opioid use, avoidance of urine catheters and fluid management are recommended elements. In the post-operative and follow-up phase, early oral hydration and nutrition to enable the removal of intravenous therapy, early mobilisation within 24 hours, early chest drain removal to facilitate discharge with a recommendation for telephone follow-up if applicable; these recommendations are becoming more common in thoracic surgery. Results In specialties such as colorectal, gastric and liver surgery the ERAS pathways are well established with good supporting evidence demonstrating a reduction in hospital length of stay, postoperative complication rates and cost reductions. Recommendations and guidance in thoracic surgery ERAS programmes has been published by the Enhanced Recovery after Surgery Society and the European Society for Thoracic Surgery (1). Some recommendations are based on high quality evidence; however in some cases thoracic surgery specific evidence is simply not available to support the recommendations therefore evidence from other surgical specialities has been extrapolated to thoracic surgery. The key recommendations include: pre surgery smoking cessation - a known risk factor for developing post-operative pulmonary complications (however there is a strong debate around smoking cessation timing prior to surgery); malnutrition increases risk of complications therefore nutritional screening is highly recommended as well as minimising starvation; the use of carbohydrate loading the evidence is low but the recommendation is strong due to proven reduction in insulin resistance in the context of general surgery. Patient education has been shown to reduce anxiety and improve expectations for both patients and carers. It is not clear if patients with good lung function and exercise capacity benefit from Prehabilitation but the evidence for the high risk group is strong, thus is highly recommended. There also is a strong recommendation for avoiding sedatives and the use of regional/non-opiate analgesia for pain relief, adequate control of nausea and vomiting, video-assisted approach when possible with early removal of chest drains. The guidance recommendation is high for dedicated pre-op counselling, prehabilitation, carbohydrate loading, use of regional anaesthetic techniques and short acting anaesthetic agents, dexamethasone to prevent post of nausea and pain, use of digital drainage with no external suction and early mobilisation after surgery but the evidence level is low. The impact of ERAS on the long term outcomes is another aspect that is yet to be determined. As the recommendation grade for most of the elements is strong, the use of a systematic perioperative care pathway has the potential to improve outcomes after surgery. Conclusion These guidelines outline recommendations for the perioperative management of patients undergoing lung surgery based on the best available evidence. However there are barriers to implement many aspects of the ERAS programme due to lack of evidence, so there is still a need for large-scale, multicenter randomised trials to test aspects of the pathway. (1) Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS)



Keywords: Enhanced recovery, Thoracic surgery

IBS07 ENHANCING RECOVERY IN THE TREATMENT OF THORACIC MALIGNANCY
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS07.02 THE IMPACT OF PREHABILITATION ON PATIENTS HAVING LUNG CANCER SURGERY

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Surgical resection remains the best treatment option for patients with early stage of non-small cell lung cancer. However, it may be responsible of postoperative complication and mortality, especially in patients with impaired pulmonary function. Enhanced recovery after surgery (ERAS) programs have been focused mainly in minimal invasive surgery approach during lung resection and respiratory rehabilitation after surgery. Preoperative exercise-based intervention (Prehabilitation) has demonstrated reduction of morbi-mortality in other surgeries but in thoracic surgery continues to be under discussion. Impaired lung function with low predicted postoperative forced expiratory volume in first second (ppoFEV1) or/and diffusing capacity for carbon monoxide (ppoDLCO) are considered risk factors for anatomic lung resection. Cardio-pulmonary exercise test (CPET) is the gold standard technique to predict postoperative morbi-mortality. It seems reasonable to think that if we are able to improve FEV1 or CPET we will reduce postoperative risks.The implementation of a preoperative respiratory rehabilitation could optimize patient's physical capacity before surgery and improve outcomes and enhance recovery. The aim of this presentation is to identify the effectiveness and safety of prehabilitation programs in thoracic surgery and review its impact on patients having lung cancer surgery. Define the type of exercise and its duration, and the group of patients with best benefit. During the presentation we will be able to check that Prehabilitation is a safe intervention without side effects in patients. High-intensity interval training (HIT) with duration of 2 to 6 weeks seems to be the best exercise programme in a prehabilitation intervention but it exists heterogeneity in terms of intensity and duration. Prehabilitation increase exercise capacity and significantly enhances pulmonary function. But the reduction of postoperative complication and mortality has not been clearly demonstrated. Different criteria selection, type of intervention and small sample size, in addition to no randomization, could justify disparate results. It seems that not all patients can benefit from prehabilitation and it could be indicated only in patients with impaired lung function. Further randomized clinical trials with enough patients, correct duration of HIT (2 to 6 weeks) and focused in COPD patients are needed to clarify the suitability of prehabilitation. Meanwhile, safety of prehabilitation and good results of some studies support this intervention in high-risk patients. This conclusion is supported by the recent published ERAS society and Eurpoean Society of Thoracic Surgeons (ESTS) guidelines for enhanced recovery after lung

surgery, which recommends prehabilitation should be considered for patients with borderline lung function or exercise capacity, despite the low scientific evidence.

Keywords: ERAS, Prehabilitation, risk of anatomic lung resection

IBS08 ROLE OF PATHOLOGIST IN THE ERA OF IMMUNOTHERAPIES
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS08.01 HARMONIZATION OF PD-L1 IHC INCLUDING LDT

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Given the great advances in immuno-oncology, systematic testing of virtually all NSCLC for PD-L1 expression by IHC has become a standard in many pathology laboratories. This has initially been driven by the approval of Pembrolizumab for first line monotherapy of metastatic NSCLC with a tumor proportion score (TPS) of at least 50%. At the same time, the pathology and oncology community has been challenged by as many as five different PD-L1 IHC assays related to different clinical trials with different PD1/PD-L1 checkpoint inhibitors in NSCLC and cancers of other organs. The use of different antibody clones and assays for IHC within different trials cannot be explained by a specific rationale but rather by economic reasons and opportunities. Unfortunately, most pharmaceutical companies would not adopt an assay that has previously been developed and used by a competitor. They rather team up with an antibody manufacturer to develop their own predictive marker for their own drug. Pathologist are then left with sorting out the dilemma and look for the most feasible solution to provide reliable predictive PD-L1 testing and enable the best possible treatment decisions. Clearly, it is out of question that pathology laboratories would be able or willing to provide all available assays using different automated immunostainer platforms for two major reasons: First, it is usually unknown to the pathologist at the time of testing, which particular PD1/PD-L1 inhibitor will be the chosen for an individual patient, as this depends on the preference of the medical oncologists and the actual result of the PD-L1 IH testing. Second, for many institutions, it is too expensive to maintain different automated immunstainer platforms and to establish different expensive PD-L1 assays in parallel, all of which need to undergo continuous or periodical internal and external quality control. Therefore, whenever possible, pathology laboratories try to establish one single PD-L1 IHC test that is as concordant as possible with several trial-related PD-L1 assays. Notably, the predictive IHC assays with the trial-related antibody clones are much more expensive than typical diagnostic antibodies used in pathology for decades, and this extra expense if often not properly reimbursed by the health insurance system. This explains why many laboratories still use laboratory developed tests (LDTs) for PD-L1 IHC using the non-clinical trial related antibody E1L3N (Cell Signaling) or concentrated, trial-related anti-PD-L1 antibodies. Given this apparent dilemma there have been numerous studies aiming at harmonizing the landscape of PD-L1 IHC testing. They have repeatedly shown that the concordance between the currently most relevant assays (DAKO 28-8, -DAKO 22C3, and Ventana SP263) was sufficient to allow for interchangeable use. This enables laboratories of to provide PD-L1 assay testing to select patients for treatment with Pembrolizumab, Nivolumab and Durvalumab on either the Ventana Benchmark Ultra or the DAKO AL48 immunostainer platform. On the other hand, the Ventana SP142 assay related to Atezolizumab has clearly lower sensitivity for PD-L1 expression on tumor cells (TC), and is thus suitable to select for treatment with nivolumab or pembrolizumab based on different TPS threshold. Similarly, the latest DAKO clone 73-10 that is related to Avelumab, appears to be the most sensitive one and might therefore not be interchangeable with any of the other PD-L1 assays. Published data and results from external quality assurance (EQA) programs indicate that it is possible to set up LDTs that match the staining results of the PD-L1 IHC assays. Nevertheless, LTDs still have higher failure rates emphasizing the necessity of rigorous validation and quality control. PD-L1 IHC has been adopted by several programs of external EQA programs including NordiQC, Quip, and UK NEQAS. Notably, NordiQC showed good results of trial-related related commercial PD-L1 IHC assays, and the results of LTDs improved over time. In particular, the sufficiency rate for E1L3N rose from a low 25% (2/9) in the first run to a high 89% (8/9) in the second run. Post-analytical PD-L1 scoring is also a challenge. Training and continuous exposure to PD-L1 IHC in routine practice can help to shorten the learning curve. In fact, the interobserver concordance of TC scoring was found to be higher among pathologist who had received specific training. Continuous monitoring of PD-L1 IHC values for comparison with the results of other institutions via an online database is emerging as another useful tool to control and fine tune of performance of PD-L1 IHC analysis of single pathologists or institutions, as demonstrated by the BIO-PATH biomarker tracker (https://www.biopath.ch/mha/). 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PD-L1 testing of non-small cell lung cancer using different antibodies and platforms: a Swiss cross-validation study. Virchows Arch. 2019 May 24 [Epub ahead of print] NordiQC results for quality assessment of PD-L1 in NSCLC, Available online: https://www.nordiqc.org/epitope.php?id=107

Keywords: PD-L1, harmonization, immunohistochemistry

IBS08 ROLE OF PATHOLOGIST IN THE ERA OF IMMUNOTHERAPIES
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS08.02 BEYOND PD-L1 IHC (TMB, IMMUNE MICROENVIRONMENT)

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PD-L1 expression by immunohistochemistry (IHC) is currently the only FDA-approved biomarker for immune checkpoint inhibitor therapy (ICI). However, there are multiple issues associated with PD-L1 IHC including the presence of multiple IHC platforms, each anti-PD-1/PD-L1 agent coupled to the specific PD-L1 IHC assay and spatial and temporal heterogeneity of PD-L1 expression in the tumor. Importantly, PD-L1 expression is not the best biomarker to predict response to PD-1/PD-L1 blockade given the relatively low specificity.(1) To improve the prediction of response to ICI, several biomarkers have been studied. Of those, tumor mutation burden (TMB) and immune microenvironment are emerging as predictive biomarkers. TMB is commonly defined as the total number of somatic coding mutations and is considered a surrogate for the amount of neoantigens based on the notion that the greater the number of nonsynonymous mutations in a given tumor, the more probable it is that some of the mutations will be immunogenic, providing targets for T-cell attack.(2) Rizvi and colleagues have shown higher synonymous mutation burden in tumors associated with improved objective response, durable clinical benefit, and progression-free survival (PFS) in two independent NSCLC patient cohorts treated with pembrolizumab.(3) Subsequently, the efficacy of TMB predicting response to ICI has been reported in several clinical trials. In the CheckMate 026,(4) which failed to confirm the efficacy of Nivolumab compared to the standard chemotherapy for advanced NSCLC patients as the first line, the biomarker subanalysis revealed that PFS of patients with high TMB was significantly longer than those with low and medium TMB when treated with Nivolumab, but the reverse was true when treated with chemotherapy. Further, upon stratified by both TMB and PD-L1 expression level, patients with both high TMB and high PD-L1 expression showed a high response rate (75%) and dramatically improved PFS compared to other groups when treated with Nivolumab, but there were no significant differences in PFS among the groups when treated with chemotherapy. Of note, TMB was measured using whole-exome sequencing (WES) in this study. In the CheckMate 227 study,(5) high TMB ($\geq$10 mutations/Mb) was associated with significantly improved outcomes with nivolumab/ipilimumab, with 1-year OFS of 43% versus 13% for chemotherapy, and the median PFS was 7.2 months versus 5.5 months (hazard ratio of 0.58, P<0.001). For patients with lower TMB, immunotherapy was not superior. Other studies have measured TMB in the blood and reported similar results for treatment with atezolizumab.(6) It is important to note that TMB and PD-L1 expression are independent variables and composite of TMB + PD-L1 expression further enrich for benefits from ICI.(7) Unfortunately, similar to PD-L1 IHC, the TMB

assessment has not been standardized yet. Although conducting comprehensive WES is ideal to assess TMB, it is currently not feasible in daily practice given the high costs, long turn-around time and suboptimal quality and quantity of tissue available from advanced lung cancer patients. Now, targeted panel sequencing or next generation sequencing (NGS) has become a part of clinical practice; thus, it would be desirable to leverage it to assess TMB. However, size and composition of panels, and read depth and coverage are diverse between NGS platforms; thus, the cut-off for high TMB is plat-form dependent. Importantly, TMB values represent a continuum rather than distinct clusters, NGS platforms with small gene panels may be difficult to predict TMB comparably to WES, while larger panels such as the 468-gene MSK-IMPACT panel and 315-gene FoundationOne panel could. Currently, the harmonization efforts on TMB are being conducted in the US (Friends of Cancer Research [FoCR]) and Germany (Qualitatssicherungs-Initiative Pathologie QuIP GmbH [QuIP]) in hope of enabling international and cross-sector standardization of TMB measurement and reporting.(8) As for the immune microenvironment, there are many types of immune cells, including T cells, B cells, myeloid-derived suppressor cells, tumor-associated macrophages and neutrophils. Of those, CD8+ cytotoxic T cells have been recognized as an important player and their density and location have been reported in association with response to ICI.(9) However, not all CD8+ T cells are in the same functional status. For instance, they may be activated characterized by the production of Granzyme B and Perforin and high Ki-67 proliferative index, and they may be exhausted characterized by the expression of LAG3, TIM3 and/or B7H3, among others. Interestingly, Gettinger and colleagues using multiplexed quantitative immunofluorescence have shown that a dormant tumor infiltrating T lymphocyte (TIL) phenotype, characterized by elevated CD3+ TILs with low activation (Granzyme B in CD3) and low proliferation (Ki-67 in CD3), is associated with survival benefit in patients treated with ICI.(10) Thus, we need to evaluate multiple immune markers at the same time to understand the immune microenvironment, preferably using a multiplex platform.
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Keywords: Tumor Mutation Burden, immune microenvironment, immune checkpoint inhibitor

IBS09 CHALLENGES IN TRANSLATING SMALL CELL AND NEUROENDOCRINE TUMOR RESEARCH INTO CLINICAL PRACTICE
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS09.01 IBS09 CHALLENGES IN TRANSLATING SMALL CELL AND NEUROENDOCRINE TUMOR RESEARCH INTO CLINICAL PRACTICE

A. Adjei

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Challenges in Translating Small Cell and Neuroendocrine Tumor Research into Clinical Practice Alex A. Adjei, MD;PhD Mayo Clinic, Rochester, MN, USA According to World Health Organization (WHO) classification of lung tumors in 2015, small cell lung cancer (SCLC) is one of four lung tumors of neuroendocrine origin. Key morphological features of SCLC are dense sheets of small cells, scant cytoplasm, ill-defined cell borders and distinctive nuclear quality. These tumors are typically high grade, manifesting a high proliferation rate, apoptosis and necrosis. Ki-67 is typically 50-100%, and there is neuroendocrine differentiation documented by expression of synaptophysin, chromogranin A, NCAM1 and insulinoma-associated protein 1 (INSM1). These tumors are very aggressive with high metastatic potential. While they are very responsive to initial therapy, there is invariably relapse and 5 year survival overall is less than 10%. A number of agents thought to be very promising, including the antibody drug conjugate Rova-T, and PARP inhibitors have yielded negative results. In this presentation we will review some of these studies to discern any lessons that can be learned from the failed studies. We will discuss promising new agents such as lurbinectedin, and EZH2 inhibitors and DNA damage response modifiers. A number of molecular vulnerabilities of SCLC have been identified. These include loss of TP53 and RB function, expression of the ASCL1, MYC, and Notch signaling pathways and unique neuronal characteristics. In addition, SCLC subtypes defined by differential expression of four key transcription regulators, the achaete-scute homologue 1 (ASCL1), neurogenic differentiation factor 1 (NeuroD1), yes-associated protein 1 (YAP1) and POU class 2 homeobox 3 (POU2F3), have been described. These new insights will be discussed in this presentation. The most significant advancements in the last year shown in Figure 1 below will be described

Keywords: sclc, novel targets

IBS09 CHALLENGES IN TRANSLATING SMALL CELL AND NEUROENDOCRINE TUMOR RESEARCH INTO CLINICAL PRACTICE
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS09.02 IMMUNOTHERAPY FOR SMALL CELL AND NEUROENDOCRINE TUMORS

S. Goldberg

Yale School of Medicine, New Haven/United States of America

A subset of patients with small cell lung cancer (SCLC) will achieve significant benefit from immunotherapy. Both nivolumab and pembrolizumab have demonstrated responses in patients with advanced SCLC, and atezolizumab in combination with chemotherapy results in an improvement in overall survival (OS) compared to chemotherapy alone. However, the ability to translate findings from the laboratory into patient care has been limited by several challenges. Though some patients will have durable response to PD-1 or PD-L1 agents, the majority of patients will not benefit. Combination strategies have been proposed and subsequently tested to potentially improve outcomes. Although ipilimumab was not effective as a single-agent for patients with SCLC, it has been combined with nivolumab in a phase I trial. The combination appears to be promising with response rates and OS that numerically exceeds that of single-agent PD-1 inhibitor therapy, although a randomized comparison trial has not yet been performed. Still, the majority of patients will not respond to the combination of PD-1 and CTLA-4 inhibition. Other immunotherapy targets have been explored pre-clinically though none have proven to be effective in patients to date. Another challenge in improving outcomes for patients with SCLC is that predictive biomarkers have been elusive. In contrast to non-small cell lung cancer, SCLCs rarely express PD-L1 on tumor cells and its presence has limited predictive value. However, immune cells in the tumor microenvironment more commonly express PD-L1 and may be predictive of benefit from immunotherapy. High tumor mutation burden (TMB) is also found in the majority of patients with SCLC likely due to the heavy smoking history in most patients with the disease. Patients with SCLC with a high TMB have been shown to have better outcomes with PD-1 inhibitors that those with lower TMB, however even those with the highest TMB have a fairly low chance of response or prolonged survival. Despite PD-L1 expression on immune cells and high TMB in most tumors, frequency of tumor infiltrating lymphocytes (TILs) is typically low in SCLC, possibly explaining the lack of response to immunotherapy in most patients with this disease. The benefit of immunotherapy for a subset of patients with SCLC has been proven, yet we are still faced with several challenges to optimize this treatment, including finding effective combination strategies that benefit more patients and developing predictive biomarkers to select those who are most likely to benefit.

Keywords: SCLC, immunotherapy

IBS10 TRACHEAL TUMOURS
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS10.01 SURGERICAL TREATMENT OF TRACHEAL TUMOURS

W. Klepetko

Medical University Vienna, Vienna/Austria

Tracheal tumors are relatively rare and account only for <1% of all malignant diseases.[1] The most common types of primary tracheal tumors are squamous cell carcinoma and adenoid cystic carcinoma, which represent together two thirds of all primary tracheal tumors.[2] Additionally, patients with secondary tracheal tumors might benefit from resection of the tumor including the trachea. Surgical procedures involving the trachea require a meticulous pre-operative planning, advanced surgical techniques and infrastructural prerequisites. Therefore, surgical resections of tracheal tumors are highly elective procedures at specialized centers. The preoperative work-up includes the histological verification of the tumor via bronchoscopy, which is usually combined with the determination of the estimated extend of resection. Moreover, radiologic imaging, preferably PET-CT, completes the tumor staging. Patients with locally advanced and initially unresectable tracheal tumors might be candidates for neoadjuvant therapy. Usually, neoadjuvant treatment consisting of sole chemotherapy is preferred, as radiation therapy may negatively impact the anastomotic healing. If the patient received induction therapy, the radiological imaging as well as the bronchoscopic evaluation has to be repeated after completion of the induction therapy to confirm the response to the therapy and to plan the surgical procedure. The most common approaches for tracheal resection include cervicotomy, partial or complete sternofissure, and posterolateral thoracotomy. The optimal surgical approach has to be chosen according the location and extent of the tumor. During surgery, special care should be taken to preserve the lateral blood supply of the trachea, to protect the recurrent nerves and to avoid excessive tension on the anastomosis. Inadequate surgical technique increases the risk for anastomotic insufficiency, which is a potentially life-threatening complication. In the literature, anastomotic complications (i.e. partial or complete dehiscence, granuloma or re-stenosis) occur in approximately 9% cases after tracheal surgery. The risk for anastomotic complications increases with the length of resection, diabetes mellitus and previous treatments.[3] As the airway in tracheal surgery has to be shared with the anesthesiologist, an appropriate ventilation strategy during induction of anesthesia, surgical preparation and at the end of the surgical procedure has to be defined. Although the double-lumen tube is routinely used in thoracic surgery, it has only a negligible role in airway surgery. The preferably used devices in airway surgery are the laryngeal mask, single-lumen endotracheal tube, high-frequency jet ventilation catheters and cross-table ventilation using a sterile endotracheal tube. Moreover, extracorporal membranoxygenation (ECMO) support is a valid option for selected, complex resections. It provides the advantage to operate on the patient without any airway device in the surgical field. A veno-venous ECMO is sufficient to fully substitute respiration. However, cardiorespiratory support by a veno-arterial ECMO configuration might be a valid option in some patients. In summary, the ventilation strategy is dependent on the location of the location, availability of devices, experience of the team and personal preferences. Therefore, planning the ventilation strategy is crucial for a successful surgical procedure. Similar to the surgical treatment of other solid malignancies, the major aim of tracheal surgery is the radical resection of the tumor including all loco-regional lymph nodes. The adenoid-cystic carcinoma represents an exemption from this rule. Due to its low-malignant tumor biology and the susceptibility to radiotherapy, even incomplete resection is acceptable in this tumor entity. As the adenoid-cystic carcinoma is characterized by a longitudinal, submucosal growth pattern (Figure 1), there might be a discrepancy between the resection length needed to obtain a complete resection and the technical possibility to perform a tension-free anastomosis. An incomplete resection combined with an adjuvant radiation therapy is therefore a valid treatment option in patients with adenoid-cystic carcinoma. Radiotherapy can be initiated as bronchoscopy confirms complete healing of the anastomosis approximately 6-8 weeks after surgery. Although the treatment of patients with tracheal tumors is demanding, an excellent perioperative and long-term outcome of patients with tracheal tumors can be achieved. In experienced hands, the peri-operative mortality after tracheal resection is <1%.[4] Moreover, surgery in multimodality treatment concept provides a very good long-term overall survival, which is especially true for adenoid- cystic carcinoma in which a 5-year overall survival up to 91% can be achieved.[5] In summary, the surgical treatment of tracheal tumors is technically demanding and should therefore be performed at high-volume centers. Within the heterogeneity of tracheal tumors, the adenoid-cystic carcinoma represents a unique tumor entity. Embedded in a multimodal treatment concept, excellent long-term outcome can be achieved despite incomplete surgical resection. After careful planning by a multidisciplinary team, even extended tracheal resections for malignant disease can be performed safely with a very low morbidity and mortality.

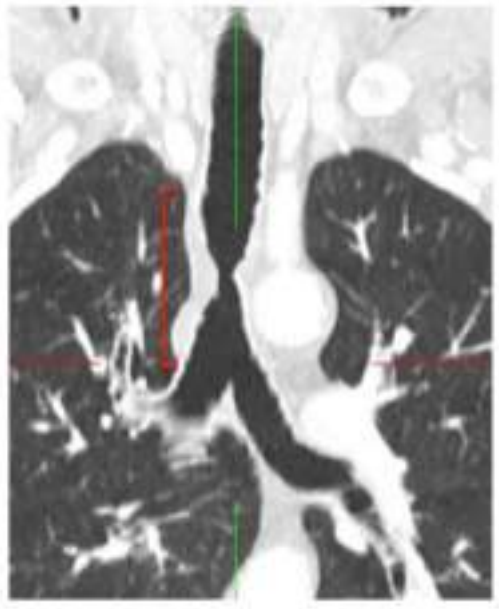

Figure 1: Computed tomography of a 70 year-old with adenoid cystic carcinoma of the trachea. Note the longitudinal tumor growth pattern (red bracket). 1. Grillo HC. Surgery of the trachea and bronchi. Hamilton, Ont.; Lewiston, NY: BC Decker; 2004. 2. Mallick S, Benson R, Giridhar P, Rajan Singh A, Rath GK. Demography, patterns of care and survival outcomes in patients with malignant tumors of trachea: A systematic review and individual patient data analysis of 733 patients. *Lung Cancer.* 2019;132:87-93. 3. Wright CD, Grillo HC, Wain JC, et al. Anastomotic complications after tracheal resection: prognostic factors and management. *The Journal of thoracic and cardiovascular surgery.* 2004;128(5):731-739. 4. Auchincloss HG, Wright CD. Complications after tracheal resection and reconstruction: prevention and treatment. *J Thorac Dis.* 2016;8(Suppl 2):S160-167. 5. Urdaneta AI, Yu JB, Wilson LD. Population based cancer registry analysis of primary tracheal carcinoma. *Am J Clin Oncol.* 2011;34(1):32-37.

IBS10 TRACHEAL TUMOURS
SUNDAY, SEPTEMBER 8 07:00–08:00

IBS10.02 ENDOSCOPIC TREATMENT OF UNRESECTABLE TUMORS OF THE TRACHEA

J. Sun

Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai/China

Surgical excision and reconstruction remain the recommended treatment approachs for patients with trachea tumors. However, it is associated with significant trauma and the risk of severely damaged pulmonary function, and not all patients are therefore willing to receive or fit for surgical resection. Traditional chemotherapy and radiotherapy can't improve the prognosis of these patients, which requires a multidisciplinary treatment. Endoscopic treatments, including electrocoagulation, argon plasma coagulation (APC), laser, photodynamic therapy (PDT), cryotherapy, balloon dilatation, stent placement, etc., have been demonstrated to be effective methods in the treatment of the trachea tumors. For tracheostenosis caused by malignant tumors, the first thing we should do is to relieve the symptoms and keep stable vital signs, so that we can seek chance for the patients to receive other therapies. Ablation therapy only or ablation therapy combined with stent placement are recommended for intraluminal obstructive stenosis. For external pressure stenosis

and mixed stenosis, stent placement only and ablation therapy combined with stent placement are recommended, respectively. Some endoscopic treatments are also recommended for patient with early central lung cancer that is ineligible for surgery by British Thoracic Society Guidelines and American College of Chest Physicians Guidelines [1,2]. Endobronchial ultrasonography can help determine the depth of tumor invasion of the tracheobronchial wall, which can be used for the staging of early central lung cancer to provide guidance for the treatment [3]. Previous study demonstrated that cryotherapy was an effective method in early superficial bronchogenic carcinoma, which could be proposed as a first-line therapy in the population with high carcinogenic risk [4]. Hybrid technology, an innovate technique, combining water jet function with APC, is being used in the clinical practice. It can create a water cushion, providing shelter for the tissues under submucosa, and then the lesion can be ablated effectively and safely (Figure 1) [5]. Endoscopic treatments are performed through natural orifice and have advantages of less trauma, repeatability and lower cost, which is becoming one of the most important treatment methods. Patients can benefit more from endoscopic treatments, especially in patients with unresectable tumors, low-grade malignant trachea tumors, early central lung cancers, and benign trachea tumors.

Reference 1. Kennedy TC, McWilliams A, Edell E, et al. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132(3 Suppl):221S-233S. 2. Du Rand IA, Barber PV, Goldring J, et al. Summary of the British Thoracic Society guidelines for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Thorax 2011; 66(11):1014-1015. 3. Kurimoto N, Murayama M, Yoshioka S, et al. Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion. Chest 1999; 115(6):1500-1506. 4. Deygas N, Froudarakis M, Ozenne G, et al. Cryotherapy in early superficial bronchogenic carcinoma. Chest 2001; 120(1):26-31. 5. Zheng X, Herth FJ, Sun J. Initial Experience with Hybrid-Argon Plasma Coagulation as a Novel Local Treatment Method for Tracheobronchial Mucoepidermoid Carcinoma. Respiration 2019. Accepted.

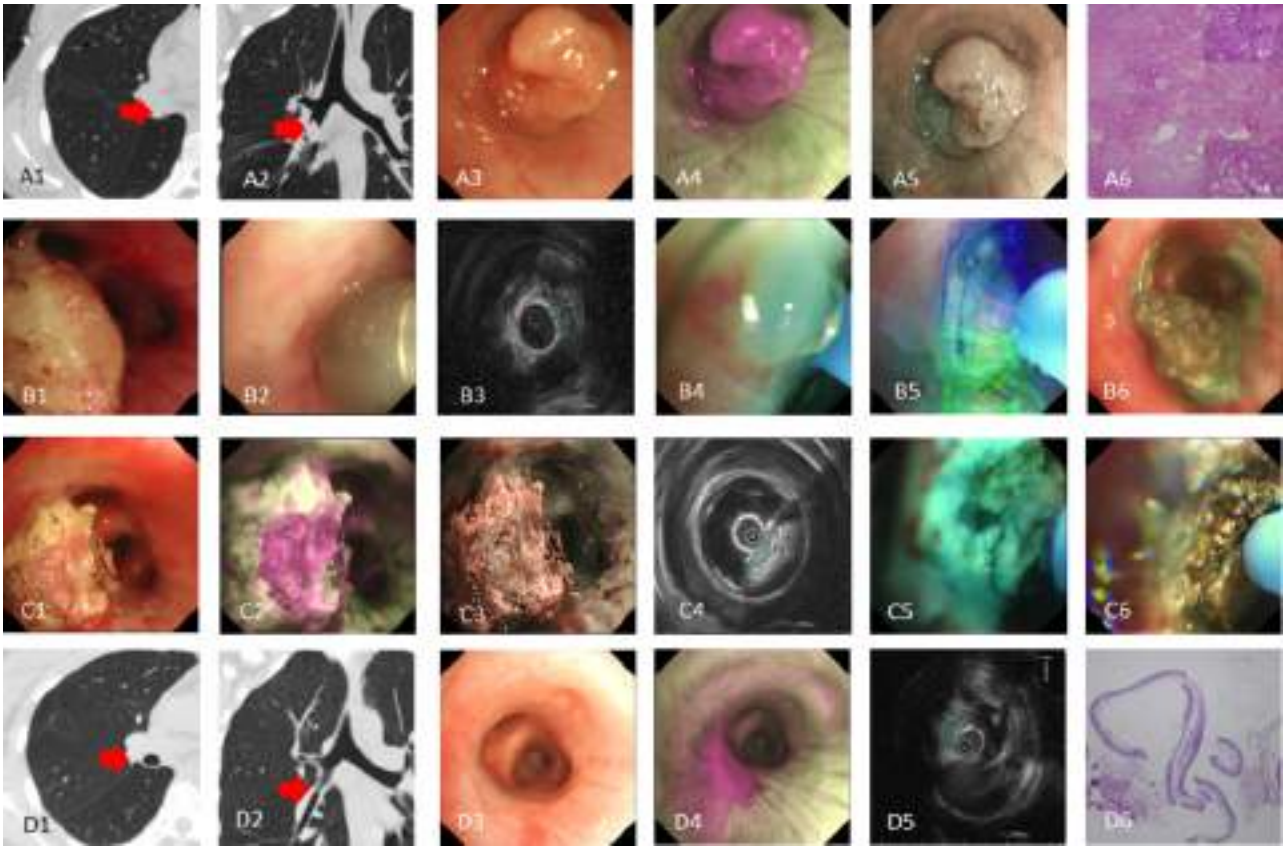

Figure 1. Hybrid-Argon Plasma Coagulation (APC) therapy in the treatment of an adult patient with tracheobronchial mucoepidermoid carcinoma. CT showed a nodule in intermediate bronchus, completely obstructing the airway (A1-2); large neoplasm in the intermediate bronchus detected by WLB, AFI, and NBI (A3-5); pathologic images indicated MEC (A6-8); invasivion size evaluated by rpEBUS after snare incision (B1-3); light blue water cushion created by Hybrid-APC (B4); Hybrid-APC ablation (B5-6); bronchoscopic inspection by WLB, AFI, and NBI, and evaluation by rpEBUS after first Hybrid-APC therapy (C1-4); light blue cushion created by Hybrid-APC (C5); 2nd Hybrid-APC ablation (C6); CT scan at 4-month follow-up revealed no recurrence (D1-2); bronchoscopy reexamination by WLB and AFI and invasive evaluation by rpEBUS at 4-month follow-up (D3-5); pathological images at 4-month follow-up revealed no recurrence (D6).

Keywords: endoscopic treatment, trachea tumor, hybrid technology

IBS11 ELECTRONIC CIGARETTES AND HEAT-NOT-BURN TOBACCO PRODUCTS - HOW ARE THEY DIFFERENT
MONDAY, SEPTEMBER 9 07:00–08:00

IBS11.01 IBS11 ELECTRONIC CIGARETTES AND HEAT-NOT-BURN TOBACCO PRODUCTS - HOW ARE THEY DIFFERENT

M. Goniewicz

Roswell Park Comprehensive Cancer Center, Buffalo/United States of America

Introduction: Although combustible tobacco cigarettes remain the most popular nicotine-containing products worldwide, non-cigarette products are evolving rapidly. Use of combustible tobacco remains the number one preventable cause of disease, disability, and death, however the effects of non-cigarette products on population-level health is unknown. Over the last 10 years electronic cigarettes (e-cigarettes) have gained considerable popularity, especially among smokers and youth. With the introduction of the 'Heat-not-Burn' (HnB) products (iQOS from Philip Morris International, Ploom TECH from Japan Tobacco International, and Glo from British American Tobacco) the landscape of tobacco product exposure has changed yet again. Population studies: Some early models of HnB products were developed in the late 1980s; however they did not reach a significant number of consumers and were withdrawn from the market. The introduction of HnB products in Japan in 2014 has been accompanied by an enormous decline in combustible cigarettes. Results from an international survey (International Tobacco Control (ITC) project) showed that that a high percentage of respondents believed HnB and e-cigarettes to be less harmful than cigarettes. Interestingly, smokers in Japan were most likely of 22 countries to believe that HnB were less harmful than cigarettes. Relative harmfulness beliefs of HnB may be both a cause and an effect of their popularity in Japan, fueled by marketing efforts. Ongoing studies will relate these beliefs to reasons for using HnB products, and, with future cohort data, transitions to/from HnB and cigarettes. Concerns have been raised that novel HnB tobacco products may be appealing to youth. Our research have showed that awareness and interest in HnB products among youth in Canada, England and USA was stable between 2017 and 2018, and concentrated primarily among smokers. Perceptions of HnB products are more similar to e-cigarettes than combustible tobacco. Toxicity: HnB tobacco products purport to deliver nicotine while reducing exposure to toxicants compared with combustible nicotine products such as tobacco cigarettes by avoiding directly burning tobacco and instead heating tobacco. We measured nicotine in HnB product and found that it delivered 1.4 mg nicotine from a single cartridge, while e-cigarette and tobacco cigarettes delivered 1.3 mg and 2.1 mg nicotine, respectively. In conventional cigarettes, once tobacco is heated above 600°C, combustion occurs, and smoke containing harmful chemicals is released. HnB have an electrical heating component, like e-cigarettes, that heats processed tobacco to 350°C releasing volatile components that often are not detectable in e-cigarettes. In general, yields of carbonyl and aromatic compounds and amines (except for nicotine) in HnB products have been shown to be between one and two orders of magnitude lower than yields of combustible cigarettes, but relatively similar to those of e-cigarettes. Hypothetically, reducing the aerosol generation temperature can result in lower emissions of tobacco combustion byproducts and reduced toxicity as compared to conventional tobacco cigarettes. Although many combustion by-products may be eliminated in HnB devices, carcinogenic nitrosamines are generated in the process of tobacco curing rather than during combustion, and may be transferred from the HnB into the aerosol that it generates. Our group tested nicotine and four Tobacco-Specific Nitrosamines (TSNAs), potent lung carcinogens, in HnB product iQOS. We compared TSNA levels in aerosols from HnB, e-cigarette and cigarette smoke. TSNA yields were significantly higher in the HnB product than those found in e-cigarettes but significantly lower than those found in tobacco cigarettes. TSNA yields in a smoke from single tobacco cigarette were between 7-17 times higher than TSNA yields in emissions from a single HnB cartridge. Potential health effects: Claims of lowered risk or health benefits for HnB compared to conventional cigarettes are based almost exclusively on industry-funded research, and except limited number of product testing studies, independent research is not available to support these claims as of 2019. To determine the cytotoxic and proinflammatory effects of HnB products, we exposed bronchial epithelial cells aerosol generated from HnB, e-cigarette aerosol, tobacco smoke or air (control) using an air–liquid interface system. Exposure to HnB resulted in decreased cell viability and increased release of pro-inflammatory interleukins as compared to air controls. Tobacco cigarette was the most toxic product. Interestingly, HnB product showed reduced toxicity as compared to tobacco cigarettes but increased toxicity compared to e-cigarettes. Finally, we used animal model to evaluate if short term in vivo exposure to HnB aerosols has the potential to recruit immune cells into the lung. We exposed mice to emissions from HnB, e-cigarette, and tobacco cigarettes. After 2-week exposure, we have made the novel observation that there was a hierarchy in the inflammatory response in the lung following exposure to the different products, with tobacco cigarettes causing the strongest and e-cigarette the weakest responses. Summary: HnB are different from conventional cigarettes and overall appears to deliver less of some toxicants. It is currently not clear whether HnB products may pose lower, the same or higher health risks than combustible cigarettes depending on the disease. HnB products emit more of several important toxicants and carcinogens with more adverse health effects than e-cigarettes.

Comparison of tobacco cigarettes, Heat-Not-Burn (HnB) products, and e-cigarettes.

	Tobacco Cigarettes (TC)	Heat-not-Burn (HnB)	E-cigarettes (EC)
Nicotine	YES	YES	**YES** (most products)
Tobacco	YES	YES	NO
Combustion	YES	NO	NO
Temperature	**YES** (very high during puffs)	**YES** (lower than TC)	**YES** (lower than TC; can be over-heated)
Electronic system	NO	YES	YES
Relative risk *(hypothetical)*	Higher than HnB and EC	Lower than TC but higher than EC	Lower than TC and HnB

Keywords: Tobacco, E-cigarettes, Heat-not-Burn (HnB) tobacco products

IBS11 ELECTRONIC CIGARETTES AND HEAT-NOT-BURN TOBACCO PRODUCTS - HOW ARE THEY DIFFERENT
MONDAY, SEPTEMBER 9 07:00–08:00

IBS11.02 E CIGARETTES/ ELECTRONIC NICOTINE DELIVERY SYSTEMS: A WORD OF CAUTION ON HEALTH

M. Unger

Thomas Jefferson University, Philadelphia/United States of America

This presentation discusses the introduction, development, and proliferation of new electronic nicotine delivery systems (ENDS) including E-cigarettes and Heat Not Burn Tobacco products. The use of these products is considered a means for improving public health and reducing the mortality attributed to cigarette smoking. The epidemiology and effects of use of various ENDS and their components are described. To date, multiple studies indicate that, despite differences in toxicity, there is insufficient evidence that use of ENDS leads to effective smoking cessation. Research questions will be proposed to address key unanswered questions about the effects of such systems and their role in tobacco risk mitigation in various populations.

Keywords: ENDS, Risk smoking cessation

IBS11 ELECTRONIC CIGARETTES AND HEAT-NOT-BURN TOBACCO PRODUCTS - HOW ARE THEY DIFFERENT
MONDAY, SEPTEMBER 9 07:00–08:00

IBS11.03 CANNABIS AND LUNG CANCER

J. Jett

National Jewish Health, Napa/United States of America

Cannabis is a generic term that includes cannabinoids, marijuana (MJ) and hemp derived from the plant Cannabis sativa. Documented use dates back several centuries BC. In 1970 the Controlled Substance Act classified cannabis as a Schedule I drug with high abuse potential and no medical use. Other Class I drugs are heroin, LSD and cocaine. Similarly, cannabis is illegal in many other countries. There are many different cannabinoids in cannabis but the two main ones are delta-9-tetrahydrocabinol (THC) and cannabidiol (CBD). The THC is associated with psychoactive effects of euphoria and relaxation and CBD is not associated with the euphoric effects but is associated with anxiolysis. Pharmaceutical grade cannabinoids are scheduled/classified differently and there are several FDA approved medicines in the USA and available is many other countries. Dronabinol (THC) and nabilone are available for chemotherapy induced nausea and vomiting (CINV). Nabiximol (1:1 mixture of THC and CBD) is used for analgesic effects and spacicity due to multiple sclerosis. It is approved for use in many countries but not the USA. (NASEM; Jett et al) Cannabis products can be smoked, vaporized, ingested or applied topically. Smoked or vaporized cannabis reaches the brain within 30 seconds to a few minutes and the effects subside over 1-3.5 hours which makes it easier to titrate the dose/effects than ingested products which results in effects 30 minutes to 2 hours after ingestion and may last 5-8 hours. The average THC levels in MJ were 4% in 1995 and increased to 12% in 2012. However, in recent years with new products such as wax, honey oil, dabs etc that may have concentrations of THC of 40-80% so the effects on the user may be more psychologically and physically intense and effects may include paranoia, anxiety, panic attacks and hallucination. Cannabis containing many of the same toxins and carcinogens as tobacco smoke. Regular smoking of MJ is associated with airway inflammation similar to cigarette smoking and regular use of cannabis alone (without tobacco) may result in symptoms of chronic bronchitis. (Douglas IS et al) There is no conclusive evidence that cannabis smoking is associated with an increased incidence of lung cancer. The best available evidence comes from six case-control studies within the International Lung Cancer Consortium (Zhang LR et al, NASEM). An epidemiologic review of six lung cancer studies concluded that these studies did not support an association of MJ use and lung cancer (Huang Y-HJ et al). A limitation of these pooled studies is the small number of heavy and chronic users of cannabis. The National Academy of Science, Engineering and Medicine (NASEM) expert panel concluded that there is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer. There is an increasing body of evidence that cannabinoids have some anti-cancer effects in cell cultures and animal studies. However, there are no convincing clinical trials demonstrating that cannabis is effective in cancer patients.(NASEM) There is insufficient evidence to support the use of cannabinoids in cancer patients, in spite of claims on the web/internet that concentrated cannabis oils can cure cancer. There is evidence that use of cannabinoids are of benefit for treating chronic pain, including neuropathy. Whiting et al performed a meta-analysis of 28 studies that mainly used pharmaceutical grade (Schedule III) cannabinoid based drugs such as nabiximol or nabilone and some smoked or inhaled THC trials. All but one was placebo controlled. The odds ratio was 1.4 of reporting 30% or more improvement in pain with cannabinoids. The NASEM concluded that there is substantial evidence that cannabis is an effective treatment for chronic pain. There have been patient reported outcomes that suggest that cannabis is beneficial for pain, anxiety and depression and may reduce the use of prescription drugs. (Corroon JM et al; Zaki P et al; Anderson SP et al). The NASEM panel concluded stated that there is conclusive evidence that oral cannabinoids are effective antiemetics for treatment of chemotherapy induced nausea and vomiting (CINV). Nabilone and dronabinol are FDA approved drugs for CINV. Good quality studies of inhaled or ingested plant based cannabis for CINV are limited. Most of these randomized trials for CINV were before the use of 5-hydroxytryptamine (5HT3) receptor antagonists. Accordingly, many oncologists would use a 5HT3 antagonist initially. Nabilone or dronabinol may be used for rescue or refractory nausea and vomiting as backup treatment options. Patient reported outcomes have noted benefit from medical marijuana products for nausea and vomiting (Anderson SP et al). The FDA has approved use of dronabinol for human HIV induced anorexia but there is currently insufficient evidence to support or refute the effectiveness of cannabinoids for cancer associated anorexia-cachexia (NASEM). However, cannabis has been reported to increase appetite and patient reported outcomes have again suggested benefit from medical marijuana. In summary, there is no current evidence that smoking MJ results in an increased incidence of lung cancer. However, the landscape is changing rapidly with the legalization of medical and recreational cannabis. This along with the increasing concentration and dose of the available products may result in an increased number of heavy and chronic users. This will require careful follow-up. Other areas of urgent need, as related to this review, for controlled clinical trials include: 1) Do cannabinoids have any role in treatment of cancer? 2) Do cannabinoids have any efficacy in reduction of opioid use or dose? 3) Is there any role for cannabinoids in treatment of cancer anorexia-cachexia. References: NASEM: National Academies of Sciences, Engineering and Medicine Jett JR et al; J Thorac Oncol 2017; 13:480-487 Douglas IS et al; Ann Am Thorac Soc 2015; 12:1700-1710 Zhang LR et al; Int J Cancer 2015; 136:894-903 Huang Y-HJ et al; Cancer Epidemiol Biomark Prev 2015; 24:15-31 Whiting PF et al; JAMA 2015; 313:2456-2473 Corroon JM et al; J Pain Res 2017; 10:989-998 Zaki P et al; J Pain Manage 2017; 10:353-362 Anderson SP et al; J Oncol Prac pub online March 12, 2019

Keywords: supportive care, Lung cancer, Cannabis

IBS12 CASE-BASED MANAGEMENT OF BRAIN METASTASIS (BM) IN ADVANCED LUNG CANCER PATIENTS: CHANGING THE STANDARDS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS12.01 QUESTIONS TO BE ADDRESSED

M. Guckenberger

University Hospital Zurich, Zurich/Switzerland

Brain metastases develop in relevant numbers of patients through their courses of metastatic non-small cell lung cancer (NSCLC) and are associated with worsening of quality-of-live and survival. Traditionally, outcome was very poor due to the lack of effective treatment options, for the brain metastases but also for extracranial metastatic disease. Recent advances in imaging, local and systemic treatment options have changed the prognosis of patients with NSCLC brain metastases and have challenged traditional treatment strategies. Management of patients with brain metastases today needs a more individualized approach due to the multiple factors influencing the decision making process: patient performance status; number, location and size of brain metastases; presence of symptoms and neurological deficits; presence and extend of extracranial disease; histology and presence of activating driver mutations; available systematic treatment options and their CNS activity; patient preference. From a local treatment perspective, radiosurgery and neurosurgical resection are treatment options, which have shown to improve survival in patients with limited brain metastases. Whole brain radiotherapy is not recommended after radiosurgery and neurosurgical resection; however stereotactic radiotherapy should be added to the resection cavity to improve local metastasis control. The value of radiosurgery without whole brain irradiation for multiple brain metastases is currently under investigation. Whole brain irradiation is today still recommended for patients with multiple and in particular symptomatic brain metastases; whether hippocampal avoidance can reduce the risk of damage to the neurocognitive system is not finally answered. The landscape is currently changing rapidly and fundamentally due to identification of activating driver mutations and the existence of effective targeted drugs. Additionally, treatment with immune checkpoint inhibition has also shown intracranial activity. Consequently, there is in particular a need to identify optimal combined modality strategies of local radiotherapy and systemic targeted drugs and immunotherapy.

Keywords: Brain metastases, NSCLC

IBS12 CASE-BASED MANAGEMENT OF BRAIN METASTASIS (BM) IN ADVANCED LUNG CANCER PATIENTS: CHANGING THE STANDARDS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS12.02 QUESTIONS TO BE ADDRESSED

E. Smit

Netherlands Cancer Institute, Amsterdam/Netherlands

Case-Based Management of Brain Metastasis (Bm) in Advanced Lung Cancer Patients: Changing the Standards. Questions to Be Addressed M. Guckenberger, E.F. Smit Dept. of Radiation Oncology, USZ, Switserland, Dept. of Thoracic Oncology, NCI, The Netherlands. Brain metastases develop in relevant numbers of patients through their courses of metastatic non-small cell lung cancer (NSCLC) and are associated with worsening of quality-of-live and survival. Traditionally, outcome was very poor due to the lack of effective treatment options, for the brain metastases but also for extracranial metastatic disease. Recent advances in imaging, local and systemic treatment options have changed the prognosis of patients with NSCLC brain metastases and have challenged traditional treatment strategies. Management of patients with brain metastases today needs a more individualized approach due to the multiple factors influencing the decision making process: patient performance status; number, location and size of brain metastases; presence of symptoms and neurological deficits; presence and extend of extracranial disease; histology and presence of activating driver mutations; available systematic treatment options and their CNS activity; patient preference. From a local treatment perspective, radiosurgery and neurosurgical resection are treatment options, which have shown to improve survival in patients with limited brain metastases. Whole brain radiotherapy is not recommended after radiosurgery and neurosurgical resection; however stereotactic radiotherapy should be added to the resection cavity to improve local metastasis control. The value of radiosurgery without whole brain irradiation for multiple brain metastases is currently under investigation. Whole brain irradiation is today still recommended for patients with multiple and in particular symptomatic brain metastases; whether hippocampal avoidance can reduce the risk of damage to the neurocognitive system is not finally answered. The landscape is currently changing rapidly and fundamentally due to identification of activating driver mutations and the existence of effective targeted drugs. Additionally, treatment with immune checkpoint inhibition has also shown intracranial activity. Consequently, there is in particular a need to identify optimal combined modality strategies of local radiotherapy and systemic targeted drugs and immunotherapy. From a systemic treatment perspective, it has become apparent that brain metastases may also be sensitive to tyrosine kinase inhibitors against a variety of targets and emerging data suggest that immune checkpoint inhibitors display activity as well. Therefore, in case of asymptomatic brain metastases at diagnosis when the primary lung cancer is characterized by an oncogenic driver, nowadays many would favour initial treatment with tyrosine kinase inhibitors in an effort to delay radiotherapy to the brain as long as possible. Whether symptomatic brain metastases at diagnosis may be managed in a similar manner, especially when refractory to high dose steroids, is less clear. The third generation EGFR TKI (osimertinib) and second/third generation Alk inhibitors (ceritinib, alectinib, brigatinib and lorlatinib) are associated with response rates in the brain in the relapse setting on treatment of first/second generation EGFR TKi's or first generation Alk inhibitor that are not different from extracranial response rates. Thus, also in this clinical situation, systemic treatment plays an important role in delaying radiotherapy – in particular whole brain radiotherapy- as long as possible. It should be noted however, that there are no formal randomized comparisons available of these treatment modalities.

Keywords: NSCLC, brain metastases

IBS13 HOW TO IDENTIFY AND MANAGE TOXICITY IN STAGE III
MONDAY, SEPTEMBER 9 07:00–08:00

IBS13.01 RADIATION RELATED TOXICITIES IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (LA-NSCLC)

A. Sun

Princess Margaret Cancer Centre, Toronto/Canada

Dr. Alexander Sun, MD, FRCPC Addie MacNaughton Chair in Thoracic Radiation Oncology Princess Margaret Cancer Centre/University of Toronto Lung Cancer Site Group Leader, Radiation Medicine Program Associate Professor, University of Toronto Principal Investigator for PMH – RTOG/NRG Oncology Co-Chair, Lung Disease Site Committee, Canadian Cancer Trials Group (CCTG) Radical radiotherapy is uesd as definitive therapy in locally advanced non-small cell lung cancer (LA-NSCLC), either alone or in combination with chemotherapy and/or surgery. However, definitive doses of radiotherapy are associated with potential toxicity related to the organs at risk (OAR). The major OAR's related to radical radiotherapy for LA-NSCLC include the lung and esophagus. Therefore, we need to be able to identify and manage radiation pneumonitis and esophagitis during and after a course of definitive radiotherapy. For good performance status, unresectable stage III NSCLC, radical radiotherapy is delivered either concurrently or sequentially with chemotherapy to total doses of 60Gy or higher. Although the best outcomes have been obtained with concurrent chemoradiotherapy, higher rates of toxicity have also been observed. With the advent of the establishment of adjuvant durvalumab after definitive concurrent chemoradiotherapy, the management of pneumonitis in particular has become even more of a challenge given the potential overlapping toxicities. For poorer performance status patients, radical radiotherapy may be used alone. For resectable patients with LA-NSCLC, radical radiotherapy can be given concurrently with chemotherapy prior to surgical resection as part of trimodality therapy. In other instances, radical radiotherapy can be given adjuvantly post-operatively for positive margins and can be considered in pathological N2 disease. Prophylactic Cranial Irradiation (PCI) has also been delivered in LA-NSCLC, although mostly in clinical trials as PCI has not been established as part of routine standard of care in stage III NSCLC. In this session, a discussion as well as case presentations will be used to illustrate how to identify and manage the above toxicities in stage III NSCLC. References (max 10) Baker S, Fairchild A. Radiation-induced esophagitis in lung cancer. Lung Cancer: Targets and Therapy 2016:7 119–127. (Review Article). Mehmood Q, Sun A, Becker N, et al. Predicting Radiation Esophagitis Using 18F-FDG PET During Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2016: 1;11(2):213-21. Verma V, Simone CB, Werner-Wasik M. Acute and Late Toxicities of Concurrent Chemoradiotherapy for Locally-Advanced Non-Small Cell Lung Cancer. Cancers. 2017; 9:120. (Review Article). Jain V and Berman AT. Radiation Pneumonitis: Old Problem, New Tricks. Cancers (Basel). 2018 Jul 3; 10(7). (Review Article). Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018; 2018 Sep 25. Shaverdian, N, Lisberg AE, Bornazyan, K et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase I trial. Lancet Oncol. 2017, 18(7), 895–903. Chuzi S, Tavora F, Cruz M, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor related pneumonitis. Cancer Manag Res. 2017;9:207-213. (Review Article). Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 2011; 29: 279–86. Le Pechoux C, Sun A, Slotman BJ, et al. Prophylactic cranial irradiation for patients with lung cancer. Lancet Oncol 2016; 17(7): e277–293. (Review Article). Sun A, Hu C, Wong SJ, et al. Prophylactic Cranial Irradiation vs Observation in Patients With Locally Advanced Non-Small Cell Lung Cancer: A Long-term Update of the NRG Oncology/RTOG 0214 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2019 Mar 14.

Keywords: Radiation Toxicity LA-NSCLC

IBS13 HOW TO IDENTIFY AND MANAGE TOXICITY IN STAGE III
MONDAY, SEPTEMBER 9 07:00–08:00

IBS13.02 SURGICAL MANAGEMENT FOR PERIOPERATIVE COMPLICATIONS IN ADVANCED LUNG CANCER AFTER CHEMORADIOTHERAPY

H. Date

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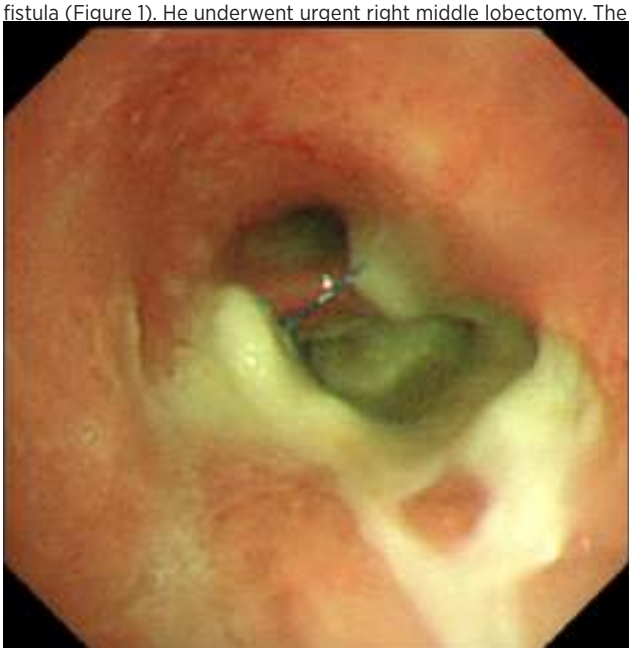
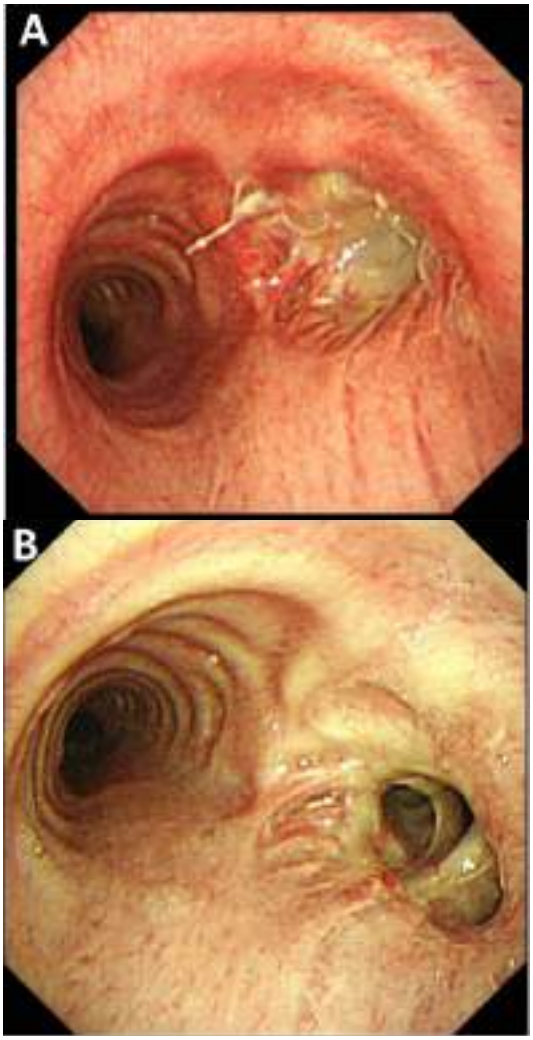
Complete resection of residual lung tumor after induction or definitive chemoradiotherapy may be indicated for selected patients with advanced lung cancer. However, perioperative complication is a great concern. Here, we present videos of four cases requiring surgical intervention for perioperative complications. Case 1 A 59-year-old man was diagnosed with squamous cell carcinoma invading right diaphragm, left atrium and subcarinal lymph node (cT4N2M0). After induction chemoradiotherapy, he was downstaged to cT4N1M0 and underwent right thoracotomy. We realized that the tumor was invading liver through diaphragm. During partial hepatectomy, IVC was injured and massive bleeding occurred. Cardiopulmonary bypass was established and left lower lobectomy with combined resection of diaphragm, liver and left atrium was performed. Case 2 A 50-year-old man was diagnosed with unresectable left upper lobe squamous cell carcinoma invading aorta and #6 lymph node (cT4N2M0). Definitive chemoradiotherapy significantly shrank the tumor. One year later, he was referred to us for salvage surgery. At thoracotomy, we found no fissure between the left upper and lower lobes. The left basal bronchus was accidentally stabled by false recognition of lingula bronchus. The staple lines were removed, and the basal bronchus was reconstructed by end-to-end anastomosis. Then the left upper lobectomy with combined resection of aortic adventitia was performed. Case 3 A 69-year old man was diagnosed with right lower lobe adenocarcinoma with right #2 lymph node metastasis (cT2N2M0). After induction chemoradiotherapy, he underwent uneventful left lower lobectomy with extensive hilar and mediastinal lymph node dissection. He developed radiation pneumonitis and received steroid treatment. On day 52, he readmitted due to sever cough, fever and purulent sputum. Bronchoscopic examination showed left lower bronchial fistula (Figure 1). He underwent urgent right middle lobectomy. The



Case 4 A 55-year-old man underwent a right upper sleeve lobectomy for T2N1M0 squamous cell carcinoma originating in the right upper lobe and developed a symptomatic anastomotic stenosis at two months postoperatively (Figure 2a). He required repeated bronchoscopic dilations to relieve his symptoms, which at 1 year postoperatively were complicated with a perforation of the right middle lobe bronchus. Emergent completion pneumonectomy and auto-transplantation of the right lower lobe were performed. Satisfactory bronchial healing was obtained (Figure 2b).



Keywords: complication, surgery, chemoradiation

IBS14 BEST MANAGEMENT OF EARLY STAGE NSCLC IN ILD PATIENTS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS14.02 IBS14 BEST MANAGEMENT OF EARLY STAGE NSCLC IN ILD PATIENTS

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Interstitial lung disease (ILD) is characterized by diffuse inflammation and fibrosis within the lung parenchyma.[1]Although a heterogeneous group of diseases, invariably, it is associated with a restrictive defect on pulmonary function testing, and a reduced ability for gas exchange.[2] On imaging, features of ILD can include reticulation, traction bronchiectasis and honeycombing. Interestingly, a diagnosis of ILD is an independent risk factor for the development of lung cancer.[3] Stereotactic ablative radiotherapy (SABR) is a common radical treatment modality for patients with early stage NSCLC and is characterized by its convenience, tolerability, and high efficacy.[4] Given these features, it has been popularized as an attractive option in early stage NSCLC patients with significant medical co-morbidities. Early stage NSCLC patients with co-existing ILD, however, are a high-risk group for any type of treatment, both for treatment-related toxicities and for acute exacerbations of ILD. These toxicities can be severe, and in extreme scenarios, fatal. The focus of this abstract will be on the use of SABR for early stage NSCLC patients with ILD, with an aim to discuss emerging data and future research directions. Despite the generally favorable toxicity profile of SABR, there are an increasing number of reports of serious toxicities in patients with pre-existing ILD. These reports have largely been retrospective in nature, heterogeneous in the radiation doses employed, with findings of extreme ranges in treatment related death rates. Arguments can be made on whether some of these

reports, especially in those with exceptionally high rates of extreme toxicity, confer an element of publication bias. This refers to the phenomenon whereby there is an inclination to report results that are more remarkable (i.e. major toxicity or treatment-related death). Therefore, although it is likely that SABR incurs a greater risk in this setting compared to standard lung SABR cases, the true risk is unclear. To further delve into this issue, our group recently performed a systematic review and meta-analysis of outcomes following several different treatment modalities for early-stage lung cancer patients with ILD.[5] From this initiative, 13 studies assessing outcomes after SABR were identified, and recognizing the caveats of the available data, we concluded that there was a 1 in 4 risk of severe radiation pneumonitis (defined as grade ≥3), and a 15% risk of treatment-related grade 5 toxicity. A specific diagnosis of idiopathic pulmonary fibrosis (IPF) appeared to be associated with the greatest risk, whereby treatment related mortality was 1 in 3, as compared to 14% for non-IPF fibrotic ILD. When considering this potential increased risk, it is important to recognize that the IPF patient population has a significant background risk of acute exacerbations of their disease, with an annual reported range of 5-19%.[6] The Canadian Pulmonary Radiotherapy Investigators group (www.capriclinicaltrials.com) has designed a single arm phase II trial to evaluate the role of SABR in T1-2N0M0 NSCLC patients with co-existing ILD who are not surgical candidates. The trial (clinicaltirals.gov, NCT03485378) is entitled: *Assessment of Precision Irradiation in Early Non-Small Cell Lung Cancer and Interstitial Lung Disease* (ASPIRE-ILD). To our knowledge, this will be the first prospective trial evaluating this clinical scenario, and it is novel in that patients will be stratified using the ILD-GAP score, which is an index that incorporates ILD mortality risk according to Gender, Age and Physiology.[7] The starting SABR dose will be 50 Gy in 5 fractions, and the dose fractionation will be escalated or de-escalated depending on toxicities observed in different cohorts of the trial. The appropriateness of SABR in any, or some of these patients can certainly be questioned in light of the potential serious toxicity. On the other hand, the median survival of untreated stage I NSCLC has consistently been reported to be less than 1 year in various studies.[8] Therefore, the value of treatment would ideally be answered through a randomized controlled trial, however, this is probably unfeasible as patients and physicians alike may be uncomfortable with randomization. Given the inherent risks of both untreated cancer as well as any cancer-directed treatment, we encourage investigators to continue to report on their experiences in this challenging clinical dillemma, whether positive or negative, so that additional research can inform shared decision making. REFERENCES 1. Maher EJ, Timothy A, Squire CJ, et al. Audit: the use of radiotherapy for NSCLC in the UK. *Clin Oncol (R Coll Radiol)*1993;5:72-79. 2. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*2008;63 Suppl 5:v1-58. 3. Naccache JM, Gibiot Q, Monnet I, et al. Lung cancer and interstitial lung disease: a literature review. *J Thorac Dis*2018;10:3829-3844. 4. Louie AV, Palma DA, Dahele M, et al. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: Controversies, insights, and changing horizons. *Radiother Oncol*2015;114:138-147. 5. Chen H, Senan S, Nossent EJ, et al. Treatment-Related Toxicity in Patients with Early-Stage Non-Small Cell Lung Cancer and Co-Existing Interstitial Lung Disease: A Systematic Review. *International Journal of Radiation Oncology*Biology*Physics*. 6. Hyzy R, Huang S, Myers J, et al. Acute exacerbation of idiopathic pulmonary fibrosis. *Chest*2007;132:1652-1658. 7. Milne KM, Kwan JM, Guler S, et al. Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease. *Respirology*2017;22:728-734. 8. Nanda RH, Liu Y, Gillespie TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: A National Cancer Data Base analysis. *Cancer*2015.

Keywords: toxicity, interstitial lung disease, Early Stage Lung Cancer

IBS15 BIOLOGY AND GENETICS IN ICI TREATMENTS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS15.01 CURRENT STATUS OF IO IN LUNG CANCER

S. Gettinger

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Only a decade ago, lung cancer was largely considered a non-immunogenic tumor. The focus of most clinical efforts at the time was development of molecularly targeted agents in hopes to personalize the systemic treatment of lung cancer. Although much has been accomplished over the last 15 years, with regulatory approvals of several targeted agents for EGFR, ALK, ROS1, BRAF and NTRK driven tumors, and emerging targeted therapies for other molecularly defined cohorts (e.g. MET, RET, HER2 driven tumors), the majority of patients with lung cancer do not have readily targetable molecular alterations. Arguably, the most impactful advance in the systemic treatment of lung cancer over the last several decades has been the appreciation and utilization of immunotherapy to attack and control typical lung cancer. Indeed, five- year survival rates from the first phase I trials of programmed death (PD)-1 inhibitor trials (BMS-003 and KEYNOTE-001) in patients with pre-treated advanced non-small cell lung cancer (NSCLC) are an unprecedented 16% (n=578, median duration of response 17 - 39 months), with five- year survival rate from one trial (KEYNOTE-001) evaluating chemo naive advanced lung cancer patients of 23% (n=101, median duration of response 17 months) (ref: PMID 29570421, 31154919). Based on subsequent randomized clinical trials, PD-1 axis inhibitor therapy has become standard first line therapy for the majority of patients with advanced NSCLC (those without readily targetable tumor molecular alterations), either alone (pembrolizumab) if tumor PD- ligand 1 (L1) expression is high (≥ 50%), or with standard platinum doublet chemotherapy if tumor PD-L1 expression is low/ negative/ unknown (pembrolizumab regardless of NSCLC histology; atezolizumab for non-squamous NSCLC) (ref: PMID 30620668, 29658856, 30280635, 2986395). PD-1 axis inhibitor therapy with durvalumab is additionally approved as consolidation therapy for patients with locally advanced NSCLC after receiving definitive concurrent chemoradiation without progression (ref: PMID 30280658). PD-1 axis inhibitor therapy has also shown activity in advanced small cell lung cancer (SCLC), with regulatory approvals of atezolizumab combined with first line etoposide/ platinum chemotherapy, and nivolumab or pembrolizumab as 3rd line therapy (in practice, nivolumab is often combined with ipilimumab after failure of chemotherapy as endorsed by the National Comprehensive Cancer Network) (ref: PMID 30280641, 27269741). Several phase III immunotherapy lung cancer studies are ongoing in the adjuvant and metastatic setting, with additional regulatory approvals anticipated in the coming years. Despite the success with PD-1 axis inhibitors, and tremendous impact on treatment paradigms for lung cancer, most treated patients do not clearly benefit from therapy, and most of those who do respond will ultimately develop resistance with recurrence/ progression of their cancer. Little is known about mechanisms of resistance, and coordinated translational efforts across cancer centers will be required to understand both acquired and primary resistance (to date, we are only aware of two published reports describing potential mechanisms of acquired resistance to PD-1 axis inhibitors in lung cancer; one implicating acquired loss of beta-2 microglobulin with resultant lack of MHC1 expression, the other, loss of tumor specific neoantigens through elimination of tumor subclones or chromosomal loss of truncal alterations) (ref: PMID: 28031159, 29025772). Currently, several trials are evaluating novel immunotherapeutic agents, including other immune checkpoint inhibitors, costimulatory agonists, vaccines, oncolytic viruses and cellular therapies. In most of these trials, patients are not selected by unique molecular/ immunologic characteristics of their tumor. Rather, empiric combinations of therapy (often including a PD-1 axis inhibitor) are generally trialed with tumor biopsies to help understand mechanisms of response and resistance. In clinical practice, a handful of unanswered questions repeatedly surface when treating lung cancer patients with immunotherapy. These include: What is the optimal duration of PD-1 axis inhibitor therapy? *Although there is little data to guide us here, we generally consider treatment holiday after 2 years of therapy without progression. However, PD-1 axis therapy can be continued indefinitely as was done in most registrational trials.* What is the role of immunotherapy in never smokers and those with targetable molecular alterations driving their disease? *There remains pessimism about use of immunotherapy in these populations, with the belief that tumors in such patients are less immunogenic (lower mutational burden with*

less neoantigens). However, there are limited numbers of patients who do respond, and efforts are underway to understand these responses. Novel immunotherapeutic approaches are also being developed. Currently, many thoracic oncologists will reserve PD-1 axis inhibitor therapy until no other standard targeted therapies (or trials evaluating novel targeted therapy) or chemotherapy remain. When should we concede that a patient's tumor is primarily resistant to PD-1 axis inhibitor therapy. i.e., how much time on therapy should be allowed to exclude delayed response or pseudo-progression. *Generally, if a patient's performance status has not deteriorated at the first tumor assessment on immunotherapy (6-8 weeks), many thoracic oncologists will continue therapy for another 6 weeks. If assessment at that time shows further progression, therapy is discontinued.* Should immunotherapy ever be continued with addition of other systemic therapy on progression of disease? *Generally, this is not recommended, unless a patient is having a mixed response or acquired resistance with oligo-progressive disease. That said, there is some rationale here, as PD-L1 may be induced in tumors by subsequent therapy.* Is there any role for consolidation durvalumab in patients with locally advanced NSCLC after concurrent chemoradiation followed by lung resection? *The PACIFIC trial leading to approval of consolidation durvalumab did not include such patients; currently, durvalumab is not indicated after surgery.* Should salvage nivolumab combined with ipilimumab be considered in patients with extensive stage small cell lung cancer after progression on standard chemotherapy plus/ minus atezolizumab. *Although nivolumab plus ipilimumab is not approved for use in the United States as salvage therapy for SCLC, it is occasionally prescribed as endorsed by the NCCN. It is unclear if the combination would have any activity in a patient who failed prior atezolizumab in combination with etoposide/ platinum.*

Keywords: Immunotherapy

IBS15 BIOLOGY AND GENETICS IN ICI TREATMENTS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS15.02 DETERMINANTS OF RESPONSE TO ICI

F.R. Hirsch

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While great promise has emerged with the development of immunotherapy (IT) in lung cancer, we are still struggling with how to select the right treatment to the right patients and how to select the patients, who will benefit from IT. Only 20-30 % of the patients with NSCLC will have a clear benefit from IT compared to chemotherapy alone, and the challenge is to select those patients. PD-L1 protein expression demonstrated by immunohistochemistry (IHC) has been pursuit as primary selection biomarker in the clinical trial development. However, the major challenge for evaluation of PD-L1 and top compare the results from one study to another was the use of different antibodies/assays and processing by the different companies. A comparison of the different PD-L1 assays was performed in the "PD-L1 Blueprint Project", and three antibodies/assays was found to be performing similarly and could be interchangeable (1,2). While higher PD-L1 expression seems to be associated with gradually increased outcome of IT, a tumor proportion score (TPS) ≥ 50% seems to be useful in the choice of IT (e.g. pembrolizumab) monotherapy versus IT plus chemotherapy (CT). The results (PFS/ OS) of IT monotherapy for patients with high PD-L1 expression is not significantly different than for IT+CT, although not directly compared, while for patients with tumors having lower PD-L1 expression, the combination of IT+CT seems better (3, 4). Thus, the predictive role of PD-L1 expression might be different between IT alone and IT+CT. The prognostic role of PD-L1 (e. g. association to outcome without any therapy) is still not clear with conflicting reported outcomes in the literature. Tumor mutation burden (TMB) has in some clinical trials demonstrated to be of predictive value, both based on tissue and plasma (5, 6, 7). In several studies it has been shown that the patient population with high TMB has little overlap with the patient population with high PD-L1 expression (6). Prospective clinical trials arer today performed evaluating plasma TMB as predictive biomarker (b-FIRST). However, also challenges related to TMB reports occur; different assay platforms have been used in different clinical trials, different definitions (e. g cut-offs) have been applied in the definition of high TMB vs low TMB, and also for TMB an comparison of results /assays seems to be needed. Such comparison studies are on-going both in the US (i.e. Friends of Cancer) and in Europe. On this stage, it is not clear whether TMB can replace PD-L1 IHC in treatment decisions; who will benefit from IT or not? Some studies (i.e. CheckMate 227) (8), indicate also that the two predictive assays are not "competing" but complementary. It has been shown that for patients having tumors with low (≤1%)- or no PD-L1 expression, but high TMB a treatment option of combined therapy with nivolumab+ ipilumumab seems justified. There are also conflicting results reported on the prognostic role of TMB associated to no systemic therapy or predictive role associated to chemotherapy alone. Other candidate biomarkers are under investigations and will be discussed. REFERENCES: Hirsch FR et al. J Thorac Oncol 2017 (2): 208-222 Tsao MS et al: J Thorac Oncol 2018 (9): 1302-1311 Gandhi L et al; N Engl J Med 2018 378(22): 2078-2092 Reck M et al; N Engl J Med 2016 375(19): 1823-1833 Carbone DP et a;; N Engl J Med 2017 376(25): 2415-2426 Gandara DR et al. Nat Med 2018 (9): 1441-1448 Samstein RM et al; Nat Genet 2019 (2): 202-206 Hellman MD et al; N Engl J Med 2018 378(22): 2093-2114

IBS16 INVASIVE DIAGNOSIS AND SURGERY IN LUNG CANCER SCREENING PARTICIPANTS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS16.01 LUNG CANCER SCREENING AND ITS EFFECT ON SURGERY

G. Veronesi

Humanitas Clinical and Research Center, Milan/Italy

The diagnostic revolution started in 1999 when the group of Prof. Henschke in New York published the results of Elcap study showing that Low Dose CT scan had 7 times higher sensitivity than chest-Xray to detect stage I lung cancer in 1000 high risk individuals. Subsequently in 2006 the I-elcap published 80% cancer specific survival rate at 10 years of the 484 patients with a screening cancers detected in 31.000 screened subjects. More evidence was required by before implementing Lung Cancer Screening on a wider scale, and the US randomised controlled trial NLST released data in 2012. The investigators reached the objective of 20% mortality rate reduction in the screening arm so that they stopped the trial and suggested to partecipants of the control arm to be screened.We needed to wait additional 6 years to have the released data of Nelson study, the European largest RCT, which mortality reduction was unexpectedly better than NLST with a mortality reduction 26-39% in men and women at 10 years for the screening arm with LDCT compared to no screening. Despite the evidence is available, in Europe only few countries have started a national implementation. One of the potential obstacle is related to uncertainties on sustainability. In Italy to stimulate a policy maker decision, our group have calculated the potential economical impact to implement LDCT in the population at risk (the analysis was presented at WCLC in Toronto). In collaboration with the Bocconi university we have found one of the lowest ICER for LDCT screening, 3049 for QALY. In Italy the potential target population of LDCT program includes 2.166.000 millions high risk individuals (smokers or former smokers, 55 years or older with 30 packs year smoking history) and 120 milions euros /year is the potential cost to screen all the high risk individuals according to this preliminary CEA analysis. The other obstacle is related to safety of LDCT screening on a large scale outside the academic environment. How characteristic of lung cancer changed with introduction of screening? and which is the impact on surgical approaches? In our experience and other screening programs most cancer cases were diagnosed in stage I with a mean size of 1.6 cm. In addition recall rate was very low, 5-10 % compared to 20-27% on NLST, risk of overdiagnosis was very limited around 10% of screening cancers; Estimated risk of lung cancer due to LDCT radiation exposure was less than 1 out of 108 detected in the worst scenario, false positive cases less than 2 %. It was clear that traditional open lobectomy was an overtreatment and minimally invasive lung sparing resection was required. Different retrospective studies have shown that sublobar resection are adequate oncological operation for very early stage lung cancers (in particular subsolid, slow growing or low suv tumors). More data on this topic will come from the two ongoing randomised trials in Us and Japan comparing lobectomy and segmentectomies for stage Ia and Ib NSCLC. In this scenario among the different types of minimally invasive approaches the robotic technique has recognised a wide diffusion all over the world with a great success due to the indisputable technical advantages including optimal 3D view, increased degrees of freedom, motion scaling, stable camera platform. We described in 2014 the technique and results of robotic approach to afford typical segmentectomies and concluded that robotic system by improving ergonomic, surgeon view and precise movements, may make minimally invasive segmentectomy easier to adoptand perform.

In addition many surgeons find very useful to inject the ICG ev after isolation and resection to better define the intersegmental plane and thus perform a more radical resection according to the technique we described in 2014. In this way many small centrally located tumors with high suspiciousness of malignancy can be treated with a diagnostic and therapeutic resection using MIS and lung sparing procedure. One of the most discussed issue in the treatment of lung cancer is related to extension of lymph node dissection. We analysed a consecutive series of clinical N0 screen detected cancers to identify predictive criteria of nodal involvement and found that in very small (less than 1 cm) or PET negative tumorslymph node dissection can be avoided with no risk of nodal involvement. Major goals of surgical participation in lung cancer screening programs include: 1. Optimization of the management of screen detected nodules; 2. Reduction of false positive rates and surgical diagnosis of benign diseases; 3. Reduction of surgical incision-related trauma; 4.Avoid overtreatment and favor tailored resection; 5. Collect sample for biomarker research for diagnostic and prognostic molecular non-invasive tests; 6. Participate to multidisciplinary meeting with radiologists; 7. Participate in national or international registries for quality control. Henschke, C. I. et al., Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 354 (9173), 99 (1999) Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409. De Koning H et al PL02.05 Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. J Thoracic Oncology, 2018;13,10: Supp.S185. DOI: https://doi.org/10.1016/j.jtho.2018.08.012. Veronesi G, et al. Analysis indicates low incremental cost-effectiveness ratio for implementation of lung cancer screening in Italy. WCLC 2018 Toronto Veronesi G, et al. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. J Thorac Oncol. 2014;9(7):935-9. Nakamura k, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (jcog0802/wjog4607l). jpn j clin oncol. 2010;40:271-274. Altorki NK, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (calgb/alliance 140503). lancet respir med. 2018;6:915-924. Pardolesi A, et al. Use of indocyanine green to facilitate intersegmental plane identification during robotic anatomic segmentectomy. JTCVS, 148, 737-738 Veronesi G, Maisonneuve P, Pelosi G et al. Screening-detected lung cancers: is systematic nodal dissection always essential? J Thorac Oncol. 2011;6(3):525-30. Osarogiagbon RU, etr al. Early-Stage NSCLC: Advances in Thoracic Oncology 2018. JTO1556-0864

Keywords: Lung cancer, Screening, segmentectomy

IBS16 INVASIVE DIAGNOSIS AND SURGERY IN LUNG CANCER SCREENING PARTICIPANTS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS16.02 MINIMALLY INVASIVE LUNG CANCER SCREENING

W. Rzyman

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Lung cancer screening is a challenge for the specialists that are involved in this multidisciplinary venture. There is a huge number of individuals with CT-findings that are non-malignant and a lot of indeterminate pulmonary nodules that are difficult to assess. High sensitivity is required not to overlook early lung cancer but simultaneously acceptable specificity have to be ensured in order to reduce futile invasive diagnostics and treatment procedures related to false positive diagnoses (1,2,3). The experience of the multidisciplinary team and adoption of the specific radiological protocol that is strictly followed is a mainstay of successful lung cancer screening program. Thoracic radiologist is responsible for the reduction of false positive rate to a safe minimum. This goal can only be achieved by strict adherence to the guidelines and protocol for the assessment of nodules. LungRads or volumetry with assessment of volume doubling time should be applied to minimize false positive rate. The multidisciplinary discussion on tumor board meeting of the suspected cases is another element leading to the reduction of unnecessary invasive diagnostics and surgery in non-malignat leasions that produces harm, entails risk of complictions and increases costs (3). In Gdańsk where two screening programs were conducted during last 10 years most harmfull aspects were reduced almost doublefold (tab.1). several studies have shown that by applying an effective diagnostic algorithm together with multidisciplinary discussion of positive cases detected by CT screening, the frequency and extent of surgery for non-malignant disease can be minimized while a high cure rate for individuals diagnosed with lung cancer can be obtained (1,3,4). Mainly radiologists and thoracic surgeons involved in multidisciplinary tumor board have the important responsibility to minimize the risk of useless invasive procedures for benign disease and avoid overtreatment of very early cancers or precancerous lesions (1,3) The proportion of patients that are sent for invasive diagnostic procedures varies between 2-7% and depends on the quality of the screening center. In Gdańsk, although in both programs approximately 3,5% of individuals participating in the screening were sent for the diagnostics, lung cancer detection rate in these groups were 30% and 57% respectively so diagnostic accuracy increased significantly. The invasive diagnostic work –up is based on FNAB and CNB where radiologists play crucial role as in majority of the institutions they perform biopsies. Pulmonary nodules biopsy in the best institutions is performed with 80-90% specificity and sensitivity and reasonably low complication rate. Pneumothorax is among most frequently observed complications requiring pleural drainage in 10-20% of cases. Bronchoscopy, EBUS, EUS and PET-CT are additional tools that completing the diagnosis and staging. Endobronchial navigation bronchoscopy (ENB) is a supplementary method that enhances the diagnostic yield of flexible bronchoscopy from 36-68% to 63-77% depending on the size and location of peripheral pulmonary lesion. This method has great potential in the future treatment of small nodules detected in lung cancer screening programs. Lately two ablation systems are intensively tested that can be applied by ENB. The minimally invasive techniques in the future treatment of screening detected cancers are the only treatment options that could be accepted in this context. The application of ultrasound or radiofrequency ablation by ENB system in the treatment of pure GGO and mixed GGO lesions that are progressing would be the very promising solution. Although lobectomy is still a gold standard in the treatment of stage I NSCLC this dogma most probably is going to be changed in the near future, at least for T1N0 tumors. Many retrospective studies report no difference in overall and recurrence free survival of patients operated with lobectomy and sublobar resection. There are however many studies that are showing conflicting results. In the analysis of 6000 operated stage I NSCLC patients based on national lung cancer registry in Poland Dziedzic et al. have shown significantly inferior overall survival in wedge resection group comparing to lobectomy and segementectomy groups (5). Segmentectomy provides two benefits comparing to wegde resection: allows to obtain a wide resection margin and to perform hilar lymphnode resection. It is however much more technically demanding when VATS procedure is considered. In the presentation the crucial aspects of “minimally invasive” LDCT lung cancer screening will be discussed. References: 1. 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Stage I non-small-cell lung cancer: long-term results of lobectomy versus sublobar resection from the Polish National Lung Cancer Registry. Eur J Cardiothorac Surg. 2017 Aug 1;52(2):363-369. Tab.1 Comparison of two lung cancer screening programs performed in Gdańsk, Poland between 2009–2011 and 2016-2018 in terms of selected results affecting quality of screening.

	PILOT *2009-2011*	**MOLTEST** *2016-2018*
Lung cancer (det. rate)	**1,2%**	**2%**
False positive rate	**34,7%**	**17,6%**
Invasive work-up	**3,6%**	**3,5%**
Futile surgery	**29%**	**16%**

Keywords: minimal invasive surgery, FNAB, lung cancer screening

IBS17 UNDERTAKING NURSING AND ALLIED HEALTH RESEARCH.. HOW TO SURVIVE IT AND GET PUBLISHED
MONDAY, SEPTEMBER 9 07:00–08:00

IBS17.01 UNDERTAKING NURSING AND ALLIED HEALTH RESEARCH - HOW TO SURVIVE IT AND GET PUBLISHED

K. White

Private Practice, Bexley North/Australia

The nursing and allied health professions include a diverse range of disciplines, such as many different specialist nurses, physiotherapy, occupational therapy, speech and language pathology, dietetics, social work, and others. The foundation of modern health service interventions is that of evidence-based practice, to ensure that patients are receiving interventions that have been proven, through robust research, to provide benefit for the patient. Nursing interventions have a longer history of research underpinning them than allied health. In the allied health professions, there remains a dearth of robust research providing a clear evidence base for interventions routinely used. This presentation will focus on the challenges faced by both nurses and allied health professionals, particularly clinicians, in undertaking research and, once a research study is completed, how to get the research published. This is even more challenging in the general speciality of oncology and within the sub-specialty of lung cancer. The lack of research among nursing and the allied health professions is not a new phenomenon. My unpublished undergraduate thesis for the BAppSc(OT) in 1994 was titled 'The replication of research in the health sciences', investigating the level of replication of research in occupational therapy, physiotherapy, speech pathology and nursing. The aim of this research was to ensure the scientific knowledge base of the interventions being utilised were valid and reliable. The outcome of the research demonstrated a significant limitation in the replication of research, with many interventions being utilised by these professions not having a strong evidence base, or any evidence base at all. Twenty-five years later the scientific base for these professions, as well as dieticians and new and emerging allied health professions, has improved. In the field of occupational therapy most national professional bodies now have a focus on supporting research through funding and the dissemination of research findings. How does a novice clinical researcher go about funding, designing, implementing and publishing a research study? One of the keys for novice researchers is to find an academic or clinical research mentor, who is able to support you in navigating the muddy waters of clinical research. Clinical research is key to ensuring research projects are designed to meet the needs of our rapidly changing clinical environment, emerging clinical areas and interventions. There are many challenges in being a clinical researcher. These include a lack of research competency and training, the pressure of large clinical caseloads, a lack of support from within nursing and allied health departments, as well as at a hospital level, where the priority is primarily for patient intervention, not research. In this presentation I will outline how I navigated my initial clinical research in lung cancer and progressed over time to become an applied public health researcher in cancer control. Throughout this research progression I have had the support of mentors and supervisors while completing higher degrees, as well as clinical champions in my workplaces. I will outline the steps required to develop a research project, including protocol development, practical tips for managing Human Research Ethics and Governance Committee applications, data collection and management. Once your research study is complete what next? Publish or perish remains a key concept for nursing and allied health professionals. While in some health conditions, such as paediatrics, spinal cord injury, and acquired brain injury to name a few, there is a strong body of evidence for allied health interventions, in oncology, specifically lung cancer, a dearth of evidence from the allied health professions continues. There has been an improvement in research in some specific areas of lung cancer management which involves allied health professionals, such as in exercise, rehabilitation, and psychosocial support. However, significant gaps in the evidence base for allied health interventions for people living with lung cancer remain.There has been a growth in nursing research, particularly in lung cancer, but how robust is this research output? Is the nursing profession producing robust RCT studies that inform clinical practice? Internationally, both nursing and allied health professionals may be completing research or quality improvement activities that are building on their evidence base. However, they may not be publishing these important findings. It is critical that the work being done is published and further built on, with ongoing research and investigation, to ensure a robust and evolving evidence base for all nursing and allied health interventions being provided to patients. There continues to be a dearth of research studies by allied health professionals, particularly in the area of oncology and more specifically lung cancer. For our professions to continue to grow in this speciality area and demonstrate our benefit, we need to engage and support clinicians to bring research into their daily clinical practice, to ensure a robust evidence base in oncology, and more specifically lung cancer, is developed.

Keywords: Nursing, Allied health, Clinical research

IBS17 UNDERTAKING NURSING AND ALLIED HEALTH RESEARCH.. HOW TO SURVIVE IT AND GET PUBLISHED
MONDAY, SEPTEMBER 9 07:00–08:00

IBS17.02 HOW TO GET YOUR RESEARCH PUBLISHED

T. John

Austin Health, Olivia Newton-John Cancer Research Institute, Melbourne/ Australia

It is becoming increasingly important for researchers to not only ask and answer questions, but to disseminate the information gained to the wider community. One of the most important and indeed respected means of disseminating information is publish your results in a peer reviewed journal. While this may sound very straightforward, those who have tried to publish their data will be familiar with the frustration with peer reviewers, of rejection without peer review, rejection following extensive peer review or the need to submit a completely revised manuscript. Here I will discuss some of the key principles of getting your paper published, based on my experience as an author, reviewer and associate editor. I will go cover a range of areas from writing a good cover letter, what to include in the paper, to how to respond to reviewers. There are no guarantees to getting your paper published where you want the first time round, but these pointers will hopefully enable you to pick the right type of publication, the right journal and the best way to frame your paper.

IBS18 ESSENTIALS IN BIOMARKER TESTING FOR LUNG CANCER
MONDAY, SEPTEMBER 9 07:00–08:00

IBS18.01 TESTING GUIDELINES IN 2019

M.B. Beasley

Mount Sinai Medical Center, New York/United States of America

Molecular alterations occurring in lung cancer which are either amenable or potentially amenable to treatment with targeted therapies have been identified at an exponential rate in the past decade. Consequently, an increasing number of post-treatment resistance mechanisms have also been identified. Adequate molecular testing is therefore critical for the identification of such alterations for appropriate treatment planning. As such, the first joint CAP/IASLC/AMP molecular testing guidelines were published in 2013 and were expanded in the updated 2018 guidelines. The necessity for this was due not only to the rapid advances in identification of targetable mutations but also to improved technologies with which genetic variants could be identified. Briefly, the 2018 guidelines recommend that, at a minimum, testing for *EGFR* hot-spot mutations as well as *ALK* and *ROS* translocations must be performed. Testing for *BRAF, RET, ERBB2, KRAS and MET* alterations were not recommended as stand-alone assays but were deemed appropriate as part of larger multiplex panels. *EGFR* T790M testing was the only strong recommendation for patients with targetable mutations who relapsed on targeted therapy. The guidelines were recommended for advanced stage adenocarcinomas or tumors with an adenocarcinoma component. Much latitude was left to individual practices in regard to testing early stage cancers and tumors with non-adenocarcinoma histology. European guidelines from ESMO provide similar recommendations regarding *EGFR* and *ALK* testing. In the time since the publications of these guidelines in 2018, the number of therapeutic targets has continued to increase. Additionally, there has been increased focus on neoadjuvant use of targeted therapies. While these neoadjuvant trials primarily focus on *EGFR*, *ALK* and *ROS* abnormalities, some extend beyond this scope to include mutations in genes such as *MET*, which are not part of the 2018 minimal testing criteria. All of these factors contribute to the increasing challenges of providing sufficient testing for optimal

patient care. Coverage of the ever-expanding list of targetable alterations is somewhat ameliorated by the recommendation of multiplexed next-generation sequencing panels (NGS) over single gene testing in order to identify treatment options beyond the minimal recommendations. NGS allows for a larger number of tests to be performed on a smaller amount of material, which is particularly critical given that most patients are diagnosed at an advanced stage and may only have a small biopsy or cytology specimen available as opposed to a resection. While misconceptions remain, cytology specimens are perfectly adequate for molecular testing provided sufficient material is present, an issue which can be a factor in any small biopsy specimen. Molecular testing on cytology specimens is typically performed on cell block preparations; however, results have also been achieved from other types of cytology preparations and supernatant material. In spite of these advances, it is recognized that significant knowledge gaps and limitations exists in regard to testing. As such, a significant number of lung cancer specimens do not undergo appropriate molecular testing. Further, access to testing, debates regarding cost-effectiveness, issues with reimbursement and optimal approaches in resource-limited areas remain a challenge. Selected references: Bellevicine C, Troncone G. The cytopathologist's expanding role in the 2018updated molecular testing guidelines for lung cancer. Cancer Cytopathol. 2018 Sep;126(9):753-755. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, O'Byrne K,Stahel R, Peters S, Felip E; Panel Members; Panel Members. Second ESMO consensusconference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol. 2014 Sep;25(9):1681-90. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH,et al.Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018 Mar;142(3):321-346.

Keywords: Lung Cancer, Molecular testing, NGS

IBS18 ESSENTIALS IN BIOMARKER TESTING FOR LUNG CANCER
MONDAY, SEPTEMBER 9 07:00–08:00

IBS18.02 TESTS BY NEXT GENERATION SEQUENCING

L. Sholl

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Next generation sequencing (NGS) encompasses a family of technologies that effectively multiplex and digitize nucleic acid sequencing. The major technical platforms used in clinical practice include hybrid capture and amplicon sequencing, either of which can be applied to tumor or cell free DNA testing. Essential steps for any NGS assay include: 1) capture of some or all of the genome; 2) massively parallel sequencing; 3) alignment of the sequencing reads to a reference genome; 4) variant calling and 5) variant interpretation. Each of these steps has a major influence on the assay output, including breadth of coverage (how much of the genome to sequence?), depth of sequencing (how sensitive is the assay?), accuracy, and clinical relevance. In general, DNA hybrid capture assays are optimized for breadth, both in terms of overall genomic real estate (from 100s of genes to the entire genome) and for capturing complex changes such as copy alterations and structural variants. The drawback to the approach, however, is high cost, limited analytic sensitivity, and suboptimal capture and sequencing of highly repetitive regions, leading to poorly-covered or uncovered areas of the genome. Amplicon based sequencing, in contrast, requires a much more focused design. This approach uses PCR to capture the genomic regions of interest and then employs massively parallel sequencing to interrogate each individual PCR amplicon. This approach is lower cost, more sensitive, and faster than hybrid capture, but is best suited for small targeted panels (10s to 100s of genes), is less reliable for detection of copy number changes and rearrangements, and is prone to PCR-related errors. Many of the large academic and commercial NGS panels rely on hybrid capture technology to detect a range of mutations, losses and amplifications, and insertion-deletion/rearrangement events occurring across several hundred genes implicated in human tumorigenesis.[1,2] In addition to revealing the mutational status of characterized oncogenes and tumor suppressor genes, these panels can uncover a host of changes to the DNA representing underlying mutagenic processes or DNA repair defects. For example, mismatch repair deficiency/microsatellite instability is characterized by insertion-deletion events in association with repetitive stretches of DNA and/or certain patterns of nucleotide substitution (C>T changes with an adjacent 3' or 5' guanine). Many laboratories have leveraged existing panel sequencing assays to detect mismatch repair deficiency and are beginning to replace PCR and/or immunohistochemistry screening to identify patients at risk of Lynch syndrome and/or as a biomarker for response to PD-1 inhibition.[1,3] Beyond detection of specific DNA damage signatures, the ability to quantify mutational changes on NGS platforms has given rise to the concept of tumor mutational burden (TMB) and the recognition that this may serve as a biomarker for response to immune checkpoint inhibitors. Attempts to compare TMB values across testing platforms has focused attention on the wide technical and informatic variation intrinsic to different NGS assays that may influence TMB calculation, including gene content, choice of tumor-only vs tumor/normal paired sequencing, germline filtration methods, and unrelated clonal processes (such as clonal hematopoeisis). [4] As a result, identification of a single cutpoint for predicting therapeutic response to immunotherapy is challenging and has driven efforts to standardize NGS panels for TMB detection. [5] While most DNA-based NGS panels in use today are sufficiently sensitive for reliable detection of single nucleotide substitutions (e.g. KRAS G12D; EGFR L858R) or small insertion deletions (EGFR exon 19 deletion mutations), these panels often fall short in detection of large structural variants including rearrangements.[6] Functional rearrangements typically result from gene breakages and fusions occurring within intronic (non-coding) sequences. On a per gene basis, introns tend to be significantly larger than coding exons, which means that an NGS assay designed with cost and sensitivity concerns in mind must have restricted overall intronic coverage. In addition, introns tend to contain a much higher proportion of repetitive elements, thus the tools used for rearrangement detection must be able to discern the presence of these variants despite low sequencing coverage and nonspecific sequence mismatches. In practice, these issues lead to reduced clinical sensitivity for detection of large deletions and rearrangement events. RNA-based NGS platforms, including targeted RNAseq and anchored multiplex PCR, detect the fusion transcript directly, eliminating the need to target introns. Labs may now employ workflows in which a DNA assay is used for mutation and copy changes and an RNA assay is used for rearrangement detection. A substantial minority of DNA sequencing-negative lung cancers may have a fusion detected by an RNA assay, leading some groups to advocate for sequential DNA then RNA testing protocols in driver negative lung adenocarcinomas.[7] NGS is a powerful tool to guide the diagnosis and treatment of patients with lung cancer. Improvements in assay design, chemistry, bioinformatics and variant interpretation will continue to increase its reliability and use across tumor and specimen types. Coordination with experts versed in the limitations of the technology is essential for appropriate implementation in clinical practice. References: 1. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med* 2017; 23(6): 703-13. 2. Sholl LM, Do K, Shivdasani P, et al. Institutional implementation of clinical tumor profiling on an unselected cancer population. *JCI Insight* 2016; 1(19): e87062. 3. Papke DJ, Jr., Nowak JA, Yurgelun MB, et al. Validation of a targeted next-generation sequencing approach to detect mismatch repair deficiency in colorectal adenocarcinoma. *Mod Pathol* 2018; 31(12): 1882-90. 4. Garofalo A, Sholl L, Reardon B, et al. 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Keywords: rearrangement, hybrid capture, Tumor Mutation Burden

IBS19 NOVEL APPROACHES IN RADIATION ONCOLOGY FOR SMALL CELL AND NEUROENDOCRINE CANCERS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS19.01 NOVEL RADIOTHERAPY APPROACHES IN SMALL CELL LUNG CARCINOMA – APPLICATIONS TO THORACIC, OLIGOMETASTATIC AND CRANIAL TUMOR CONTROL

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Radiotherapy (RT) plays a very important role in the management of Small cell Lung Cancer (SCLC), and jointly with chemotherapy can lead to cures in locally advanced SCLC[1]. Advances in RT techniques and understanding of its impact on tumor control are paving the way for a number of novel RT approached in the management of thoracic disease, as well as metastatic disease and brain control in SCLC. Thoracic radiation currently plays a role in extensive stage SCLC[2], particularly in terms of reduction of symptomatic progression of intrathoracic disease. There is room to optimizing the indications, techniques, volumes and perhaps even dose of RT in that setting, and timing with respect to other treatments is worth exploring[3-5]. Whether there is an "oligometastatic" state in SCLC is not clear. One randomized trial of consolidative RT for patients with 1-3 extrathoracic metastases[6] showed worse outcomes if all sites were treated with RT, so at this time we cannot recommend such an approach. However, immunotherapy is now part of systemic management of SCLC and studies have documented an important synergy of RT and immunotherapy[7]. Thus, the question of consolidative RT to areas of either residual disease, or to areas of oligo-progression, should be explored further, particularly if there are improved biological markers to differentiate patients with a lower burden of cancer, or slower natural history of disease. Prophylactic cranial irradiation (PCI) has been more controversial given some mixed evidence of its impact on survival from randomized controlled trials[8,9], but all trials agree that PCI does reduce the risk of brain metastases in patients with SCLC. There are two current approaches to minimizing the risks of PCI – hippocampal sparing[10] and omission of PCI, with MRI surveillance, and perhaps utilization of stereotactic RT if patients present with one or few brain metastases[11]. This approach, which has been of great benefit in reducing the negative impact of brain radiation while maximizing brain tumor control in non-small cell lung cancer, is emerging as a new paradigm in the management of patients with SCLC, although its applicability may be limited. References: 1. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18(8):1116–1125. 2. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015; 385: 36–42. 3. Slotman BJ, Faivre-Finn C, van Tinteren H, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the Phase III CREST trial. Lung Cancer 108 (2017) 150–153. 4. Palmer DA, Warner A, Louie AV et al. Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis. Clinical Lung Cancer, 2015, Vol. 17, No. 4, 239-44. 5. Rathod S, Jeremic B, Dubey A. et al. Role of thoracic consolidation radiation in extensive stage small cell lung cancer: A systematic review and meta-analysis of randomised controlled trials. European Journal of Cancer 110 (2019) 110-119. 6. Gore EM, Hu C, Sun AY, et al. NRG Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone To Prophylactic Cranial Irradiation And Consolidative Extra-Cranial Irradiation For Extensive Disease Small Cell Lung Cancer (ED-SCLC): NRG Oncology RTOG 093. J Thorac Oncol. 2017 October; 12(10): 1561–1570. 7. Bang A, Schoenfeld JD. "Immunotherapy and radiotherapy for metastatic disease". Ann Palliat Med. 2018; (in press) 8. Slotman B, Faivre-Finn C, Kramer G, et al. EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. (2007), 357(7):664-72. 9. Takahashi T, Takeharu Y, Takashi S, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicenter, randomized, open-label, phase 3 trial. The Lancet Oncology 2017, 18: 663-71. 10. Gondi V, Pugh SL, Tome WA, et al.Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial J Clin Oncol. 2014 Dec 1; 32(34): 3810–3816. 11. Robin TP, Jones BL, Amini A, et al. Radiosurgery alone is associated with favorable outcomes for brain metastases from small-cell lung cancer. Lung cancer (2018), 120, 88-90

Keywords: Prophylactic cranial irradiation (PCI), Thoracic Radiotherapy, small cell lung cancer

IBS19 NOVEL APPROACHES IN RADIATION ONCOLOGY FOR SMALL CELL AND NEUROENDOCRINE CANCERS
MONDAY, SEPTEMBER 9 07:00–08:00

IBS19.02 NOVEL RADIOTHERAPY APPROACHES IN SMALL CELL LUNG CARCINOMA – HAS SABR AND RADIONUCLIDE THERAPY GOT A ROLE TO PLAY?

G. Hanna

Peter MacCallum Cancer Centre, Melbourne/Australia

Novel Radiotherapy Approaches in Small Cell Lung Carcinoma – has SABR and Radionuclide therapy got a role to play? Thoracic radiotherapy has been shown in to increase overall survival when added to systemic therapy in patients with small cell lung carcinoma (SCLC) and M0 stage. The dose, fractionation, treatment time and timing issues have not been fully resolved. A recent study did not show the superiority of 66Gy in 33 daily fractions over 6.5 weeks over twice-daily radiotherapy to a dose of 45 Gy in 30 fractions over 3 weeks twice daily [1]. For stage I non-small cell lung carcinoma (NSCLC), stereotactic ablative body radiotherapy (SABR) has been clearly shown to be superior to conventional fractionation [2]. Given the clear benefit seen in early stage NSCLC, it is postulated that SABR may have a role to play in early stage SCLC. A recent multi-institutional cohort study has reported favourable outcomes in this setting [3]. However, randomised data of equivalence or indeed superiority are lacking. Furthermore, questions remain as the timing and role of systemic therapy and prophylactic cranial irradiation when SABR is used in this setting. In advanced SCLC, many tumors display neuroendocrine clinical and cytological features and many SCLC tumors express somatostatin receptor and this can be imaged using radiolabeled somatostatin analogs such as 68Ga-DOTATATE [4]. Given the uptake by some SCLC tumors of 68Ga-DOTATATE, higher doses of the tracer have been used in an attempt to provide radiolabelled radiotherapy treatment in metastatic disease in what has been described as peptide receptor radionuclide therapy (PRRT) [5]. This molecularly target radiotherapy is a potentially exciting therapeutic approach, but the ideal positioning of such therapy in tumors which are suitable for treatment with PRRT and the safety of PRRT with systemic therapy have yet to be determined. References: 1. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18(8):1116–1125. doi:10.1016/S1470-2045(17)30318-2 2. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small cell lung cancer (TROG 09.02. CHISEL): a phase 3, open-label, randomised controlled trial. The Lancet. 2019; 20: 494-503 3. Verma V, Simone CB, 2nd, Allen PK, et al. Multi-Institutional Experience of Stereotactic Ablative Radiation Therapy for Stage I Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2017;97:362-71 4. Sollini M, Farioli D, Froio A, et al. Brief Report on the Use of Radiolabeled Somatostatin Analogs for the Diagnosis and Treatment of Metastatic Small-Cell Lung Cancer Patients. J Thor Oncol 2013;8(8):1095-1101. 5. Lapa C, Hänscheid H, Wild V, et al. Somatostatin receptor expression in small cell lung cancer as a prognostic marker and a target for peptide receptor radionuclide therapy. Oncotarget. 2016 Apr 12;7(15):20033-40.

Keywords: SCLC, SABR, radiotherapy

IBS20 ENDOSCOPIC SOLUTION TO IATROGENIC COMPLICATIONS (INTERACTIVE Q AND A)
MONDAY, SEPTEMBER 9 07:00–08:00

IBS20.01 AIRWAY FISTULAS

J. Daniels

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Introduction Airway fistula as an iatrogenic complication of lung cancer treatments present a particular challenge to the multidisciplinary lung cancer team. It is a rare but very severe complication which requires prompt treatment because of the involved disruption of the natural tissue barriers against infection. Different types of fistulas

exist, the most common airway fistulas that are encountered after lung cancer treatment are bronchopleural fistula (BPF) and tracheo or broncho-oesophageal fistula (T/BEF). These are two very different entities that require their own specific management. *Bronchopleural fistula* BPF is a feared complication after anatomical resection of lung cancer, occurring in 1-4% of the patients [1-3]. Rare causes of BPF in lung cancer patients can include destruction of the airway wall by direct tumor invasion and airway wall necrosis after high-dose radiotherapy. Presenting symptoms can be cough, empyema, persistent air leak and hemoptysis. Significant dyspnea can occur because of increased dead space ventilation if there is a massive air leak. The diagnosis can be made by bronchoscopy and if the bronchoscopist cannot see a fistula, deposition of methylene blue at the site of the stump can help. In case of persistent air leak and no identifiable airway fistula, an alveolar-pleural fistula (more common) should be considered. Imaging techniques such as chest X-ray and CT scan can help to diagnose ensuing pneumothorax and empyema and in large fistulas can sometimes be visualized. The management of BPF can be challenging, especially in complicated empyema, frail patients who have already deteriorated during the postoperative phase and patients that underwent salvage surgery after high-dose radiotherapy [4]. Small BPF (up to 8 mm) without surrounding necrosis can be managed by endoscopically with the help of polyvinyl alcohol sponge and cyanoacrylate glue [5,6]. Larger BPF, presence of airway wall necrosis or failure to close the BPF endoscopically is a reason for surgery. Reconstruction of the stump or anastomosis can be followed by adding a muscle flap to improve perfusion. In case of necrosis, debridement should precede these procedures. Extensive airway necrosis sometimes renders surgical repair impossible. In case of complex empyema, open window thoracostomy can be necessary, especially if more conservative measures have been unsuccessful. *Tracheo-esophageal and broncho-esophageal fistula* T/BEF is a relatively common complication in patients with esophageal cancer (5-15%), but rare in lung cancer patients (1%)[7-10]. Symptoms include cough, especially during intake of food or liquids, infection (bronchitis, pneumonia), recurrent aspiration and weight loss. In patients with lung cancer, the most important causes are malignant invasion of the membranous part of the trachea or bronchi and high-dose radiotherapy with involvement of airways in close proximity to the esophagus (trachea and proximal left main bronchus). The diagnosis can be made with contrast-enhanced esophagography, demonstrating displacement of the contrast into the lung. Bronchoscopy can be used to localize the fistula, to determine its extent, to assess the vitality of the surrounding airway wall and to evacuate aspirated liquids and mucus from the central airways. Immediate treatment is crucial to avoid deterioration of the patient. To minimize further aspiration, oral intake should be eliminated and adequate measures should be taken to minimize reflux and ensure adequate feeding (e.g. gastro-/jejunostomy or total parenteral nutrition). Small fistulas (up to 5 mm) can be treated endoscopically with cyanoacrylate glue or clips. Larger fistulas can be treated with an esophageal stent, airway stent or a combination: double stenting. In case of insufficient effect of a esophageal stent or concomitant airway obstruction, double stenting is preferable and seems to provide better survival than a single stent [11,12]. It is important to realize that pressure on the fragile tissues between both stents can further enlarge the T/BEF. Often multiple endoscopic interventions are required to achieve and maintain adequate palliation. During this presentation the management of airway fistulas will be discussed, with emphasis on the bronchoscopic techniques such as (double) stenting and the application of cyanoacrylate glue. Selection of patients, alternative solutions and specific endoscopic techniques will be important topics. *References* Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. Bronchopleural fistulas associated with lung cancer operations univariate and multivariate analysis of risk factors, management, and outcome. J Thorac Cardiovasc Surg 1992;104:1456–63. Boudaya MS, Smadhi H, Zribi H, et al. Conservative management of postoperative bronchopleural fistulas. J Thorac Cardiovasc Surg 2013;146:575–9. Bazzocchi R, Bini A, Grazia M, Petrella F. Bronchopleural fistula prevention after major pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg 2002;22:160. 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Keywords: Lung cancer, Airway fistula, Bronchoscopy

IBS20 ENDOSCOPIC SOLUTION TO IATROGENIC COMPLICATIONS (INTERACTIVE Q AND A)
MONDAY, SEPTEMBER 9 07:00–08:00

IBS20.02 AIRWAY STENOSIS

M. Bezzi

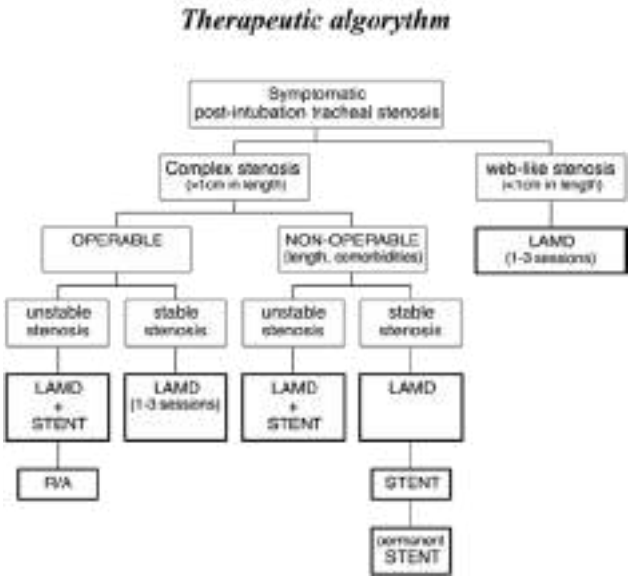
ASST Spedali Civili Brescia, Brescia/Italy

Tracheal stenosis is suspected in individuals with risk factors presenting with signs and symptoms of airway narrowing. The condition may be suspected based on spirometry with a flow-volume loop and CT imaging of the neck and chest but fiberoptic bronchoscopy is required to confirm the presence and severity of tracheal stenosis. The symptoms of tracheal stenosis are similar to those of other conditions so it is important to carefully evaluate patients history. The symptoms of tracheal stenosis typically are wheezing, coughing or shortness of breath, cornage, upper respiratory infections, asthma that doesn't respond to treatment. Benign tracheal stenoses are more commonly the result of an injury to the trachea due to prolonged intubation or tracheostomy but also Infections (tuberculosis), autoimmune disorders such as Granulomatosis with polyangiitisand amyloidosis or radiation therapy to the neck or chest. The morphological classification of airway stenosis includes granulomas, pseudoglottic stenosis, and "true stenosis" divided into web-like and complex stenoses. *Web-like stenoses* are circumferential strictures of the trachea involving the mucosa of a short segment (maximum 1 cm long)without any damage to the cartilages. *Complex stenoses*are sleeve strictures of the trachea more than 1 cm long, often associated with various degrees of cartilage involvement, malacia and inflammation. Several treatment options that can be used for tracheal stenosis depending on the cause, location and severity of the tracheal narrowing. Resection and anastomosis of the involved tract of the trachea is the gold standard treatment. Interventional Pulmonology (IP) offers minimally invasive techniques. Some IP treatment options can provide immediate relief but are considered temporary solutions, while others can provide a better long-term solution. Short-term treatment options for the condition include laser surgery and mechanical dilation with rigid scopes.Treatment options that are generally considered to work long term include stenting and tracheal reconstruction when only a short portion of the trachea is involved. Choice of procedure depends on the exact location and extent of the stenosis, but also on patient age and comorbidities.The most common treatment options for tracheal stenosis include: In 2007 Cavaliere et al. published the results of Laser Assisted Mechanical Dilation in 113 post-intubation tracheal stenoses

Sex	Age(Y)	Cause of stenosis		Type of stenosis	
M 47	50±21 (12-84)	Intuba-tion 38	Tracheot-omy 35	Web-like 13	Complex 60

Tab 1 - Patient carachterstics Therapeutic bronchoscopies were performed using rigid bronchoscopes (Efer, Dumon-Harrel type; FR) and general anesthesia.Endoscopic treatment was based on the use of three main techniques: laser photo-resection (multiple radial incisions), gentle dilation and removable silicon stents.

Fig 1 Web like stenosis, Complex stenosis, Silicon stent



Most web-like stenoses were successfully treated with Laser Assisted Mechanical Dilation (LAMD) alone; among complex stenoses LAMD was sufficient to treat 13 patients (22%), whereas 47 patients (78%) required stent placement: 22 had their stent removed after one year and did not require any further therapy, 13 inoperable patients required permanent stent and 12 were referred to surgery after failure of multiple endoscopic treatments. No permanent complications secondary to endoscopic treatment were observed. Forty-eight patients (66%) obtained a stable, good result with the endoscopic procedure, 13 (18%) required a permanent stent while 12 patients (16%) were referred to surgery. These authors indicate that bronchoscopic treatment of post-intubation tracheal stenoses can be considered a safe first-line therapy, leaving some selected cases and the relapsing stenosis for surgical resection. 1.Shapshay SM, Beamis JF, Jr, Hybels RL, Bohigian RK. Endoscopic treatment of subglottic and tracheal stenosis by radial laser incision and dilation. Ann Otol Rhinol Laryngol. 1987;96:661–664. 2. Bacon JL, Patterson CM, Madden BP. Indications and interventional options for non-resectable tracheal stenosis. J Thorac Dis. 2014;6:258–70. 3. Galluccio G, Lucantoni G, Battistoni P, Paone G, Batzella S, Lucifora V et al. Interventional endoscopy in the management of benign tracheal stenoses: definitive treatment at long-term follow-up. Eur J Cardiothorac Surg. 2009;35:429–33. 4. Murgu SD, Colt HG, Mukai D, Brenner M. Multimodal imaging guidance for laser ablation in tracheal stenosis. Laryngoscope. 2010;120:1840–6. *5. Cavaliere S, Bezzi M, Toninelli C, Foccoli P* Management of post-intubation tracheal stenoses using the endoscopic approach. Follow-up of 73consecutive patients over a four-year period. Monaldi arch Chest Dis 2007 Jun; 67(2):73-80

IBS21 COMBATING TOXICITY OF IO-CHEMOTHERAPY COMBINATIONS
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS21.01 ENHANCED TOXICITY OF IO WITH CONCURRENT CHEMOTHERAPY

C. Barrios, A. Gelatti

Latin American Cooperative Oncology Group, Porto Alegre/Brazil

Of the more than 18 million new cancer cases seen worldwide in 2018, approximately 2 million (11%) were lung cancer. More importantly, 1.7 million deaths were seen due to the disease, representing 18% of all cancer related deaths. Global age standardized incidence/mortality rates (22.5/18.6) clearly indicate that today, most patients diagnosed with lung cancer succumb to the disease. With the increasing incidence and mortality seen particularly in developing countries lung cancer is one of the most important global public health current challenges. With recent advances seen over the last couple of decades, therapeutic decisions for NSCLC are based not only on disease stage, comorbidities, performance status and histology, but also should consider the mutational and immunological profile of the tumor and obviously each patient's preferences as well. Until recently, for tumors without any identifiable molecular driver, platinum doublets were the standard treatment for advanced disease. In these patients, despite extensive studies trying to improve current results, "old" targeted agents (bevacizumab, cetuximab) added to standard chemotherapy regimens suggested very modest if any benefit at all. Immune check-point inhibitors introduced over the last few years, have revolutionized our treatment approach and stand to change the natural history of the disease. As single agents, immune check-point inhibitors are effective in a proportion of patients, however a large majority either do not respond or develop resistance. On the basis of still very limited knowledge of primary and secondary mechanisms of resistance, combination approaches with other standard therapies and other immunotherapy strategies have been explored. Unfortunately, in most cases, lack of specific information on the molecular interactions between these therapies remains an important barrier. Albeit basically empirically designed, combinations of PD1/PDL1 inhibitors with standard platinum doublets have demonstrated benefits and are apparently increasing the proportion of patients benefiting from single agent immunotherapies. For many years, chemotherapy has been considered as an immunosuppressant. This is clearly the case in some situations depending on the specific agent and the dose being administered. However, in preclinical models, chemotherapy has shown the potential to increase the immunogenicity of cancer cells increasing the release of tumor antigens, attracting DCs, downregulating PDL1/PDL2 in DCs, enhancing tumor cell recognition and lysis and at the same decreasing microenvironment immunosuppressive factors. With the current need of designing rational combinations, it becomes extremely important to recognize that different chemotherapeutic agents have different interactions with the immune system and that addressing these differences is mandatory to achieve the best possible results. So, with these reasoning, it is fair to say that, among the multitude of specific cytotoxic effects of the different available chemotherapeutic agents and regimens it can be hypothesized that the combination of chemotherapy and IO may enhance immune effects. The combination of chemotherapy and immunotherapy (CIT) has attracted attention of clinicians and researchers and has been investigated in multiple clinical trials. Improved efficacy has been seen with these combinations but as expected, toxicity issues have also been observed. In this particular setting, we will address the intriguing question of how combining chemotherapy and immunotherapy may interfere in chemotherapy related adverse events. A recent metanalysis explored this particular issue and collected trial information from 6 randomized studies in the first line treatment of NSCLC patients. Compared with standard chemotherapy, the combination of PD-1/PD-L1 inhibitors with chemotherapy is statistically associated with a 38% reduction in the risk of disease progression, a 32% reduction in the risk of death and increases 1.6 times the probability of achieving an objective response. These results are achieved at the expense of increased treatment-related adverse events. In particular, the combination was associated with an increased risk of developing grade 3 or worse severity adverse events, an increase in treatment related drug discontinuations and an increase in serious adverse events. However, the number of treatment related deaths was similar with both treatments. Importantly, we need to consider that these data, as most of the information we have available form randomized phase III trials reflect the effects in the limited patient populations included in these trials and do not apply to special populations such as elderly patients, patients with

autoimmune diseases, patients with worse ECOG PS (>2), patients with HIV or with hepatitis B/C and patients on chronic use of steroids. RWD and further trials specifically exploring these groups of patients will be essential to better inform the optimal management of these cases. Nevertheless, recent presented information on the long-term benefits of mainly single agent immunotherapy with a proportion of patients with advanced NSCLC surviving in excess of 3-5 years, raises the issue of a clear impact on the natural history of the disease. This has been previously shown in diseases that explored immunotherapy earlier such as melanoma for example. Further research should try to rationally approach combination regimens and to specifically select patient populations that could derive more benefit. At the same time this will help defining and improving the risk benefit relationship of these regimens. *References: Galluzzi L, et. al. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer Cell 28, December 14, 2015. Hato SV, et al. Molecular Pathways: The Immunogenic Effects of Platinum-Based Chemotherapeutics Clin Cancer Res; 20(11); 2831–7, 2014 Zhou Y, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. Journal for Immuno Therapy of Cancer (2018) 6:155. Kanwal B, et al. Immunotherapy in Advanced Non-small Cell Lung Cancer Patients: Ushering Chemotherapy Through the Checkpoint Inhibitors?Cureus. 2018 Sep; 10(9): e3254.*

Keywords: Immunotherapy, Chemotherapy, NSCLC

IBS21 COMBATING TOXICITY OF IO-CHEMOTHERAPY COMBINATIONS
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS21.02 REAL WORLD TOXICITIES OF RADIATION PLUS IO IN NSCLC

R. Kelly

Baylor University Medical Center, Dallas/United States of America

As the indications for immune checkpoint inhibitors expand in stage III and stage IV non small cell lung cancer, medical and radiation oncologists will need to risk-stratify patients for the development of immune related toxicities most notably checkpoint-inhibitor pneumonitis (CIP) and to differentiate this from radiation induced pneumonitis. Real-world patient data is providing new insights into the epidemiological and clinical characteristics of CIP and emerging data which needs to be validated suggest a higher incidence of CIP approaching 19% in non- trial patients compared to 3-5% reported in clinical trials. A seasonal pattern of CIP with an increase in the number of cases in the Winter months when viral infections are at a high and in patients that may be more susceptible due to existing comorbidities than ECOG 0-1 trial patients need to be further evaluated. Additionally, it appears the risk of developing CIP is histology dependent with a lower risk being seen in nonsquamous lung cancer. A variety of radiographic patterns ranging from organizing pneumonia to ground glass or interstitial patterns are seen and time-to-onset analysis suggest that there may be two differing phenotypes most notably early onset CIP which is high grade and associated with higher mortality and late-onset CIP which is of lower grade and has less mortality. At the present time, no specific radiotherapy-related treatment parameter such as technique (stereotactic body RTor intensity-modulated RT), timing or number of courses have been associated with CIP, however, there is a trend associated with curative-intent radiotherapy compared with palliative intent radiation. Interestingly, the development of non-pulmonary immune related adverse events has been associated with an improved response and overall survival to checkpoint inhibitors. While these phenomena require further investigation it has been suggested that the poor outcomes associated with CIP relate to the fact that hypoxia from pneumonitis is poorly tolerated in patients who already have respiratory compromise as a result of lung cancer and may precipitate multiorgan failure due to decreased oxygenation. The creation of multi-disciplinary teams that have a specific interest in the management of immune related toxicities may help improve patient outcomes due to early identification but a more comprehensive understanding of the underlying biology is needed if we are to refine our existing diagnostic and treatment algorithms to appropriately manage life-threatening complications associated with changing paradigms of care.

Keywords: Real-world patients, immuno-oncology, toxicities

IBS22 JTO WORKSHOP: HOW TO GET YOUR MANUSCRIPT PUBLISHED
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS22.02 JTO WORKSHOP: THE LIFE CYCLE OF A MANUSCRIPT

M. Todd

IASLC, New York/United States of America

This session will describe the process of a manuscript from initial submission to final publication. The session will focus on ways that submitting authors can ensure a seamless and timely handling of their manuscripts. Interactions between authors and editorial offices offer insight into common situations and themes. Participants will learn why editorial offices and publishers require what they require. Time will also be devoted to promotion of published work.

Keywords: JTO

IBS23 IBS23 TREATMENT OF NSCLC OMD IN CLINICAL PRACTICE
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS23.01 RADIOTHERAPY OF OMD IN DAILY CLINICAL PRACTICE

R. Komaki-Cox

Baylor College of Medicine, Houston/United States of America

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer related death in the world.1 Analysis of patterns of failure after first-line systemic therapy for metastatic NSCLC suggest that most progression events, either within or outside the central nervous system (CNS), occur only at sites of disease known to exist at baseline, rather than in new sites.2 Once systemic treatment becomes more efficacious, for patients with limited numbers of metastases, ablation of those metastases may be advantageous in terms of cytoreduction or removal of dominant disease sites that may seed other sites in the future. Stage IV disease that is limited to only a small number of sites ("oligometastatic" disease (OMD)) may reflect a more indolent phenotype that could benefit from local ablative therapy (e.g. surgery or radiation) for consolidation, as suggested by some preclinical and translational analyses.3,4 Several retrospective and small prospective trials have suggested that local therapy may be beneficial for patients with stage IV NSCLC presenting with limited metastases .5-8 At MDACC, we have performed a randomized, phase II study (NCT01725165) to evaluate progression-free survival (PFS) after aggressive local consolidative therapy (LCT) versus maintenance therapy or observation for patients with stage IV NSCLC with ≤3 metastases remaining after front line systemic therapy. As secondary aims, we explored: (1) the safety and incidence of high-grade toxicity, (2) overall survival (OS), (3) patterns of failure and the effect of salvage therapy among patients who crossed over to the local consolidation group, (4) time to development of disease at new metastatic sites, and (5) predictors of PFS. Findings of our randomized trial of aggressive LCT followed by standard maintenance therapy versus maintenance therapy alone for patients with oligometastatic NSCLC that did not progress after initial systemic therapy were as follows.10 We found that the PFS time for the standard (maintenance therapy) group was almost exactly as had been hypothesized from prior studies (3.9 months observed vs. 4 months hypothesized), whereas that of the experimental (LCT) group was substantially longer than predicted (11.9 months observed vs. 7 months hypothesized). Notably, our hypothesis was based on retrospective data in which sites of new disease versus sites of known disease could be followed more thoroughly for progression. In addition, time to the appearance of a new lesion was longer for patients in the LCT arm than for in the no-LCT arm (11.9 months vs. 5.7 months, p=0.0497), suggesting that the LCT could be altering the natural history of the disease2, either by limiting the potential for later spread or possibly by altering systemic anticancer immune responses to facilitate longer control of subclinical disease. Our trial used SBRT or surgery for local treatment for the oligometastasis. However more recent trial was done by consolidative radiotherapy for the limited oligometastatic NSCLC showing SBRT(SABR) Prior to the maintenance chemotherapy improved PFG compared to maintenance chemotherapy alone.10 Common oligometastatic lesions we usually treat by radiotherapy are brain, bone, adrenal gland, lung, liver lymph node, mediastinum,

pleura and muscle. Daily clinical practice, we need to use image guided radiotherapy with 4 D simulation. We should use SBRT or SABR to eliminate oligometasis without overlapping previously irradiated area and avoid critical organs. Take home message: 1) We have enough evidence that treating oligometastasis by aggressive local treatment improved PFS and less appearance of new lesions. 2) Patients are able to tolerate local aggressive RT by SBRT (SABR). 3) Need to consider patients with oligometastases to be treated agressibly by SBRT (SABR). 4) Efficacy to improve OS by additional immunotherapy to the SBRT or SABR to the oligometastasis requires a prospective randomized studies in future. References 1.Siegel RL, Miller KD, Jemal A, CA, Cancer J for Clinicians: Cancer Statistics 2019 Volume 69 (1): 1-84. 2.Rusthoven KE, Hammerman SF, Kavanagh BD, Birtwhistle MJ, Stares M, Camidge DR. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 2009; 48(4): 578-83. 3.Wong AC, Watson SP, Pitroda SP, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer 2016. 4.Lussier YA, Xing HR, Salama JK, et al. MicroRNA expression characterizes oligometastasis(es). PLoS One 2011; 6(12): e28650. 5. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. Clin Cancer Res 2008; 14(16): 5255-9. 6.Inoue T, Katoh N, Aoyama H, et al. Clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. Jpn J Clin Oncol 2010; 40(8): 788-94. 7.Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. Lung Cancer 2010; 69(3): 251-8. 8. De Ruysscher D, Wanders R, van Baardwijk A, Dingermans AC, et al, Radiacal Treatment of Non Small Cell Lung cancer Patients with Synchronous Oligometastases: Long Term Results of a prospective Phase II trial (Nct01282450) Journal of Thoracic Oncology 2012 ;7(10) 1547-1555 9. Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. e-Pub Vol 17,1672-1682, 10/2016. PMID: 27789196 10. Iyengar P, Wardak Z, Gerbrer D, et al :Consolidative Radiotherapy for Limited Metastatic Non-Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial.JAMA Oncology 4(1) 2018 ,1-8

Keywords: oligometastatic disease, local therapy, SBRT

IBS23 TREATMENT OF NSCLC OMD IN CLINICAL PRACTICE
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS23.02 ONCOLOGICAL TREATMENT OF OMD IN DAILY CLINICAL PRACTICE

S. Popat

Royal Marsden Hospital, London/United Kingdom

The front line systemic treatment of metastatic non-small cell lung cancer (NSCLC) has changed rapidly over the past 10 years, from the establishment of histology-specific chemotherapy, the introduction of molecular targeted therapies for specific somatic sensitizing gene mutations/fusions, and now the routine use of immune checkpoint inhibitors either as monotherapy or in combination with chemotherapy. Current data suggests that oncogene addicted tumours have little benefit from checkpoint inhibitor monotherapy, and so advanced NSCLC can be functionally categorized into those that are oncogene addicted and ideally treated with molecular targeted therapy – either as monotherapy or in combination with other therapies- or immune sensitive, ideally treated with immune checkpoint inhibitors again as monotherapy or in combination with chemotherapy. At the same time, advances in radiotherapy delivery have meant that small volume metastatic disease can be treated at ablative doses of radiotherapy. How these two modalities should be integrated in patients with oligometastatic disease for optimal survival and minimal toxicities has been debated over recent months. In parallel our understanding of the natural history of different types of NSCLC has become better understood, alongside the phenotypic and genotypic selection pressures put on them by systemic therapy. Thus, recognizing that patients with oncogene addicted disease such as ALK and ROS1 fusions or EGFR mutations have a high propensity to CNS metastases, and that next generation CNS-penetrant kinase inhibitors are optimally used up front, SRS to brain metastases may be deferred and used on demand in case of late progression, effectively withholding whole brain radiotherapy until much later in the patient care timeline. However, trial data to support this decision making is currently lacking and awaited. Understanding that patients with oncogene addicted disease now have a median survival quadrupled to that previously (now in excess of 4 years) with optimal sequencing of kinase inhibitors, allows a more thoughtful way to integrate a more radical approach into those with small volume oligometastatic disease. We therefore now recognize several states of oligometastatic disease, with much of our information and treatment paradigms evolving from the treatment of patients with oncogene addicted disease. Patients may have the now well-known synchronous or metachronous oligometastatic disease state. Moreover, the integration of kinase inhibitors has identified an oligoprogressive disease occurring in around 30% of cases, and the ability to treat such cases with radical radiotherapy or a surgical approach. In such cases, tissue sampling may be required not only to plan the next steps of systemic therapy by tissue genotyping for acquired resistance mechanisms and new molecular target identification, but also for fiducial placement. Another less well defined disease entity is that of oligopersistent disease- defined as small volume radically treatable disease present after the bulk of oligo- or poly-metastatic disease has responded well to initial therapy, with patient series data suggesting a survival benefit for radically consolidating (oligo-consolidation) or optimally debulking in this approach. The integration of immune checkpoint inhibitors has again changed patterns of disease response and progression. Certainly, major durable responders are observed with checkpoint inhibitors alone, and the role of radically consolidating such patients may be debatable given that around 30% of patients with 50%+ PDL1 expression treated with front-line pembrolizumab monotherapy survive 5 years. However, acquired checkpoint inhibitor resistance is common and single centre series have suggested a rate of 30% of patients progressing with oligoprogression, suitable for ablative therapy or resection. In this presentation, I will discuss all these issues, including concerns about toxicities, and duration of therapy, arguing for a consensus on oligo-definitions, and molecular stratification within trials, encouraging enrolment into ongoing clinical trials to quantify the magnitude of benefit afforded by radically treating the oligometastatic state.

Keywords: Oligometastatic, oncogene, Immunotherapy

IBS23 TREATMENT OF NSCLC OMD IN CLINICAL PRACTICE
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS23.03 SURGICAL TREATMENT OF OMD IN DAILY CLINICAL PRACTICE

P. De-Leyn, H. Decaluwe

University Hospitals Leuven, Leuven/Belgium

Patients with metastatic non-small cell lung cancer (stage IV) are usually deemed to be incurable and no local aggressive treatment is generally indicated. However, stage IV NSCLC cancer is a heterogeneous group. This is confirmed by the 8 thh TNM NSCLC staging system. Stage M1a are patients with separate tumor nodules (s) in a contralateral lobe, tumor metastatic pleural or pericardial nodule, or malignant pleural pericardial effusion. M1b is single extra thoracic metastatic disease in one organ and M1c are patients with multiple extra thoracic metastasis in one or several organs. Oligometastatic disease is widely recognized as patients with a limited number of controllable secondary lesions. The exact number of metastasis and definition is still debate. Over the last years remarkable advances in chemotherapy strategy and immunotherapy have resulted in substantial survival benefits in patients with stage IV NSCLC. This questions in some patients the need of aggressive treatment of residual or recurrent disease. In literature, there are several studies on the role of surgery in patients with lung cancer and single metastasis in the brain, adrenal or contralateral lung. Most of the evidence is based on small retrospective series that were collected over an extended period of time. More recently, there is some experience with multimodal treatment including surgery in patients with oligometastatic disease and more metastasis also in different organs. There are several prognostic factors. Mediastinal nodal involvement and tumor size are important. In all patients, FDG- PET could be performed. Since prognosis is very small in N2 patients, invasive mediastinal staging (endoscopically or surgically) should be performed before embarking on an aggressive multimodal

surgical treatment of oligometastatic disease. Over the last years, robotic surgery or uniportal VATS is becoming less invasive with less postoperative complications and better tolerance of neoadjuvant or adjuvant therapy. When surgery is part of multimodal treatment of patients with oligometastatic disease pneumonectomy should be avoided.

Keywords: surgery, Oligometastatic

IBS24 OPTIMAL IMMUNOTHERAPY SEQUENCE IN STAGE IV NSCLC
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS24.01 IO/CT FIRST LINE ALWAYS

S. Puri[1], J.E. Gray[2]

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Combination therapy with anti-programed death protein (ligand) 1 inhibitor (PD-1/PD-L1) and platinum-doublet chemotherapy (CT) plus/minus vascular endothelial growth factor inhibition (VEGFi) has recently emerged as the standard first-line treatment for patients with metastatic non-small cell lung cancer (mNSCLC) without a targetable oncogene. The rationale for using the immunotherapy chemotherapy (IO-CT) combination comes primarily from a clinical effort to improve the efficacy of the first-line treatment of mNSCLC by combining two independently active therapies with non-overlapping toxicity profiles. Additional proof-of-principle comes from pre-clinical studies showing synergy between checkpoint inhibitors (CPIs) and CT through platinum mediated immunomodulation of the tumor microenvironment.[1, 2] Several randomized phase II-III clinical trials have evaluated the combination of platinum doublet CT with CPIs for first line therapy of mNSCLC (Table 1). Pembrolizumab (anti-PD-1) plus platinum-pemetrexed was the first IO-CT combination with promising activity in this setting as noted in the phase II KEYNOTE021 trial.[3] This led to further evaluation of the combination in the phase III KEYNOTE189 trial [4] that compared platinum-pemetrexed with pembrolizumab or placebo in treatment naïve patients with non-squamous mNSCLC .The results showed a significant overall survival (OS) benefit with the pembrolizumab combination that was seen irrespective of the PD-L1 tumor proportion score (TPS) and persisted at the updated follow up analysis despite cross over to IO in 54% patients in the placebo-CT arm.[5] Similarly, the KEYNOTE407 trial enrolled untreated patients with stage IV squamous NSCLC, and noted superior outcomes with the combination of pembrolizumab plus carboplatin-(nab) paclitaxel versus placebo-carboplatin-(nab) paclitaxel.[6] These two trials have established pembrolizumab plus platinum CT as the preferred therapy for previously untreated patients with non-squamous and squamous mNSCLC, and both regimens are currently approved by the FDA for histology specific, front-line treatment of stage IV NSCLC. Additional trials have been conducted comparing the combination of atezolizumab (anti-PD-L1) plus platinum- (nab)paclitaxel versus placebo-CT for the first-line treatment of non-squamous (IMpower 130, IMpower150) and squamous (IMpower131) mNSCLC. While results of the IMpower130 study show an OS benefit of treatment with the atezolizumab-CT combination compared to CT alone [7], the IMpower131 trial showed a clear PFS benefit but no significant benefit in OS between the two arms.[8] Interestingly, the potential benefit of adding VEGFi to IO-CT was explored in the IMpower150 trial. This complex, three arm trial compared the combination of atezolizumab, carboplatin, paclitaxel and bevacizumab (ABCP) and atezolizumab, carboplatin, paclitaxel (ACP) to carboplatin, paclitaxel and bevacizumab (BCP) in CT naïve, non-squamous, mNSCLC. The trial also enrolled a subset of patients with EGFR or ALK mutations who had failed standard tyrosine kinase therapies, a population of patients that historically have a poor response to treatment with CPIs and are otherwise excluded from majority of the IO or IO-CT combination trials. The results showed a survival benefit of the four-drug regimen (ABCP vs BCP) in both the EGFR/ALK WT and mutated population, highlighting the potential role of VEGFi in improving response to CPIs, especially in oncogene driven mNSCLC.[9] Coming back to the question "should IO-CT be first line always?" The answer is yes, for the majority of eligible mNSCLC patients with no targetable mutations. mNSCLC is an aggressive malignancy associated with high mortality, and multiple trials have shown that many patients do not have the opportunity of receiving 2nd line treatment.[5,10] Platinum based CT has been the first-line treatment of choice for mNSCLC for many years. In the last decade, IO has revolutionized the treatment of advanced lung cancer. Recent data (Table 1) clearly demonstrates superior and durable clinical outcomes with the combination of platinum-based CT doublets and CPIs compared to CT alone in both squamous and non-squamous mNSCLC. These combinations are safe with little additive toxicity and should be adopted as routine standard of care therapies in the frontline setting, especially in high disease burden and PD-L1 TPS ≤1. However, there is variability in outcomes based on histological subtypes of mNSCLC and the different IO-CT combinations (Table 1). New trial design strategies are needed to determine the benefit of IO-CT versus IO alone, especially in patients with borderline performance status or PD-L1 TPS ≥50%. Additionally, it is also important to determine the subgroup of patients with the highest likelihood of benefit from addition of VEGFi to IO-CT. References 1.Galluzzi L et al. 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Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic NSCLC(IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019. 8. Jotte R et al. IMpower 131. JCO 2018, 36. (suppl;abstr LBA900) 9. Socinski MA et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *NEJM*. 2018;378(24):2288-2301. 10. Reck M et al. Pembrolizumab vs. Chemotherapy for PD-L1-Positive NSCLC. *NEJM*. 2016;375(19):1823-1833. Table 1: Summary of key phase III first line IO-CT trials in mNSCLC

Trial name	Histology	Treatment	Cross over allowed	Results
KEYNOTE189	Non squamous	Pembrolizumab + Carboplatin/Cisplatin + pemetrexed vs placebo+ carboplatin/cisplatin+ pemetrexed	Yes	OS 22.0 m vs 10.7 m (HR 0.56, 95% CI 0.45-0.70), p < .00001 PFS (HR 0.48, 95% CI 0.40-0.58, p < .00001)
IMpower150	Non squamous	Arm 1: Atezolizumab, carboplatin, paclitaxel and bevacizumab (ABCP) Arm 2: Atezolizumab, carboplatin, paclitaxel (ACP) Arm 3: Carboplatin, paclitaxel and bevacizumab (BCP)	No	Arm 1 vs. Arm 3 ABCP vs BCP OS 19.2m vs 14.7m (HR:0.78, 95%CI 0.64-0.96) p=0.02 PFS 8.3m vs 6.8m (HR:062, 95%CI 0.52-0.74), p<0.001
IMpower130	Non squamous	Atezolizumab+ carboplatin +nab paclitaxel vs. carboplatin+ nab paclitaxel	Yes	OS 18.6m vs. 13.9m (HR:0.79 95% CI 0.64-0.98), p=0.033 PFS 7m vs 5.5m (HR:0.64, 95%CI 0.54-0.77), p<0.0001
KEYNOTE407	Squamous	Pembrolizumab + carboplatin+(nab) paclitaxel vs. Placebo + carboplatin+(nab) paclitaxel	Yes	OS: 15.9m vs.11.3m (HR:0.64, 95% CI:049-0.85), p<0.001 PFS: 6.4mvs.4.8m (HR:0.56, 95% CI:045-0.70), p<0.001
IMpower131	Squamous	Atezolizumab+ carboplatin+ (nab) paclitaxel vs. carboplatin+ (nab) paclitaxel	No	OS 14.9m vs 13.9m (HR=0.96, 95%CI 0.78-1.18), p=0.69 PFS 6.3m vs 5.6m (HR=0.71, 95% CI 0.60-0.85), p=0.0001
Checkmate227	Both	Arm 1: Nivolumab + ipilimumab Arm 2: Nivolumab + platinum doublet chemotherapy Arm 3: platinum doublet chemotherapy	NA	Arm 2 vs Arm 3 PFS 5.6m vs 4.7m (HR:0.74 95%CI 0.58-0.94)

Keywords: Immunotherapy, chemotherapy, NSCLC

IBS24 OPTIMAL IMMUNOTHERAPY SEQUENCE IN STAGE IV NSCLC
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS24.02 IO FOLLOWED BY CHEMO OR CHEMO FOLLOWED BY IO

B. Melosky

BC Cancer, Vancouver/Canada

For our patients presenting with stage IV advanced NSCLC, the goals of therapy are primarily palliative. These goals need to be carefully balanced to meet the individual needs of each patient: while we want to keep our patients living as long as possible, we also want to provide them with the highest quality of life. Many patients with advanced NSCLC are treated with the combination of immunotherapy and chemotherapy. This comes at a cost of toxicity and may not be the best strategy for long term survival. We need to compare the evidence to determine which agent, immunotherapy or chemotherapy, to use first in patients with stage IV advanced NSCLC without a targetable mutation (wild-type). Immunotherapy followed by Chemotherapy Numerous phase III trials have compared immunotherapy to chemotherapy for patients with stage IV NSCLC. Some of the trials to be discussed include KEYNOTE 024[1], KEYNOTE 189[2], KEYNOTE 407[3], KEYNOTE 042[4], CheckMate 227[5] and MYSTIC[6]. For each trial, the outcomes and side effect profiles will be presented, and the different trials will be compared. OR Chemotherapy followed by Immunotherapy Immunotherapy agents were initially studied after patients progressed on a platinum doublet. Trials to be discussed include CheckMate 017[7] (squamous), CheckMate 057[8] (non-squamous), KEYNOTE 010[9], and OAK[10]. Again, outcomes and side effect profiles will be presented with a view to identifying which patients will experience the greatest benefit from this strategy. Conclusion & Key Points The increasing percentage of long term survivors in lung cancer is unprecedented and strengthens the argument that sequencing is important. While the evidence is clear that immunotherapy is the best choice for patients who express high PD-L1 or have high tumour mutational burden (TMB), evidence is less clear for how to treat patients without these biomarkers.

	IO followed by Chemo	Chemo followed by IO
Biomarkers	PD-L1 expression, high TMB	PD-L1 non-expressors, low TMB, non-selected population
Evidence to support	KEYNOTE 024//042, CheckMate 227, MYSTIC	CheckMate 017/057, KEYNOTE 010, OAK

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Keywords: sequencing, Immunotherapy, Chemotherapy

IBS25 OPTIMAL GGO MANAGEMENT
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS25.01 EASTERN PERSPECTIVE

H. Asamura

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The term "ground glass opacity (GGO)" is being used more often to describe the CT appearance of a focal, non-calcified lesion with a slight/moderate increase in CT density. Usually, GGO is characterized on high-resolution CT scan images with a slice thickness of 1-3mm. The CT appearance of GGO is characterized by "focal, transparent" lesion. First, GGO refers to the localized or focal lesion regardless of the multicentricity, and the diffuse ground glass appearance seen for interstitial pneumonitis should be excluded from this category. Second, GGO lesions is well-characterized by a slight/mild increase in CT density, which does not obscure preexisting lung structures such as blood vessels and bronchi. This apperance refers to the CT-transparency. When the shape of the pulmonary vessels in the nodules is not recognized in the nodule, the lesion is no longer considered GGO, and instead is called a "solid" lesion. GGO lesion can be either homogeneous or heterogeneous. The GGO lesions are classified according to the absence/presence of the solid part. In case the GGO lesions are homogeneous, and does not contain solid part, it is called "non-solid GGO" or "pure GGO". In case the GGO lesions contain a solid, cystic, or linear part inside the nodule, it is called "non-solid GGO" or "complex GGO". The solid part is more likely to be located in the center of the nodule, and surrounded by the GGO part, which is a so-called "fried egg" appearance. The solid part might be scant or prominent with various proportions of solid to GGO parts. In the classic, solid tumor, the GGO part has no longer exist within the nodule. According to the recent studies on the relationship between CT appearance and histopathology of GGOs, not all, but considerable portion of these lesions correspond to the preivasive, non-invasive, or early forms of neoplastic growths, especially those on the adenocarcinoma lineage. The clinicopathological entity of these tumors are being established only recently, and it has never been the subject of clinical studies. The histopathology of GGO has been also studied, and they are either neoplastic or inflammatory. A focal inflammation of the lung panrenchyma sometimes presents with GGO on the CT image, and pathologically it is described as "organizing pneumonia". These changes are more likely to be temporary. In contrast, the persisting GGOs are more likely to be neoplastic. According to the WHO histological classification of lung and pleural tumors, GGO lesions are associated with three pathological entities. "Atypical adenomatous hyperplasia (AAH)" is described as a preinvasive lesion, in which slightly atypical tumor cells line the involved alveoli and respiratory bronchioles. Adenocarcinoma in situ (AIS) is an adenocarcinoma with Clara cells and/or type II pneumocytes growing along alveolar walls and without stromal invasion. The important feature of AIS is "non-invasive" growth of the tumor, and therefore this lesion could be considered *in situ* carcinoma. The third category is adenocarcinoma with mixed subtypes, which shows a mixture of the histologic subtypes as well as obvious invasive growth. The *intervention strategy* for GGO lesions are being established very recently, and some of them still need future clincal trials. Several factors are related to the management stragety; the size of lesions, image characteristics (non-solid versus part-solid), and the history of previous lung cancer. Especially, the indolent nature of the small-sized, non-solid GGOs needs to be stressed. For these tumors, the immediate surgical intervention should be rather avoided. Furthermore, the physical condition of the patiets such as age, co-existing medical conditions also must be taken into consideration. When thinking of surgical interventions, the location of the lesion (outer versus inner) is also an iomportant issue from the technical point of view. For tumors located deeply in the lung parenchyma, the sublobar resection is generally amenable because of the lack in the enough surgical margin. *1. Non-solid GGOs less than 15 mm in diameter. These small lesions without any solid part in the nodule termed as non-solid GGO are basically watched carefully with the repeated high-resolution CT. The appropriate intervals between repeated CTs have not been clearly demonstrated. It might rage from 3 to 6 moths. If the overt growth in size or the newly developping solid component is shown, the surgical intervention should be considered. 2. Part-solid GGOs less than 15 mm in diameter. The solid component in the part-solid GGOs represents the fiborotic scar and/or collapse of the lung in which the proliferation of the collagen fibers and actrive gibroblast is generally seen, and thiese findings indicate the features of invasive growth. Therefore, tumors of this category should be resected, The careful watching should be indicated only for the poor physical conditions compromising the surgical resection. However, considering their minimally invasive nature and small size, the sublobar resection could be reasonablly choosed. For these tumors, the segementectomy rather than wedge resection is preferrable. The location of the tumor should be carefully evaluated. When the tumor is located in the inner two thirds of the lung panrenchyma, the segemetal resection shoul be reapected as amenable. The segmentectomy for this location cannot ensure the safe surgical margin. For such locations, the lobectomy, instead of segmentectomy, must be chosen. 3. Non-solid GGOs larger than 15 mm in diameter. As non-solid GGOs of smaller size category, these lesions should not be resected immediately. However, the larger GGOs are known to be more likely to grow faster even if the lesions still do not contain solid part. Therefore, if the lesion persists at least in the same size, after the appropriate follow-up period of 3-6 motnths, these GGOs should be resected. Similarly, the resection should be performed with sublobar resection. 4. Part-solid GGOs larger than 15 mm in diameter. The part-solid GGOs of this size are more likely to be an invasive adenocarcinomas. Especially when the solid part exceeds 50% of the whole area of the lesion, the invasive features become more common. Therefore,* the lobectomy might be better selected as the mode of resection. The evaluation of the hilar/mediastinal lymph nodes should be also performed during surgery.

Keywords: adenocarcinoma in situ, minimally invasive adenocarcibnoma, Ground glass opacity

IBS25 OPTIMAL GGO MANAGEMENT
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS25.02 WESTERN PERSPECTIVE

J. Donington

University of Chicago Comprehensive Cancer Center, Chicago/United States of America

Ground glass opacities (GGOs) are a 21st century diagnostic and therapeutic challenge. These are defined as focal areas of increased attenuation on computed tomography (CT), where visualization of normal parenchyma and pulmonary structures such as airways and vessels is preserved. Prior to the advent of high-resolution thin-slice CT scanning we had little evidence for the wide spread existence of these lesions or their association with adenocarcinomas of the lung. The opacities develop because of reduced volumes of air the alveolar airspaces due to partial by cells as they grow in a lepidic pattern along the alveolar surface, typically, the abnormal cells only occupy a portion of the airspace and therefore consolidation of the lung parenchyma does not occur. GGOs are typically divided into two categories: 1) pure GGOs, which contain no solid component and 2) part-solid GGOs, with both solid and pure ground glass regions. The introduction of CT screening for lung cancer should dramatically increase the number of patients presenting with small nodules and GGOs. Interpretation and management guidelines are essential and several have been developed and updated. They are derived by expert consensus and management recommendations are based primarily on the GGO's size, percent solid component, and number in combination with the patient's baseline risk for lung cancer development. The most prominent guidelines are from the British Thoracic Society[1] and the Fleischner Society[2]. We have a growing understanding of the role of GGOs in the pathogenesis of adenocarcinomas of the lung. A strong correlation exists between CT appearance and the extent of histologic tumor invasion, which is outlined in the IASLC/ATS/ERS Classification of Lung Adenocarcinomas.[3] There exists a continuum from pre-invasive lesions, atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS), to minimally invasive adenocarcinoma (MIA), and finally to invasive adenocarcinoma. This has also resulted in a new subclassification of T1 lesions in the 8th edition of lung cancer staging system[4] that includes precise definitions for these pre-invasive and minimally invasive lesions. Although we all agree on terminology to define these lesions radiographically and pathologically, there is less consensus on the ideal management and more specifically when to intervene surgically and what type of resection is best. The Japanese Clinical Oncology Group have served as the leaders in this realm, carrying out a series of prospective trials to define the appropriate extent of resection and lymph node dissection for pure and part-solid GGOs. I believe one of the greatest disparity between eastern and western lung cancer treatment is in the management of small GGOs. The pre-invasive and minimally invasive lesions, those < 2cm and with solid component < 5mm or with consolidation to tumor

ratio < 0.25. Numerous retrospective series and prospective trials from Asia outline the high potential for cure with a limited resection and no lymph node dissection, but most western thoracic surgeons would argue whether if resection is warranted at all for lesions that we reliably know are pre-invasive, or iss surgery for these lesions overtreatment for a "pseudo disease"? It is difficult to put forth the management ideology for the entire western hemisphere, but I believe that the concept of "do no harm" prevails with regard to these small lesions. The western thoracic community has a far greater tendency toward "watching and waiting" than our eastern counter parts. This is based on the understanding that even though these lesions exist within the adenocarcinoma spectrum, only a small percentage will become invasive cancers. Less than 30% of pure GGOs detected in the NELSON trial[5] and only < 2% in the I-ELCAP cohort[6] ever developed a solid component. We also take comfort in the fact that these lesions have slow doubling times >800 days[7], allowing for change in appearance over time to help define the potential for invasion and risk to the patient. Some of the hesitation for rapid surgical intervention in these pre-malignant lesions is because thoracic resections are invasive, even simple wedge resections typically require general anesthesia and a hospital stay and carry a risk for complication especially in the frail or elderly. In addition, the lungs are vital organs, and in that sense quite different from the breast or prostate where we have taken on a much more aggressive approach to the treatment of pre-malignant and minimally invasive tumors. Even in those tumors, we are now investigating de-escalation of treatment protocols and active surveillance for lesions that may never affect a patient's survival. There is also a tendency for multiplicity with GGOs and the potential for many interventions treatments over a patient's lifetime, if each GGO is to be removed. We are in the early phase of our clinical proficiency with GGOs; as our experience and knowledge grows there will likely be a more uniformed approach to intervention, but in 2019, management varies by geography. Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax 2015;70 Suppl 2:ii1-ii54. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology 2017;284:228-43. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2016;11:1204-23. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9. International Early Lung Cancer Action Program I, Henschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71. Lee SW, Leem CS, Kim TJ, et al. The long-term course of ground-glass opacities detected on thin- section computed tomography. Respir Med 2013;107:904-10.

Keywords: lung cancer, adenocarcinoma, ground glass opacities

IBS26 TREATMENT TECHNIQUES FOR LOCALIZED THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS26.01 TREATMENT PLANNING FOR PLEURAL IMRT (IMPRINT)

A. Rimner

Memorial Sloan Kettering Cancer Center, New York/United States of America

We have developed an Intensity-modulated pleural radiation therapy (IMPRINT) technique targeting the entire hemithoracic pleural space including the diaphragm that simultaneously spares the ipsilateral lung, heart, liver, kidneys and abdominal contents was developed.1 It provides an opportunity for safer, less toxic treatments and increased efficacy by enabling higher radiation doses to the tumor target due to a much higher level of dosimetric control and certainty leading to better target coverage than conventional radiation techniques.2 IMPRINT became technically necessary to deliver adjuvant radiation due to the increased use of lung-sparing surgical techniques such as pleurectomy/decortication (P/D) for malignant pleural mesothelioma. Here we describe the contouring and treatment planning aspects for IMPRINT and potential pitfalls. Since developing this technique the clinical delivery of IMPRINT has been shown to be safe and feasible. Our first report in 36 MPM patients with 2 intact lungs showed that hemithoracic adjuvant IMPRINT (50.4 Gy in 28 fractions) could be delivered with a 20% (n=7) ≥ grade 3 pneumonitis risk; 1 patient had grade 5 pneumonitis.1 The median survival in resectable patients was 26 months. A tomotherapy technique was published with similar toxicity outcomes (20% ≥ grade 2 pneumonitis, one fatal case of pneumonitis).3 These encouraging results have led to a 2-institution phase II trial of trimodality therapy using induction chemotherapy with cisplatin and pemetrexed, lung-sparing P/D, and adjuvant hemithoracic IMPRINT.4 Twenty-seven patients were treated and 29.6% developed radiation pneumonitis (6 grade 2; 2 grade 3). Median progression-free and overall survival was 12.4 and 23.7 months, respectively. In resectable MPM patients who received chemotherapy and IMPRINT, 2-year OS was very promising at 59%. A review of the outcomes of trimodality therapy including IMPRINT demonstrated a median OS of 20 months from the start of RT.5 Based on these findings a multi-institutional phase II study is ongoing to demonstrate the safety and exportability of IMPRINT to 5 institutions (clinicaltrials.gov: NCT00715611). All patients' treatment contours and plans are centrally reviewed and revised for uniformity. This will be followed by NRG LU-006, a randomized phase III study of P/D, chemotherapy +/- adjuvant IMPRINT which is planned to open in the fall of 2019. Target delineation of the entire pleural space is a challenging task. The higher precision of IMRT delivery requires detailed knowledge of the intrathoracic anatomy, incorporation of all diagnostic imaging tools available, pathologic findings at the time of surgery, assessment of the respiratory tumor motion using a 4D scan, and image-guided treatment delivery. A systematic review of failure patterns in 67 patients identified areas at significant risk for local failures emphasizing the need for optimization of radiation targeting and experience with this complex radiation technique.6 Increasing experience over time led to fewer marginal failures and decreased toxicity, suggesting the improvement in target delineation and RT planning. Emergence of multiple pleural nodules and pleural thickening were identified as the most common features of local recurrences.7 We have developed a contouring atlas for target delineation for IMPRINT that will be presented. Treatment planning is similarly complex and requires significant experience. Typically fixed-beam angle IMRT is delivered with six to nine coplanar 6 MV beams equispaced over 200-240 degrees around the ipsilateral hemithorax were used. More recently, rotational techniques such as volumetric arc therapy or tomotherapy have been shown to allow for even more effective sparing of organs at risk.3,8 Strict normal tissue constraints need to be applied to avoid serious toxicities, foremost radiation pneumonitis. Most recently we identified an association of radiation dose to the heart and overall survival that has led to incorporation of new dosimetric planning constraints.9 Details about dosimetric constraints will be presented. 1. Rosenzweig KE, Zauderer MG, Laser B, et al: Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. International Journal of Radiation Oncology Biology Physics 83:1278-1283, 2012 2. Krayenbuehl J, Dimmerling P, Ciernik IF, et al: Clinical outcome of postoperative highly conformal versus 3D conformal radiotherapy in patients with malignant pleural mesothelioma. Radiat Oncol 9:32, 2014 3. 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Keywords: malignant pleural mesothelioma, Intensity-modulated pleural radiation therapy (IMPRINT), Treatment planning

IBS26 TREATMENT TECHNIQUES FOR LOCALIZED THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS26.03 SURGICAL TECHNIQUE OF PLEURECTOMY/ DECORTICATION

D. Waller

St Bartholomew's Hospital, Barts Health NHS Trust, London/United Kingdom

Lung sparing radical surgery by (extended) pleurectomy decortication has become for many high volume units the surgical approach of choice rather than extrapleural pneumonectomy. However, the persuasive benefits of reduced postoperative mortality must not lead to compromise of the basic intent to obtain macroscopic complete resection of the malignant pleural mesothelioma. While it is naïve to intend to obtain a R0 resection (because of the anatomical relations of the pleura) a R2 resection should be considered a failure of surgical selection or technique. In this presentation I will consider the salient points in a stepwise fashion of the operation that I have learned over a 20 year experience of over 500 such procedures and illustrate each step with images or operative video sequences. 1.*Anaesthetic requirements* – double lumen intubation under general anaesthesia with single lung intubation is a prerequisite. Epidural analgesia is desirable as the extent of pleurectomy does not facilitate paravertebral catheter placement. Preoperative insertion of a large bore oesophageal bougie facilitates intraoperative dissection around the oesophagus reducing the risk of inadvertent injury. 2.*Exposure* – a standard posterolateral thoracotomy through the 6th intercostal space dividing just the latissimus dorsi is usually sufficient. Particularly bulky tumours in either the apex or base should be approached using a two level thoracotomy via the 4th and 8th intercostal spaces. 3.Dissection- in general the mode of dissection is by digital mobilization having found the correct tissue plane by sharp incision. I use electrocautery to divide most tissues. *Parietal pleurectomy* – I begin with the parietal dissection to confirm resectability from the chest wall. Limited chest wall resection of up to 3 ribs is acceptable but larger defects are usually associated with poor prognosis and are not justified by the increased postoperative morbidity. I continue the parietal pleurectomy down to the diaphragm to determine whether phrenectomy can be avoided but then the phrenic nerve must be preserved. The parietal pleurectomy is continued from the apex down to the azygos vein or aortic arch and then over the oesophagus onto the hilum and down to the diaphragm. *Visceral pleurectomy* – Whilst the parietal pleura can be incised over its lateral aspect I prefer to follow the main bronchus down to the pleural reflection. Then open the space beneath it by sharp dissection and then develop the subpleural plane by digital, blunt dissection across each lobe separately. A prior pleurodesis helps in this process as the fused pleural sheet can then be opened by electrocautery down onto a double gloved finger which protects the underlying lung. The stripping of the fused pleural sheet of tumour from the underlying lung parenchyma should continue in two directions away from and towards the oblique fissure. This action is best performed using a swab as a gentle abrasive putting pressure on the pleural sheet rather than the lung. Meticulous technique is imperative to reduce parenchymal damage which will reduce postoperative air leak and hence hospital stay. I find positive pressure ventilation of the underlying lung to be beneficial in providing counter-traction for the pleurectomy. It also allows for early identification and closure of parenchymal tears and sources of air leak. *Lung resection* – there are commonly areas of parenchymal adhesion or frank invasion at the peripheries of the lung at the medial aspect of the upper lobes (particularly the lingula) and the diaphragmatic surface of the lower lobe. Rather than persist in trying to preserve all lung parenchyma at the expense of air leak I have a low threshold for stapled excision of these peripheral strips of lung. Lobectomy is very rarely indicated. *Pericardiectomy* – I prefer to err on the side of resection rather than preservation of the pericardium to ensure macroscopic complete resection (MCR). *Phrenectomy* – Preservation of the diaphragm muscle whilst ensuring MCR is only applicable in the earliest stage lowest volume tumour. Over enthusiastic blunt dissection of a non-existent tissue plane may damage the underlying muscle and increases the risk of postoperative dysfunction or even herniation. As above I prefer to err on the side of resection to ensure MCR. This may require near total phrenectomy in higher volume tumours with dissection into perinephric fat in the most bulky. We have not found that this aggressive policy towards phrenectomy increase intra-abdominal disease progression, the "seeding" theory. *Lymph node dissection* – as with non small cell lung cancer the importance of accurate intraoperative nodal staging cannot be overemphasized. However, there is not as yet a formally described systematic method. I do adopt the standard method as for lung cancer resection but also, noting the different lymph node drainage of mesothelioma, incorporate dissection of the internal mammary, periphrenic and intercostal (where visible) nodes. 4.*Reconstruction Pericardium* – an absorbable mesh is used to create a non restrictive "sling" to prevent postoperative cardiac herniation. A few interrupted sutures into the pericardial resection margin are used whilst carefully observing for any haemodynamic compromise (particularly on the left) from a patch that is too tight. *Diaphragm* – I prefer a bio-absorbable material to potentially reduce the risk of persistent perioperative pleural sepsis. Secure, non-absorbable interrupted sutures are inserted into the diaphragmatic resection margin over the posterior and medial aspects. This may require direct insertion into chest wall if no diaphragm remains. Anteriorly, the patch is fixed with interrupted pericostal (non-buttressed) nonabsorbable sutures. 5.*Closure* Prior to closure in standard fashion careful attention is paid to *aerostasis* with suture closure of leaks and spraying of aerosolized tissue sealant over the lung surface. Meticulous *haemostasis* is imperative aided by the local application of haemostatic patches to the parietal surface. Prophylactic clipping of the *thoracic duct* is advisable to reduce the risk of postoperative chylothorax. 6. *Postoperative* To reduce the problem of persistent postoperative air leak, 3 large bore intercostal drains are connected to suction to bring the lung surface to the rib cage and the patient is extubated as soon as possible to reduce the damaging effects of positive pressure ventilation.

IBS27 CHESTWALL TUMORS
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS27.01 ENDOSCOPIC TREATMENT OF UNRESECTABLE MANAGEMENT OF CHEST WALL TUMORS (EXCEPT STERNUM)

G. Rocco

Memorial Sloan Kettering Cancer Center, New York/United States of America

The principles to surgically manage chest wall tumors vary according to the origin of the tumor (primary vs secondary), the pre-existing conditions of the chest wall (previously operated, irradiated or infected) and the available materials for reconstruction (1). Primary chest wall tumors require resection with at least 4 cm margin as well as careful removal of the periosteum/perichondrium of the remaining rib segments (1 to 2 cm) which may harbor the cancer-cells filled lymphatics responsible for early recurrence (2,3). As a rule, the uppermost and lowermost ribs around the primary tumor including the intercostal muscles need to be removed. For tumors located posteriorly in the first three to four ribs, reconstruction may be avoided albeit the extravasation of pleural fluid in the subcutaneous tissues may be a source of complication and affect the patient's perception of a successful result (1,2). To ensure consistent intrathoracic physiology and avoid lung herniation through anterior and lateral chest wall defects, especially if larger than 1 rib with the upper most and lowermost intercostal spaces, reconstruction is advisable (2,3). Secondary tumors can present as solitary soft tissue or bony metastases requiring localized resection or can infiltrate the chest wall in continuity (3). The latter is the case of T3/4 lung cancer which needs to be resected en-bloc with the chest wall, keeping the line of resection at least at 2 cm from the edge of the infiltration (3). The reconstructive materials to be used are represented by time-honored rigid and soft meshes (Vycril, Polypropilene, Marlex, PTFE) which can still be effectively used for primary reconstruction in the absence of complication factors, such as redo procedures, previously irradiated or infected fields (1,4,5). More recently, new materials have been introduced in the clinical practice, namely, new generation titanium plates, acellular collagen matrices, Poly-4-hydroxybutyrate (P4HB), and, cryopreserved homograft of cadaveric origin (1). These materials present a common advantage of being biocompatible, amenable to modeling and incorporable into the host without the need to remove them should local infection complicate the postoperative period (1). However, all of these prosthetic materials need to be covered with viable tissue, ie, muscle flap, fat and omentum since direct exposure to skin may cause wound seroma or breakdown (1). New perspectives are provided by obtaining adequate biomimesis in the reconstruction of large chest wall defects through 3D printing from CT chest wall templates (6). However, the choice of the reconstructive materials is still a matter of surgeon's preference, resource availability, and costs (2). Apart from some important exceptions (ie, Ewing's sarcoma),

primary chest wall tumors may be chemo- and/or radioresistant (7). The resort to a multimodality approach (ie, chemoradiotherapy followed by surgery) for the involvement of the bony as well as the neurovascular structures at the thoracic inlet has been associated to significantly improved survival rates (8). While the role of adjuvant treatment for non-Pancoast T3N0-1 lung cancer invading the chest wall is established, the recent literature identifies promising survival advantage in administering induction treatment in this selected subset of patients (9,10). Rocco G. Chest wall resection and reconstruction according to the principles of biomimesis. Semin Thorac Cardiovasc Surg. 2011;23(4):307-13. Rocco G, Martucci N, La Rocca A, et al. Postoperative local morbidity and the use of vacuum-assisted closure after complex chest wall reconstructions with new and conventional materials. Ann Thorac Surg. 2014;98(1):291-6. <>3. Weyant MJ, Bains MS, Venkatraman E, et al. Results of chest wall resection and reconstruction with and without rigid prosthesis. Ann Thorac Surg. 2006;81(1):279-85. <>5.Moradiellos J, Amor S, Córdoba M, et al. Functional Chest Wall Reconstruction With a Biomechanical Three-Dimensionally Printed Implant. Ann Thorac Surg. 2017;103(4):e389-e391. <>7.8.9.10.Kawaguchi K, Yokoi K, Niwa H, et al; Central Japan Lung Study Group. A prospective, multi-institutional phase II study of induction chemoradiotherapy followed by surgery in patients with non-small cell lung cancer involving the chest wall (CJLSG0801). Lung Cancer. 2017;104:79-84.

Keywords: Chest wall - lung cancer

IBS28 MANAGING SIDE EFFECTS FOR BETTER QUALITY OF LIFE
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS28.01 THE USE OF DIGITAL MEDICINE FOR SYMPTOMS MANAGEMENT IN LUNG CANCER PATIENTS

R. Navon

Sheba Medical Center, Ramat Gan/Israel

Lung cancer is one of the most common cancers affecting both men and women. Lung cancer is associated with high symptom burden and psychological distress. As a result, lung cancer patients' family caregivers also show high rates of distress. In addition, the common treatments, radiation and chemotherapy, may have severe side effects. Both treatments disrupt normal daily living activities and diminish well-being. Hence, symptom management in lung cancer patients may lead to improvements in various aspects, such as: quality of life, emotional stability and supportive environment. Additionally, the prolonged longevity of lung cancer patients nowadays significantly increased the burden of symptom management on the health system. Therefore, the need to optimize symptom management is of great significance. Contemporary technology enables the use of digital medicine, to provide information and interaction with patients in order to improve symptom management. It can help in overcoming several barriers and in reducing the health system's costs. For example, gathering information about the patients' needs may help health care providers to adjust and improve the services according to the principles of personalized medicine; frequent automated digital reminders may improve patients' collaboration during treatments. Patients' confusion and uncertainty that may lead patients to avoid consulting about symptoms, can be prevented by using on line follow-up regarding these symptoms. Enhancement of the care provided to people with cancer can be translated into reduction in symptom prevalence and/or burden and, possibly, reduction in unnecessary hospital admissions, hospitalization days, or clinic visits. A particular population which may benefit from the use of digital medicine is patients from rural areas. These patients lack accessibility medical services. Inaccessibility causes delays in diagnosis, treatment, and follows up, as well as unavailability of advanced care including multimodality treatment options and enrollment in clinical trials. Computer-based systems which employ interactive telecommunication technology have a great potential for a revolutionary impact on healthcare delivery by expanding accessibility and reducing costs. This is particularly true for those using computer-controlled telephony known as interactive voice response technology. This presentation will bring conclusions from several digital medicine symptom management programs, and emphasize lessons which can be learned from their results and possible directions for the future.

Keywords: digital medicine, Lung cancer, symptom management

IBS28 MANAGING SIDE EFFECTS FOR BETTER QUALITY OF LIFE
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS28.02 PALLIATIVE CARE FOR IMPROVED QUALITY OF LIFE; IT'S NOT END OF LIFE CARE (HOSPICE)

N. Mitrea

Transilvania University, Brasov/Romania

Since 1967, when the first Hospice has been opened by Dame Cicely Sounders (founder of St. Christopher's Hospice, London, England), and palliative care has been blended with hospice, several definitions have been given to palliative care and hospice terms. In 1997, the palliative care definition by Field and Cassel was short and simple: "palliative care is seeking to prevent, relieve, reduce or soothe the symptoms of disease or disorder without effecting a cure". The current most common references for palliative care definition is the World Health Organization's, 2002: "*Palliative care* is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." (Sepulveda et al., 2002). Variations in defining palliative care have recently caused controversies among professionals in the multidisciplinary teams, as it is now the case with the definition given by International Association for Hospice and palliative care: "Palliative care is the active holistic care of individuals across all ages with serious health-related suffering due to severe illness, and especially of those near the end of life. It aims to improve the quality of life of patients, their families and their caregivers." (IAHPC, 2018). Even more controversies are surrounding the term Hospice as confusion exists regarding the differences and overlaps between hospice and palliative care. In this presentation several definitions of terms will be discussed, including palliative care, quality of life, hospice and death. In order to better illustrate the case, the principles of palliative care will be remembered: holistic care, objective of care = improved quality of life, affirms life and regards death as a normal process, doesn't hasten or postpone death, patient in the center of care and families as units of care, care provided by a multidisciplinary team, bereavement support for families. Some suggestions will be made for aligning to the reality of living a finite life and for the acceptance of the universal mystery of death. Palliative care and hospice need to be destigmatized and promoted among both, the general public and the healthcare professionals, in order to be early on integrated in the trajectory of a serious disease progression. For this reason, the bow tie model of 21st century for palliative care - the enhanced model, will be described. In conclusion, palliative and hospice are about: quality of life, being human, meaningful relationships, control of pain and other symptoms, respect for the dignity of the person, growing throughout the trajectory of the disease. The take home message is valuable for all of us: "*You matter because you are you. You matter to the last moment of your life, and we will do all we can, not only to help you die peacefully, but to live until you die.*" (Dame Cicely Saunders) References: Field, M.J., & Cassel, C.K., (1997). *Approaching death: Improving care at the end of life* (Report of the Institute of Medicine Task Force). Washington, D.C.: National Academy Press. IAHPC. *Global Consensus based palliative care definition*. (2018). Houston, TX: The International Association for Hospice and Palliative Care. Retrieved from https://hospicecare.com/what-we-do/projects/consensus-based-definition-of-palliative-care/definition/ Sepulveda, C., Marlin, A., Yoshida, T. & Ulrich, A. (2002). *Palliative Care: The World Health Organization's global perspective*. Journal of Pain & Symptom Management, 24(2), 91-96.

Keywords: Quality of life, hospice, palliative care

IBS29 HOW TO SUCCESSFULLY RUN A MULTIDISCIPLINARY TUMOR BOARD
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS29.01 CAN A MULTIDISCIPLINARY TEAM MEETINGS IMPROVE LUNG CANCER SURVIVAL?

K. Fong[1], E. Stone[2], B. Page[1]

[1]*University of Queensland, Chermside/Australia,* [2]*St Vincent's Hospital Sydney, Darlinghurst/Australia*

Multidisciplinary team (MDT) management for lung cancer has been increasingly introduced globally with the aim of improving outcomes for patients. This is reflected by the recognition that lung cancer MDT management is the standard of care in some countries The proponents of MDT care note the perceived benefits of MDT care to all stakeholders, including the patient, their clinicians and the general population. On the other hand, there are potential disadvantages associated with MDT lung cancer care, particularly the costs of setting up the service, the time commitment from the clinicians involved and possible delay to treatment. Observed obstacles to implementing effective MDT management include inadequate infrastructure and organisational/administrative support, lack of enabling technologies, incomplete specialist representation and low attendance by some MDT disciplines, inadequate case preparation and sub-optimal quality information for decision making. The organisation and performance of MDT lung cancer varies round the world and even within countries. This heterogeneity may affect the effectiveness and quality of MDTs such that quality assurance for MDT is essential. This talk will identify the eidence for the effects of lung cancer MDT care on patient centred outcomes including survival in the context of unparalleled improvements in the range of therapeutic options currently available for lung cancer.

Keywords: Lung cancer, Survival, MDT care

IBS29 HOW TO SUCCESSFULLY RUN A MULTIDISCIPLINARY TUMOR BOARD
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS29.03 QUALITY CONTROL

T. Murgu

University of Chicago, Chicago/United States of America

Lung cancer diagnosis and therapy have progressed within the recent years due to significant advancements of bronchoscopic techniques for diagnosing intrathoracic adenopathy and peripheral lung lesions, radiotherapy and surgery techniques, molecular targeted therapeutic agents and immunity checkpoint inhibitors. Published evidence suggests that multidisciplinary team presentation (aka tumor board) in lung cancer has the potential to improve long-term outcomes. Clinical guidelines recognize the importance of multidisciplinary meetings in the optimal care of lung cancer patients. Evidence suggests that dedicated lung cancer tumor boards lead to increased treatment utilization rates and improved survival outcomes for patients with lung cancer. Lung cancer tumor boards also allow for education and promotion of specialty services. This is especially relevant in the fast pace of modern medicine wherein technological and drug therapy advances lead to changes in the structure of traditional lung cancer tumor board and continuously challenge our approach to managing patients suffering from lung cancer. In this session, we will describe each of these issues with reference to our own experiences and literature considerations pertinent to: Selecting needle-based or surgical techniques for obtaining a cytohistologic diagnosis from the primary tumor and/or mediastinal or hilar lymph nodes Managing potential candidates for curative surgical resection; a lung cancer tumor board should include at least a thoracic surgeon specializing in lung cancer, medical oncologist, radiation oncologist and pulmonologist Managing patients with clinical stage I and II NSCLC, even if the patients are considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy Managing patients with lung cancer who require multimodality therapy (i.e. in patients with discrete N2 involvement by NSCLC identified preoperatively) Coordinating the optimal approach to obtaining and processing biopsy/cytology specimens to provide expeditious diagnostic and molecular results.

Keywords: tumor board, Multidisciplinary

IBS30 RISK ASSESSMENT IN CT SCREENING
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS30.01 RISK ASSESSMENT TO ESTABLISH SCREENING PROGRAMS: THE AUSTRALIAN POINT OF VIEW

A. Mcwilliams[1,2]

[1]*University of Western Australia, Perth/Australia,* [2]*Fiona Stanley Hospital, Perth/Australia*

Australia has a multicultural community of 25 million people. (1) The ethnic background of Australians is predominantly Caucasian (83.6%) with 5.2% Chinese ancestry and 2.8% Indigenous Australian in 2016 census data.(1) It has one of the lowest current smoking rates in the world with only 14% of people >18 years being current smokers in 2017-2018.(2) Despite this, lung cancer remains the greatest cause of cancer death for women and men and is the fourth leading cause of all deaths in Australia. (2,3) Lung cancer cases continue to increase due to a variety of reasons including our growing and ageing population and the lag time between the tobacco epidemic and lung cancer occurrence.(4) Lung cancer rates in Indigenous Australians are approximately double compared to non-Indigenous Australians.(4) Overall, the majority of lung cancer in Australia is attributable to tobacco exposure but 20% of lung cancer occurs in never smokers.(4) There are known gender differences with ~90% of lung cancer in men attributable to tobacco exposure but only ~75% in women. (4) Other occupational exposures play an important role in lung cancer in Australia, with asbestos being one of the most important toxins contributing to lung cancer incidence.(1) A large longitudinal screening program in asbestos exposed individuals (>1700 participants) is ongoing in Western Australia, the Asbestos Review Project. The project has been utilising low dose chest computed tomography (CT) screening since 2012. Lung cancer rates in this cohort are similar to a high-risk smoking cohort despite lower tobacco exposures. The use of current screening enrolment criteria (USPSTF/NCCN) would have resulted in most lung cancer cases being missed. (5) Population based screening programs in Australia have been implemented for cervical, breast and bowel cancers but currently there is no national screening program for lung cancer. A proposed screening program must meet the Australian Screening Framework established in 2008 and be endorsed by the Standing Committee on Screening and the Australian Health Minister's Advisory Council. (6) In their last published statement in 2015, implementation of a national program has not been supported.(7) The definition of the appropriate population to screen and the likely uptake of screening requires further evaluation in the Australian population.The reduction in mortality from lung cancer screening only occurs in those at high risk so the delineation of this cohort is crucial for minimisation of harm and a cost-effective program. (8) International work evaluating various risk prediction models to define the population that would most benefit from lung cancer screening have been published. (8,9) The performance of one of the most well validated models, the $PLCO_{M2012,}$ has been retrospectively evaluated in the Australian population in a subset of the 45 and Up study.(10) In this large longitudinal cohort, 95 882 ever smokers, >45 years were included in the analysis. The predictive power of the $PLCO_{M2012}$ risk model was assessed compared to other potential lung cancer screening enrolment criteria (NLST, USPSTF). This study showed that the risk model, although derived from a North American population, performed equally as well in the Australian population. It would reduce the proportion of ever smokers >55 years, potentially eligible for screening to ~29%. However, only 2% of the cohort were of Asian ancestry and 1.6% Indigenous Australian. The PLCO risk prediction model has been utilised prospectively in the PanCanadian study and further prospective validation is ongoing in Australia, Canada and Hong Kong in the International LungScreen Trial (ILST). The further refinement of a risk prediction model incorporating occupational/environmental carcinogen exposures such as asbestos and ethnicity is needed to further improve risk assessment for lung cancer screening. Supported by National Health and Medical Research Council and Cancer Australia. References: 1. Australian Bureau of Statistics. 3101.0-Australian Demographic Statistics, Sep 2018. Dataset: 2016 Census-Cultural Diversity in Australia. Cited 7 June 2019 2. Cancer in Australia 2019. https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019 3. Deaths in Australia, Leading causes of death. https://www.aihw.gov.au/reports/life-expectancy-death/deaths-in-australia/contents/leading-causes-of-death 4. Making Lung Cancer a fair fight: a blueprint for reform. Lung Foundation Australia, October 2018. https://lungfoundation.com.au/wp-content/uploads/2018/10/Information-paper-Making-Lung-Cancer-A-Fair-Fight-A-Blueprint-for-Reform-Oct2018.pdf 5. Harris E,

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Keywords: early detection, Lung cancer, Screening

IBS30 RISK ASSESSMENT IN CT SCREENING
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS30.03 RISK ASSESSMENT TO ESTABLISH SCREENING PROGRAMS: THE CANADIAN POINT OF VIEW

S. Lam

BC Cancer Agency, Vancouver/Canada

Risk Assessment to Establish Screening Programs: The Canadian Point of View Stephen Lam MD, FRCPC BC Cancer Agency & University of British Columbia, Vancouver, Canada The Canadian Task Force on Preventive Health Care (CTFPHC) supports screening with low dose computed tomography (LDCT) of the chest to decrease lung cancer mortality.[1] The Task Force recommends annual screening up to three consecutive years in high risk adults aged 55-74 years with at least a 30 pack-year smoking history, who currently smoke or quit less than 15 years ago. Pilot LDCT screening program or studies are being conducted in Canada to help determine how to best implement organized lung cancer screening for people at high risk at the population level. Based on emerging data that suggests both the CTFPHC and the US Preventive Services Task Force (USPSTF) age and pack-years selection criteria[2] are suboptimal and that risk prediction tools such as the PLCOm2012 are more sensitive with better positive predictive power to identify ever smokers who will develop lung cancer with a lower number needed to screen to prevent one lung cancer death and are more cost-effective, [3-8] pilot studies in Canada adopt the PLCOm2012 risk prediction tool to select high risk ever smokers for LDCT screening. A prospective study is being conducted in newly diagnosed lung cancer patients in the Greater Vancouver area. In 1,076 patients, 37% were never smokers reflecting the foreign-born ethnic distribution. Of the 683 ever smokers, 60% met the PLCOm2012 model 6-year risk ≥1.5% screening criteria while only 39.5% met the USPSTF screening criteria. The International Lung Screen Trial (ILST), a multi-center prospective trial in Canada (British Columbia, Alberta), Australia, Hong Kong, and the United Kingdom, offer screening to ever smokers age 55 to 80 years if they meet the USPSTF criteria or the PLCOm2012 model 6-year risk ≥1.5% criteria. Participants receive two annual screens and are followed for six years for lung cancer outcomes. Interim results in 4,863 participants with 101 lung cancers showed that PLCOm2012 identified 26.6% more lung cancers than USPSTF criteria (99% of all lung cancers versus 78% with USPSTF). However, PLCOm2012 screened 9.9% more people than USPSTF criteria. If 2% six-year lung cancer risk threshold were used for screening selection criteria as is currently used in the Cancer Care Ontario Pilot, PLCOm2012 would be 12.7% more sensitive identifying 88.1% of lung cancers while screening 11% fewer people compared to USPSTF criteria. A 1.7% six-year lung cancer risk threshold would be 24.1% more sensitive identifying 97% of all lung cancers while screening only 1% more people than USPSTF criteria. The 1.7% threshold may be a better screening selection criterion. The worldwide burden of lung cancer is significant and projected to rise during the coming years especially in East Asian countries, namely, China, Japan, South Korea and Taiwan because of the large population size, high stable incidence rates in male and significant upward trends in females many of whom are never smokers.[9] With global migration and increasing number of new Canadians who are diagnosed with lung cancer are from Asian countries such as in Vancouver, better lung cancer risk assessment tools need to be developed that take into account ethnicity and other environmental exposures such as outdoor and household air pollution exposures.[10] Risk prediction tools may be perceived by some to be more complex to use than age and pack-years. The web based PanCan risk prediction tool, a precursor to the validated PLCOm2012 model, was tested in both English and French in 8 centers across Canada from coast to coast.[7] The tool was found to be simple to use and took approximately 5 minutes to administer over the telephone. Similar experience was found with the web based PLCOm2012 risk assessment tool for enrollment into the International Lung Screen Trial and the Cancer Care Ontario pilot screening program. Risk assessment can be readily done by a navigator or a physician for enrollment into lung cancer screening programs as part of the shared decision process. Supported by the Terry Fox Research Institute, BC Cancer Foundation, the VGH-UBC Hospital Foundation, the Alberta Cancer Foundation, and the Australian NHMRC. References: 1. Lewin G, Morissette K, Dickinson J, et al. Recommendations on screening for lung cancer. *CMAJ.* 2016;188(6):425-432. 2. Moyer VA, Force USPST. 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Keywords: Lung cancer, Screening, risk assessment

IBS31 TRIAL DESIGN AND NOVEL DRUG ACCESSIBILITY
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS31.01 ENDPOINTS AND TRIAL DESIGN FOR ONCOGENE ADDICTED NSCLC

S. Michiels

Gustave Roussy, Villejuif/France

The availability of targeted anticancer drugs or immunotherapies and the relative affordability of genomic analyses has led to a growing expectation that treatments can be chosen based on the molecular biomarkers of their tissue or blood samples. In this talk Dr. Michiels will provide an overview of the endpoints and contemporary clinical trial designs that can be used in the era of stratified medecine.

Keywords: clinical trial design, stratified medecine

IBS31 TRIAL DESIGN AND NOVEL DRUG ACCESSIBILITY
TUESDAY, SEPTEMBER 10 07:00–08:00

IBS31.02 NOVEL DRUG ACCESS: DREAM VERSUS REALITY

R. Dziadziuszko

Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdańsk/Poland

The number of targeted agents registered for treatment of non-small-cell lung cancer (NSCLC) has increased exponentially over last decade as a result of improvements of molecular biology, clinical pharmacology, and clinical research. Molecularly defined subsets of NSCLCs are now recognized from the perspective of these improvements, which directly affect survival of large unmber of NSCLC patients. These innovations are associated with exponential increase of costs to health care, resulting in inequalities among, and often within, countries and societies. Landscape of access to innovative drugs and novel approaches to maximize the access to new therapies will be presented from European perspective.

Keywords: targeted agents, new drugs, reimbursement

Grand Round Sessions

GR01 WHETHER AND HOW TO ADAPT TREATMENT OF NSCLC OLIGOMETASTATIC DISEASE TO...
SUNDAY, SEPTEMBER 8 13:30–15:00

GR01.01 DEFINITION AND MINIMAL STAGING IN OLIGOMETASTATIC DISEASE

A.M. Dingemans

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Oligometastatic non-small cell lung cancer (NSCLC) is perceived as a separate entity of metastatic NSCLC with limited metastatic potential and possibility of long term survival when treated with local radical treatment[1-3]. However, uniform definition of oligometastatic NSCLC does not exist. We showed in a recent systematic review (21 papers) that the number of metastasis, allowed in the definition of oligometastatic NSCLC, varies between 1 and 8, in only 2 out of 21 papers > 5 metastasis were allowed[4]. This has led to an European Organisation on Research and Treatment of Cancer (EORTC) – Lung Cancer Group (LCG) initiative to formulate a consensus definition of synchronous oligometastatic NSCLC. A pan-European multidisciplinary consensus group was established. Results from the systematic review, a European survey and real patient cases were taken into account when. It was concluded that the definition of synchronous oligometastatic NSCLC is relevant when a radical treatment is technically feasible for all tumor sites with acceptable toxicity, that may modify the disease course leading to long-term disease control. Based on the review, a maximum of 5 metastases and 3 organs is proposed. Mediastinal lymph node involvement is not counted as a metastatic site[5]. In addition staging with PET-CT and imaging of the brain is mandatory. This is in line with the advice of the EORTC-imaging group[6]. The eligibility criteria of recent and ongoing clinical trials in this setting will be discussed in this presentation. 1. Gomez D, Tang C, Zhang J, et al. Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial. *ASTRO 2018* 2018;abstract LBA3. 2. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *The lancet oncology* 2016;17:1672-1682. 3. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA oncology* 2018;4:e173501. 4. GiajLevra N, Levra MG, Durieux V, et al. Defining synchronous oligometastatic non-small cell lung cancer: a systematic review. *Journal of thoracic oncology:official publication of the International Association for the Study of Lung Cancer* 2019. 5. Dingemans A, Hendriks L, Berghmans T, et al. MA25.02 - Searching for a Definition of Synchronous Oligometastatic (sOMD)-NSCLC: A Consensus from Thoracic Oncology Experts *WCLC 2018*. Toronto: 2018:abstract MA 25.02. 6. deSouza NM, Liu Y, Chiti A, et al. Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group. *European journal of cancer* 2018;91:153-163.

Keywords: Oligometastatic, Non-Small Cell Lung Cancer

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GR01.03 NODAL STATUS OF THE PRIMARY DISEASE?

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Oligometastases from non-small cell lung cancer (NSCLC) can be classified as synchronous, which are diagnosed at the same time as the locoregional disease, or metachronous, developing after (successful) treatment of the locoregional disease. The title of this presentation implies that the nodes are present at the time of treatment, so the focus will be restricted to the treatment of synchronous oligometastases. In the absence of a universally accepted definition of oligometastatic disease we will assume that the term can be used where there are up to five metastatic sites. Nodal involvement as a prognostic factor in patients with oligometastatic disease. The earliest reports of attempting to improve survival outcomes for patients with limited metastastic disease were in patients with brain metastases either by resection (1) or by resection or stereotactic radiosurgery (2). Five year survivors were observed, vindicating aggressive treatment in this subset of stage IV patients with NSCLC, but patients with regional node involvement appeared to have worse survival than patients with N0 disease. This was confirmed in a subsequent large multicentre individual patient data meta-analysis reported by Ashworth et al of 757 patients who were treated with ablative treatments to all sites of disease (3). Factors that were important for survival in the meta-analysis were metachronous versus synchronous and histology (favouring adenocarcinoma) as well as N stage. Using recursive partitioning analysis, Ashworth et al were able to group patients with synchronous metastases into an intermediate risk group with N0 disease and a 5 year survival of 36.2% versus a high risk group with N1 or N2 disease and a 5 year survival of 13.8%. Why should regional node status be a prognostic factor in patients who already have distant metastatic disease? Most likely it is because nodal involvement is a surrogate for the volume of metastatic disease that may have been underestimated in the pre-PET era. Is regional nodal involvement a contraindication to an aggressive approach? Although Hu et al (2) recommended against an aggressive approach to the locoregional disease in patients with stage II or III NSCLC, the fact that 3 year survivors were observed in their cohort and 5 year survivors in the meta-analysis suggests that it is an option that should be discussed considered. in a retrospective study by Flannery et al if the thoracic disease was not treated definitively, survival at 5 years was 0% compared with 34.6% for surgical resection or chemoradiation (P < 0.0001) (4). Patients with N0 or N1 disease (grouped together) had longer survival than patients with N2 or N3 disease, but this was not statistically significant. A prospective phase II trial treated patients with up to 5 oligometastatic sites with chemotherapy followed by chemoradiation to the primary and involved nodes plus SABR or high dose radiotherapy (60 Gy in 30 fractions) to the metastases was associated with a median survival of 28 months, but there was no difference in survival whether nodes were or were not involved (5). Does nodal status influence whether locoregional disease should be treated by surgery, SABR or (chemo)radiotherapy? This will depend on the patient's fitness for surgery, and the anatomical extent and location of disease. We have no evidence to support any one strategy. We use the same principles to select treatment to the locoregional disease as if there were no oligometastatic disease present. In the Ashworth meta-analysis, surgical management of the primary was a favourable prognostic feature with a hazard ratio of 0.74 (95% CI: 0.55 – 1.00) on univariable analysis, but not on multivariable analysis (3). In the first randomized trial in patients with NSCLC oligometatases the use of ablative treatments did improve disease free survival in patients with NSCLC who had up to 3 metastases and no evidence of progression after systemic therapy.(6) In this small trial, nearly all patients had synchronous oligometastases. Treatments used for the primary disease after first-line systemic therapy included surgery, stereotactic ablative body radiotherapy (SABR) and chemoradiation. Any involved regional nodes were regarded collectively as one "oligometastatic site". There was no significant difference in progression-free survival comparing patients with N0-1 disease versus N2-3. Conclusion Where a patient has synchronous oligometastatic disease that is amenable to ablative therapy, definitive treatment to the primary site and any involved regional nodes taking into account the patient's general condition and disease stage is a reasonable option, regardless of nodal stage. References 1. Billing PS, Miller DL, Allen MS, Deschamps

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Keywords: non-small cell lung cancer, oligometastases, lymph node involvement

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GR01.04 THE RATIONALE FOR LOCAL CONSOLIDATIVE THERAPY IN ONCOGENE-DRIVEN, OLIGO-AND POLY-METASTATIC NSCLC

J. Heymach

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Immunotherapy with PD-1/PD-L1 checkpoint blockade has transformed the management of metastatic NSCLC. These agents are now commonly used as the first-line systemic therapy, either as monotherapy or in combination with chemotherapy, for most patients with metastatic disease who do not have driver mutations in *EGFR* or *ALK*. While this represents a major advance, the majority of NSCLC patients do not have an objective response to PD-1/PD-L1 blockade (Borghaei et al., 2015; Fehrenbacher et al., 2018; Vokes et al., 2018). The molecular determinants of an immunologically inert phenotype are incompletely understood, although it is often associated with a lower tumor mutational burden (TMB) and/or low tumor PD-L1 levels. In addition to TMB and PD-L1, other genomically-defined subgroups have been identified with distinct responses to immunotherapy. LKB1 or EGFR mutant NSCLC subgroups have been characterized for presenting an immunologically inert (or "cold") phenotype with relative depletion of T-effector cells and have been associated with lack of response to immunotherapy. However, other subgroups that are defined by genomic alterations in BRAF or POLD1/POLE genes have been associated with enhanced immunotherapy responses in NSCLC. Patients with *EGFR* and *ALK* alterations, which represent 10-15% of total lung adenocarcinoma, were found to have an ORR of 3.6%, with lower PD-L1 and TIL infiltration (Gainor et al., 2016). EGFR mutant patients have also been associated with lower response to immunotherapy in NSCLC (Gainor et al., 2016). Using clinical specimens from the PROSPECT resected NSCLC cohort, we conducted immunohistochemical immune profiling (n=94). EGFR mutant tumors expressed significantly lower levels of PD-L1 and granzyme B (GZMB). We evaluated mRNA expression and observed increased TGFB3 in EGFR mutant tumors and decreased GZMB. Moreover, EGFR mutant tumors displayed decreased T cell clonality compared to EGFR wild-type tumors. To determine the potential impact of different oncogenic drivers on immunotherapy responsiveness, we conducted a retrospective analysis from the MD Anderson GEMINI database. This analysis confirmed that EGFR mutant patients had shorter PFS (1.8m) and ORR (6%) to PD-1/PD-L1 checkpoint blockade than EGFR wild-type patients. KRAS mutant tumors are highly heterogeneous in their response to targeted agents and immunotherapy. We identified that genomic alterations in three genes: *STK11/LKB1*, *TP53*, and *CDKN2A* defined biologically distinct KRAS mutant subgroups with distinct immune profiles. LKB1 loss was associated with greater sensitivity to agents enhancing energetic, proteotoxic, or replicative stress such as HSP90 and PARPi (Skoulidis et al., 2015). LKB1 loss was also associated with a distinct immune phenotype with lower levels of PD-L1 and other checkpoint molecules, IFN-γ signaling and lower T-cell infiltration. Using KRAS-mutant GEMMs or syngeneic GEMM-derived cell lines, we observed that LKB1 knockout (KO) recapitulated these features in immunocompetent mice. In collaboration with Foundation Medicine, we assessed 924 patients with metastatic NSCLC. To control for TMB, we only analyzed those with intermediate/high TMB levels. The top two genes associated with lower PD-L1 levels were *STK11*/LKB1 and EGFR. *STK11*/LKB1 alterations were also the most strongly associated with a shorter duration of time on PD-1/PD-L1 blockade (Skoulidis et al., 2018b). Among KRAS mutant LUAC patients, LKB1 mutant tumors were associated with lower response to immunotherapy in three independent retrospective cohorts and the randomized phase III Checkmate 57 study (Skoulidis et al., 2018b). This group did not have a significantly lower TMB than the overall cohort, but did have lower PD-L1 levels. LKB1 mutant tumors were associated with shorter PFS and OS on immunotherapy, even in the PD-L1 positive LUAC population regardless of KRAS status. Our preliminary analysis indicates that loss of LKB1 is associated with resistance to combined chemotherapy and pembrolizumab but not associated with worse outcomes after adjuvant chemotherapy (Skoulidis et al., 2018b), suggesting it is not merely a prognostic marker. To validate this finding our group recently has studied the impact of LKB1 mutations on clinical outcomes of non-squamous NSCLC patients treated with chemo-immunotherapy. Consistent with our previous data, LKB1 genomic alterations were associated with inferior clinical outcomes in NSCLC patients treated with chemo-immunotherapy with response rates comparable to those reported for chemotherapy alone (Skoulidis et al., 2018a). BRAF is mutated in 2% to 4% of lung adenocarcinoma (Planchard et al., 2016), and approximately 1-2% of lung tumors harbor the BRAF V600E mutation, which results in activation of the MAPK pathway to promote cell proliferation. BRAF V600E mutation status has been reported to predict sensitivity to the combination of trametinib and dabrafenib, MEK and BRAF inhibitors respectively in lung adenocarcinoma (Noeparast et al., 2016) but it is not much known about the effects of this mutation in driving immunotherapy response. We analyzed BRAF mutant patients that were treated with PD-1/PD-L1 checkpoint inhibitors in our GEMINI database and we compared with patients bearing classic EGFR mutations (exon 19 deletions + exon 21 L858R), EGFR exon 20 mutations (no T790M included), and HER-2 mutations. The analysis reported that BRAF mutant tumors display an increased TMB and that patients with BRAF mutations presented an improved PFS when treated with PD-1/PD-L1 checkpoint inhibitors compared with patients bearing other driver mutations. Further studies on co-mutational status and TMB in these genomicaly-defined groups are ongoing to address potential underlying mechanisms associated with these findings. In addition to BRAF mutations, alterations in DNA repair and replication machinery genes including DNA polymerase epsilon (POLE), polymerase delta 1 (POLD1), and mutS homolog 2 (MSH2) have also been identified in patients that presented with durable clinical benefit to PD-1 blockade therapy. These studies suggest that genomic biomarkers identify subgroups of NSCLC with different responses to immunotherapy and, presumably differing mechanisms of immune modulation. Integration of genomic biomarkers such as STK11/LKB1 in addition to established immune biomarkers such TMB and PD-L1 expression is likely to provide useful information for predicting response to immunotherapy as well as a framework for the development of tailored immunotherapy approaches.

Keywords: NSCLC, Genomic biomarkers, Immunotherapy

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GR01.05 SITE OF OLIGOMETASTASES

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The concept of oligometastatic disease representing patients with only a few or "oligo"metastases, is a relatively new entity in thoracic oncology and surgery [1-2]. Most probably, an intermediate state exists between patients with locoregional disease without distant metastases and those with multiple metastatic involvement in one or more distant organs. The International Association for the Study of Lung Cancer (IASLC) adopted this concept and in the

8th Tumor-Node-Metastasis (TNM) edition a new category was introduced representing those patients with a single metastasis in a single distant organ, currently M1b involvement [3]. These patients belong to stage IVA, as well as patients with contralateral malignant nodules. In contrast, multiple metastases in a single or multiple distant organs are currently described as M1c disease, and they are grouped together in the new stage IVB category. In the IASLC database patients with clinical stage IVA disease had a median survival time (MST) and 5-year survival rate of 11.5 months and 10%, respectively, in contrast to 6.0 months and 0% for patients with stage IVB disease [4]. No consensus exists on the precise definition of oligometastatic disease. For this reason the European Organisation of Research and Treatment of Cancer (EORTC) created a task force to propose a definition of synchronous oligometastatic disease based on consensus by thoracic oncology experts [5]. A maximum of 5 metastases and 3 organs is proposed. Diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric) as well as bone marrow involvement are not accepted as specific site as these cannot be treated with radical intent. Is the specific organ involved important in management and prognosis of these patients? Patients with contralateral lung nodules, brain, bone and adrenal metastases are mostly reported in literature as these organs are quite accessible for local ablative treatment by surgical excision or stereotactic radiotherapy. For patients with bilateral / contralateral tumor nodules introduced in the IASLC prospective database by the electronic data capture (EDC) system, MST was 12 months, quite similar to patients with ipsilateral pleural/pericardial effusion. Although the numbers were quite small, for those patients with a single adrenal metastasis introduced by EDC, MST was 6.5 months, for a single bone metastasis 12.6 months, and for a single brain metastasis 12.1 months [3]. These survival times were significantly better than those for patients with multiple lesions at a single site. In general, most survival data are from retrospective series with an inherent selection or publication bias. For this reason, the EORTC decided not to consider the specific organ involved but this may change when more prospective data become available. Are there any predictive factors for survival in patients with oligometastatic disease? In an individual patient data meta-analysis of 757 patients with 1-5 synchronous or metachronous metastases from non-small cell lung cancer (NSCLC), predictive factors were synchronous versus metachronous metastases, N stage and adenocarcinoma histology [6]. Surgery was the most frequently used treatment, as well for the primary tumor as for the metastatic involvement. Low-risk patients had metachronous metastases, the intermediate risk group presented with synchronous metastases and N0 disease, and the high-risk group with synchronous disease and thoracic lymph node involvement. So, adequate lymph node staging should be performed in every patient [7]. May combined modality therapy including locoregional ablative treatment by stereotactic radiotherapy or surgery improve prognosis in patients with oligometastatic disease? A recent landmark trial investigated the role of local ablative therapy in patients with stage IV NSCLC with three or fewer metastases remaining after first-line systemic therapy [8]. In this multicentre, controlled phase II study 49 patients were randomized between local consolidative therapy group consisting of surgery, radiotherapy or a combination with the aim of ablating all residual disease, and maintenance treatment which was chosen from a predefined list of regimens approved by the Food and Drug Administration (FDA). Primary endpoint was progression-free survival. Secondary outcomes were overall survival, safety and tolerability, time to progression of previous metastatic lesions, time to appearance of new metastatic lesions, and quality of life. Most frequent metastatic sites were brain, bone, adrenal gland, pleura and metastatic lung lesions. Significantly longer progression-free and overall survival rates were noted in the local consolidative therapy group than in the maintenance treatment group. Time to the appearance of a new lesion was longer among patients in the local consolidative therapy group than among patients in the treatment group. Survival after progression was also longer in the local consolidative group [8]. Regarding specific management of oligometastatic disease related to the site of involvement, the European Society of Medical Oncology (ESMO) recently published clinical practice guidelines for metastatic NSCLC including oligometastatic disease [9]. In the presence of a solitary metastatic site on imaging studies, efforts should be made to obtain a cytological or histological confirmation of stage IV disease. Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term disease-free survival following systemic therapy and local consolidative therapy (high-dose radiotherapy or surgery). Because of the limited evidence, these patients should be discussed within a multidisciplinary tumor (MDT) board and inclusion in clinical trials is preferred. Although operative risk is low and long-term survival may be achieved, current evidence for surgery in oligometastatic disease is limited, and the relative contribution of surgery versus radiotherapy as local treatment modality has not been established yet. Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumors and, if possible, treated with curative-intent therapy [9]. Finally, even salvage surgery may be considered in highly selected patients with oligometastatic disease to improve long-term outcome [10]. REFERENCES 1. Pfannschmidt J. Lung Cancer. 2010;69:251-8 2. Shields' General Thoracic Surgery, 8th edition 2019, pp. 1289-90 3. Eberhardt WE. J Thorac Oncol. 2015;10:1515-22 4. Goldstraw P. J Thorac Oncol 2016; 11:39-51 5. Dingemans AM. IASLC 19th WCLC 2018; abstract MA25.02 6. Ashworth AB. Clin Lung Cancer 2014;15:346-55 7. Fernandez R. J Thorac Dis 2019; 11(Suppl.7):S969-S975 8. Gomez DR. 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GR02 IMPROVING PATIENTS QUALITY OF LIFE DURING TREATMENT OF METASTATIC DISEASE
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GR02.01 HOW CAN WE INCORPORATE EXERCISE PRACTICES INTO PATIENT'S LIVES?

C. Mathias

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Physical activity is any movement using skeletal muscles. There have been over 16 studies examining physical activity and lung cancer risk, 12 cohorts and four case-control studies have examined the association between physical activity and lung cancer. When stratifying by study design, the pooled risk reduction amongst the 12 cohort studies is 23%, and amongst 4 case-control studies, a pooled risk reduction of 38%[1]. Among In a meta-analysis of 11 studies comparing highest versus and lowest levels of leisure-time physical activity, including odds ratios from studies in which the association between physical activity and cancer prevention was adjusted for smoking intensity: moderate-intensity physical activity was associated with a statistically significant risk reduction in lung cancer incidence, OR=0.87 (95% CI: 0.79–0.95), and vigorous-intensity physical activity was associated with a statistically significant risk reduction in lung cancer incidence, OR=0.70 (95% CI: 0.62–0.79). During exercise, particularly moderate-intensity aerobic exercise, T-cell populations transiently, NK cell populations and activity, and neutrophil quantity and activity transiently rise[2]. Exercise or physical activity haves a profound effect on macrophage physiology, including phagocytosis, chemotaxis, metabolism and anti-tumor activity. In murine models of acute exercise, peritoneal macrophage phagocytosis was increased *in vitro*, relative as opposed to sedentary conditions[3]. Although these effects are transient during an acute bout of exercise, the repetitive effects may produce a cumulative (training) effect. Chronic bouts of physical activity have been associated with an inverted 'J-curve' such that optimal immune function is achieved with moderate-intensity physical activity and sedentary and vigorous-intensity below optimal immune-system function. Physical activity is also a useful adjunct to improve the deleterious sequelae experienced during cancer treatment including fatigue, muscular weakness, deteriorated functional capacity, and many others. There is a growing base of evidence that suggests engaging in exercise, such as brisk walking, yields fewer symptoms and side effects during treatment and retards delays the rate at which physiologic systems are affected[4]. The mechanistic models hypothesized that includes pathways relating to sex hormones, metabolic hormones, inflammation and adiposity, immune function, oxidative stress, DNA repair, and xenobiotic enzyme systems. During cancer treatment, deconditioning of the cardiovascular and pulmonary system is common and is associated with diminished levels tolerance to of physical activity. However, it appears that the adaptive capacity of the cardiorespiratory system to exercise training remains intact during treatment. Among In a meta-analysis of 17 high-quality studies, aerobic fitness—a marker of cardiorespiratory function—improved significantly in cancer survivors during treatment over the exercise intervention period. Muscle Ffatigue and muscle weakness are also common sequelae of cancer treatment, but may be amenable to exercise training. A meta-analysis of randomized controlled trials concluded that both upper body and lower body strength improve as a result of exercise training during cancer treatment, with d=0.39 (95% CI:

0.12–0.65), and *d*=0.24 (95% CI: 0.07–0.41), respectively[5]. Strength improvements in the absence of muscle hypertrophy suggest that the adaptations resulting from strength training may be largely attributable to neural adaptations from better motor unit activation (recruitment, discharge rate), synchronization, and cross education. Neural adaptations occur early on in aduring a strength training program and may explain strength improvements in most short-term training studies. Mmoderate intensity activity may optimize immune activity and promote an anti-inflammatory state. Several biomarkers of immunologic function and inflammation exist including neutrophil and lymphocyte counts, natural killer cell activity, C-reactive protein, IL-6, IL-10, and TNF- alpha. It remains unclear what benefits exercise may have on immune system function after cancer treatment[6]. Despite the large volume of studies examining muscular strength among cancer survivors during treatment, few studies have examined the role of strength training among those with cancer cachexia[7]. It is interesting, Interestingly, given the success of resistance training among cancer survivors, to increaseincreasing upper and lower body strength that use of this modality among cancer survivors with cachexia is not more commonly studied. Despite the favorable profile of physical activity along the cancer continuum, many research gaps still exist. Elucidating the optimal dose of physical activity necessary to maximize the reduction in cancer risk of cancer and the optimal dose of physical activity necessary to improve specific physiologic systems, or treatment-specific side effects is warranted. In July 2010, an expert panel from the American College of Sports Medicine reviewed current studies of exercise training and cancer survivorship and released a roundtable consensus statement, concluding that exercise training is "safe during and after cancer treatments and results in improvements in physical functioning, quality of life, and cancer-related fatigue"[8]. Incorporation of exercise practices should, therefore, be advised and stimulated to prevent lung cancer, decrease treatment related side effects, rehabilitate survivors and possibly help during the cachexia period. Interaction between medical oncologists, thoracic surgeons, pulmonologists, physical therapist and sports medicine experts is mandatory for an optimal design of needed trials that will answer several opened questions related to this topic. References 1. Emaus A et al. Physical activity and lung cancer prevention. Recent Results Cancer Res. 2011; 186:101–133 2. Shephard RJ et al. Effects of exercise and training on natural killer cell counts and cytolytic activity: a meta-analysis. Sports Med. 1999; 28(3):177–195 3.Woods JA, et al. Exercise-induced modulation of macrophage function. Immunol Cell Biol 78: 543-553, 2000 4. Schmitz KH, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42(7):1409–1426 5. Speck RM, et al. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv. 2010; 4(2):87–100 6. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008; 8(3): 205–211 7. Bossola M, et al. Cancer cachexia: it's time for more clinical trials. Ann Surg Oncol. 2007 8. Schmidt KH, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 42: 1409-1426, 2010

Keywords: Exercise, Quality of Life

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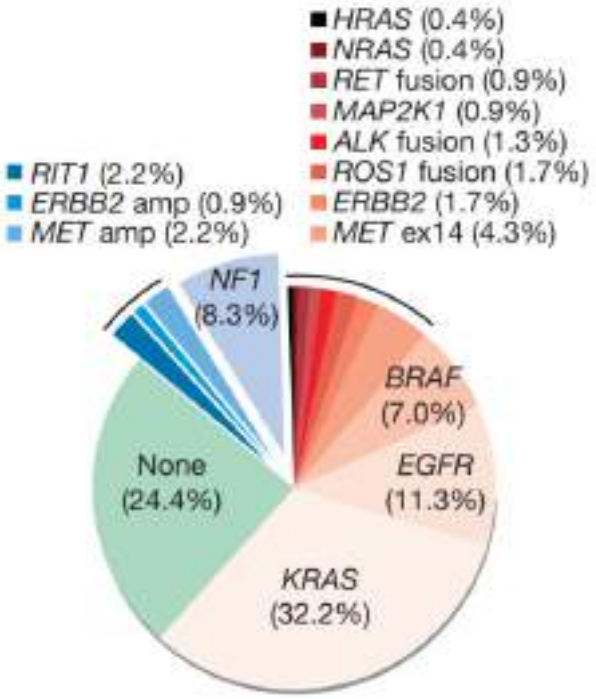
GR02.02 WHAT IS THE BEST MANAGEMENT OF TARGETED THERAPY TOXICITY?

G. Goss

The Ottawa Hospital, Ottawa/Canada

Over the past decade, the discovery of oncogenic driver mutations in NSCLC and the subsequent advent of targeted therapies against these genomic alterations have significantly altered the management of adenocarcinoma of the lung for a significant proportion of patients. While most oncogenic driver mutations are rare, some exist in up to 50% of specific demographic groups, and together, oncogene-driven disease represents the majority of adenocarcinoma cases (1). Targeted therapies permit directed anti-neoplastic efficacy, with less systemic adverse events than chemotherapy. However, these agents are not without their own unique toxicities that must be managed for optimal drug compliance and therapeutic benefit. This talk will focus on the management of toxicities resulting from the targeting of aberrant pathways and common driver mutations in adenocarcinoma of the lung. We define targeted agents as pharmaceutical interventions directed specifically at one or more of the actionable genomic alterations that result in oncogenic phenotypes (proteins, signalling, etc.). Given the breadth of agents to be tested in this indication, the primary focus of the talk will be on approved (versus experimental) and commonly used agents, including small molecules and antibodies, but not antibody-drug conjugates. Genomic alterations to be addressed include at minimum the ERBB family of genes, KRAS, ALK, ROS-1, PI3K, VEGF and BRAF. For each agent directed against one of these aforementioned alterations, we will approach management of toxicity by contrasting the normal function of the pathway with adverse events associated with inhibition of this pathway. The management of the most frequent and serious adverse events of the pathway blockade will be the focus of the presentation. In conclusion, targeted therapies have had a profound impact on progression-free survival in a significant proportion of patients with metastatic adenocarcinoma of the lung, however they can be associated with a unique set of significant toxicities. The appropriate management of these toxicities may often determine whether a patient derives benefit or not from a targeted therapy, as toxicities can impact dose, frequency of delivery and compliance. Moving forward, increasing the specificity of targeted genomic alteration blockade is required to limit unwanted effects on wild-type proteins. The future of targeted therapy mandates that we devise newer agents with minimal toxicity. 1. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543–50. 2. Kowanetz M. Vascular Endothelial Growth Factor Signaling Pathways: Therapeutic Perspective. Clin Cancer Res. 2006 Sep 1;12(17):5018–22.



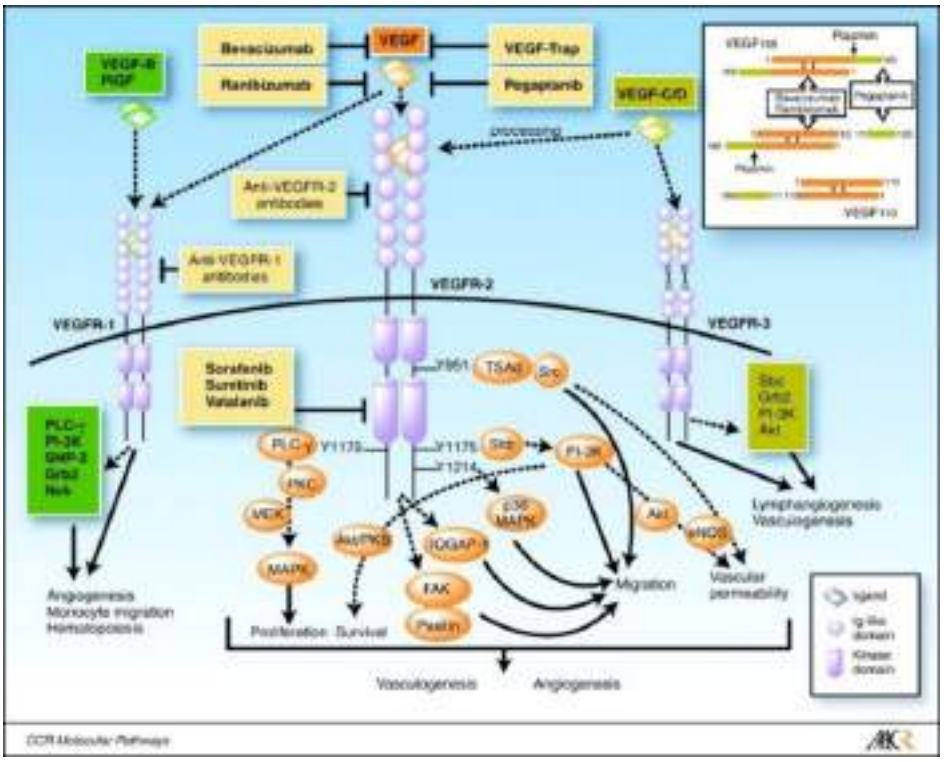


Image 1: known (red) and putative (blue) driver mutations in adenocarcinoma of the lung, TGCA sample (1) Image 2: VEGF signaling in cancer and targets of inhibition.(2)

Keywords: Targeted therapy, toxicity, adenocarcinoma

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GR02.03 WHAT IS THE BEST MANAGEMENT OF IMMUNOTHERAPY TOXICITY?

J.-M. Michot

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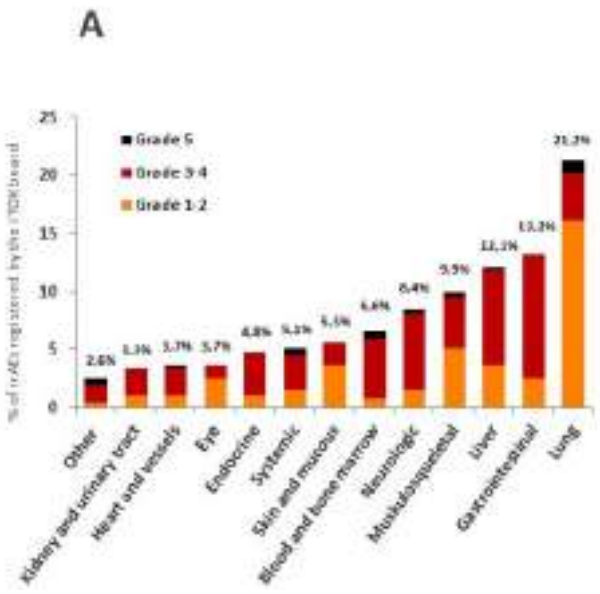
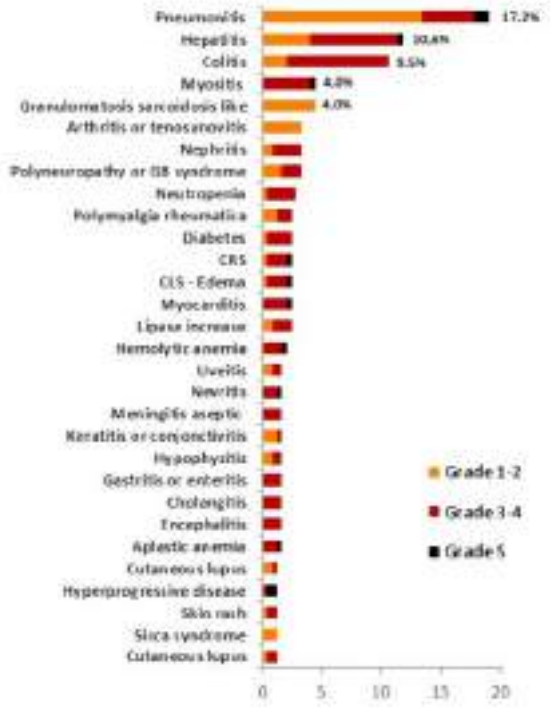
Introduction. The consultations and advices of the organ specialists for immune-related adverse events (irAEs) management can be of great help. The oncologist who uses the immune-checkpoint inhibitors (ICIs) should in his clinical practice be surrounded by different organ specialists that will support him in the management of irAEs[1-3]. Although guidelines provide detailed algorithms for the management of irAEs[4-6], few studies have assessed the real-life medical need of the oncology community. We propose here to report the activity of the immunoTOX assessment board to point the medical needs of oncologists in real life. Patients and methods. Organization of the immunoTOX assessment board. The ImmunoTOX assessment board is an academic group of physicians based at Gustave Roussy, Villejuif and at Paris-Sud University AP-HP Hospital, bringing together physicians specialized in the management of immunological toxicities[1]. Are present oncologists, pharmacovigilance pharmacists, internists and various specialists from expert bodies in the management of immunological toxicities (dermatologist, nephrologist, gastroenterologist, cardiologist, rheumatologist, hepatologist, neurologist, ear nose and throat specialist, ophthalmologist, hematologist, lung specialist and endocrinologist) Results. Over the period studied, 398 requests were sent to the immunoTOX board, for 356 patients. The median time between the occurrence of irAE and the immunoTOX board discussion was 35 days (IQ 13-72). The main requests to the immunoTOX board were about a diagnostic opinion on the relationship between immunotherapy and the side effect (n = 148, 37% of cases), followed by an opinion on the possibility of reintroduction the ICI in a patient after previous irAE (n = 109, 27% of cases), followed by an opinion about the management of a complex immunological toxicity (n = 100, 25% of cases), and by the possibility of starting an ICI in a patient with comorbidities (n = 41, 10% of cases). A certain or probable or possible causal relationship between immunotherapy and side-effect was found in 273/356 (77%) of patients. Among the 273 irAEs investigated, the main organ categories were distributed in the lung (n = 58, 21.2%), the gastrointestinal tract (n = 36, 13.2%), the liver (n = 33, 12.1%). %), musculoskeletal (n = 27, 9.9%) and nervous system (n = 23, 8.4%) (*figure 1A*).





The question of retreatment was 27% of the requests addressed to the immunoTOX board. The question of retreatment involved the possibility of resuming immunotherapy after prior irAE, which was grade 1-2 in 49% of cases and grade 3-4 in 51% of cases. The immunoTOX board gave a favorable recommendation for retreatment with caution for use in 65% of cases, a notice for maintaining temporary hold in 15% of patients, and a notice in favor of permanent discontinuation in 20% of cases. The requests question of the possibility of initiation of immunotherapy in a patient with comorbidities was one in ten. In patients with comorbidities, the immunoTOX board was in favor of initiating immunotherapy and recommended a precaution for use without formal contraindication in 93% of cases. Conclusion. The Immunotox board highlights the prominent real-life medical needs in the field of management of immunological toxicities. Questions rely mainly on toxicities affecting lung, digestive tract, hepatic and neuro-muscular system. When discussing a readministration or initiation of ICI in patients with autoimmune comorbidities, the Immunotox board was generally not opposed to give immunotherapy. A model of multidisciplinary management with oncologists working in close collaboration with organ specialists may guarantee to the patient the access to the ICI. This report will provide a basis of medical needs to define future strategies in prospective clinical trials of immunological toxicities management. Acknowledgement: The author thank the patients and their families and all investigators and site personnel. The authors thank Janine Nda, Cécile Geniez and Stéphanie Demirdjian and Sandrine Thorel for their assistance in management of patients. Figures legends. Figure 1. Distribution of irAEs organ categories (figure 1A) and irAEs types (figure 1B) registered by the immunoTOX board assessment. In the figure 2A are showed irAEs with occurrence ≥ 3. Figure 2. Characteristics of immune-related adverse events registered by the immunoTOX board assessment (among the 273 irAEs registered by the immunoTOX assessment board). CLS: Capillary leak syndrome CRS: Cytokine Release syndrome HPD: Hyperprogressive disease Hem-irAEs: Haematological immune-related adverse events irAEs: Immune-related adverse events References. 1 Champiat S, Lambotte O, Barreau E, *et al.* Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol Off J Eur Soc Med Oncol ESMO* 2016; 27: 559–74. 2 Naidoo J, Zhang J, Lipson EJ, *et al.* A Multidisciplinary Toxicity Team for Cancer Immunotherapy–Related Adverse Events. *J Natl Compr Canc Netw* 2019; 17: 712–20. 3 Cappelli LC, Shah AA, Bingham CO. Immune-Related Adverse Effects of Cancer Immunotherapy— Implications for Rheumatology. *Rheum Dis Clin N Am* 2017; 43: 65–78. 4 Brahmer JR, Lacchetti C, Schneider BJ, *et al.* Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol Off J Am Soc Clin Oncol* 2018;:JCO2017776385. 5 Haanen JB a. G, Carbonnel F, Robert C, *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol* 2017; 28: iv119–42. 6 Puzanov I, Diab A, Abdallah K, *et al.* Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; 5: 95.

Keywords: Immune-related adverse events; Immuno-oncology; Immune-checkpoint blockade; network in patient care

GR02 IMPROVING PATIENTS QUALITY OF LIFE DURING TREATMENT OF METASTATIC DISEASE
SUNDAY, SEPTEMBER 8 15:15–16:45

GR02.04 IMMUNOTHERAPY: HYPERPROGRESSION AND TREATMENT BEYOND PROGRESSION

D. Gandara

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The tidal wave of checkpoint immunotherapy (CPI) over the last few years has both opened up a myriad of new treatment options for patients with lung cancer. There are many unique aspects of these PD-1- and PD-L1-directed therapies, turning oncologists into both immunologists and endocrinologists, to better manage a large variety of immune related adverse events. This presentation with address two other aspects of CPI which currently remain both poorly understood and controversial: Hyperprogression/Fast Progression and Treatment Beyond Progression. Hyperprogression/Fast Progression (HPD/FP): A phenomenon of accelerated tumor growth, termed hyperprogressive disease (HPD), has been reported in patients receiving checkpoint inhibitor therapy. HPD has been defined as a ≥ 2-fold increase in tumor growth rate (TGR) from baseline to first evaluation, by comparison with pre-treatment Alternate criteria describing rapid progression on CPI therapy have also been described. Whether HPD is unique to CPI remains unclear, as do associated predictive factors. We developed an alternative approach termed fast progression (FP), in order to study this phenomenon retrospectively in prior Phase III trials of CPI. In addition to CT-confirmed rapid early tumor growth, FP includes early death due to PD from cancer. Using these FP criteria, we analyzed data from the Phase III OAK study, demonstrating equivalent rates of FP with atezolizumab versus docetaxel. However more patients met criteria for FP by TGR increase with atezolizumab. Further, FP was not associated with previously reported predictive factors. This presentation will update those results as well as other new data regarding the HPD/FP phenomenon. Treatment Beyond Progression (TBP): Cancer immunotherapy may alter tumor biology such that treatment effects can extend beyond radiographic progression. This effect explains the discordance between relatively modest response rate/progression free survival and more impressive overall survival in multiple CPI trials in advanced NSCLC. Presumptive benefit of TBP with CPI therapy has been observed in multiple tumor types including melanoma, renal cancer and NSCLC, leading the FDA to call for randomized trials designed to study this phenomenon. We studied TBP in the Phase III OAK trial of atezolizumab versus docetaxel, and reported that post-PD efficacy was consistent with a positive benefit-risk profile of atezolizumab TBP in patients performing well clinically at the time of PD. INSIGNA, a recently activated joint ECOG-SWOG Phase III study, is the first prospective trial to include an arm evaluating TBP. This presentation will discuss the biologic rationale for TBP with CPIs and detail other recently published data.

Keywords: HPD/FP, TBP, CPI

GR03 PROBLEM AREAS FOR THE NEXT WHO CLASSIFICATION OF LUNG CANCERS
MONDAY, SEPTEMBER 9 15:45–17:15

GR03.01 HIGH GRADE NEUROENDOCRINE TUMORS

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University of Torino at Città della Salute Hospital, TORINO/Italy

The four-tier WHO 2015 classification scheme of lung neuroendocrine neoplasms (NEN) includes morphologically and clinically heterogeneous conditions (1). High grade tumors typically encompass large and small cell neuroendocrine carcinomas (LCNEC and SCLC, respectively). The survival of these two types of poorly differentiated NENs is similar and significantly different from that of the well differentiated carcinoid tumors. Thus their appropriate classification is a clinically relevant exercise. While the morphological features of classical SCLC and those of low grade carcinoids allow to easily take these two tumors apart, the correct classification of some atypical carcinoids and of LCNEC is less straightforward. In fact, morphology alone may not be sufficient to identify the various histotypes (that still represent the most relevant prognostic parameter in NENs), and to specifically classify aggressive forms into the group of high grade carcinomas. Even immunophenotype profiling may fail to some extent and only the more recent genetic data have been able to better stratify variations within each single histological type (as recognized by the current WHO criteria). According to such criteria (1), high grade neuroendocrine (NE) carcinomas are defined as malignant tumors made of large or small cells having a solid, diffuse (or more rarely irregularly organoid) growth patterns, with extensive necrosis and a mitotic index exceeding 10 per 10 high power fields. This definition fits for a relatively wide group of tumors, whose clinical behavior is not perfectly overlapping. In particular, while SCLC are invariably associated to a high mitotic rate and high grade cytological features including classical salt&pepper chromatin pattern, LCNEC belong to a grey area that merges with atypical carcinoids on the one side (having intermediate values of mitotic index), and with SCLC on the other (with the occurrence of combined small and large cell NE carcinoma variants). Immunophenotypic markers are not always useful for accurately stratifying NENs. In fact, chromogranin A, synaptophysin and CD56 are generally expressed by the majority of NENs, though with a different intensity and distribution (for example, SCLC may be negative or only focally reactive for chromogranin, but invariably expresses synaptophysin) (2,3). Some transcription factors such as TTF1 and hASH1 are usually intensely positive in high grade tumors, both LCNEC and SCLC, as opposed to carcinoid tumors, that are generally not reactive (with the possible exception of some peripherally located spindle cell carcinoids). The proliferation index, as defined by Ki-67 immunohistochemistry, was proposed as an effective complementary tool to identify different prognostic subgroups, although its use is not officially accepted by the WHO classification with the exception of a differential diagnostic role in small biopsy specimens (1). Indeed, high grade tumors have a much higher mean Ki67 index compared to carcinoids (mean values of 60-80% versus 2-8%). For this reason, the integration of Ki67 data with the two official morphological parameters (necrosis and mitoses) proved effective in a proposed grading system (4). The spectrum of aggressive NENs is unfortunately complicated by the existence of combined NENs, having areas of brisk proliferation admixed with a relatively quiescent tumor cell population. In addition, rare cases have been demonstrated to progress from well differentiated carcinoid to high grade NE carcinomas. The relationship between low and high grade NENs is further supported by the observed heterogeneous genetic profile of high grade tumors, namely LCNEC. Apart from the original detection of the carcinoid-specific MEN1 mutations in a small fraction of "morphological" LCNECs, and of two other different groups of LCNEC, one related to SCLC and the other associated to a genetic signature of non small cell lung carcinomas (5,6), recent comprehensive genomic and transcriptomic analyses of 75 LCNEC identified two molecular subgroups, labeled "type I LCNEC" (having bi-allelic TP53 and STK11/KEAP1 gene alterations, and a NE profile with ASCL1 high / DLL3 high / NOTCH low), and "type II LCNEC" (enriched for bi-allelic inactivation of TP53 and RB1 genes, reduced NE markers, ASCL1 low / DLL3 low / NOTCH high, upregulation of immune-related pathways) (7). In this latter study, some genomic alterations were shared with pulmonary adenocarcinomas and squamous cell carcinomas. In a more recent study (8), the reverse approach was used, starting from a series of carcinoid tumors. With the aim of a full molecular NEN characterization by integrative analyses of genomic, transcriptomic, and methylome data, three molecular groups were identified: clusters A through C were enriched by typical carcinoids (TC), atypical carcinoids (AC) and LCNEC, respectively. Interestingly, the latter cluster also included a subgroup of six "morphological" ACs, here designated "supra-AC" that were molecularly similar to LCNEC, thus supporting the postulated link between the low and high grade lung NENs. Therefore, misclassification is common between AC and LCNEC, due to the existence of "carcinoid-like" LCNEC (5,7), possibly resulting from the evolution of a well- into a poorly differentiated NEN (9), as also reported in thymic LCNEC (10). In conclusion, the correct classification of high grade lung NENs is in general easily obtained in conventional forms of oat cell SCLC and of highly atypical and proliferating LCNEC. Conversely, the separation is more subtle in the presence of the rare intermediate (grey zone) cases, standing between AC and LCNEC, that probably correspond to the recently proposed category of "G3 NE Tumor" in the pancreas (11) and the gastrointestinal tract (expected in the next WHO classification of digestive system NENs). References 1 Travis et al. WHO classification of tumors of the lung. IARC press, Lyon, 2015 2 Thunissen E et al. J Thorac Oncol 2017;12:334-346 3 Yatabe et al. J Thorac Oncol 2019;14:377-407 4 Rindi G et al. Endocr Rel Cancer 2013;21:1-16 5 Rekthman N et al. Clin Cancer Res 2016; 22, 3618-3629 6 Simbolo M et al. J Pathol 2017; 241: 488–500 7 George J et al. Nat Commun 2018; 9: 1048 (1-13) 8 Alcala N et al. Nat Commun 2019 (in press) 9 Pelosi G et al. Virchows Arch 2018;472:567-577 10 Fabbri A et al. Virchows Arch 471, 31-47 11 Lloyd RV et al. WHO classification of endocrine tumors. IARC press, Lyon, 2017

Keywords: Neuroendocrine, high grade, lung carcinoma

GR03 PROBLEM AREAS FOR THE NEXT WHO CLASSIFICATION OF LUNG CANCERS
MONDAY, SEPTEMBER 9 15:45–17:15

GR03.02 ADENOCARCINOMA

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Many of the limitations in the WHO 2004 classification for adenocarcinomas (confusion over the term bronchioalveolar adenocarcinoma, usage of the term "mixed pattern" and no classification for small biopsy/cytology specimens) were addressed in the 2011 IASLC/ATS/ERS multidisciplinary classification, [1] and this proposal was adopted by the 2015 WHO classification with minor changes.[2] Adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma and invasive mucinous adenocarcinoma have now replaced the term "bronchioloalveolar adenocarcinoma", with subsequent TNM staging changes to use invasive size for T factor size.[3] However there remains significant interobserver variation between pathologists in relation to the point at which invasion starts, indicating that tighter definitions of distinguishing a lepidic pattern from other invasive patterns are needed, especially in areas where these disagreements have a clinical impact. Interobserver agreement between pathologists has been shown to be much better for distinction of invasive patterns (acinar, papillary, micropapillary, solid). Accumulating data supports the 2015 WHO proposal that the cribriform pattern be regarded as a pattern with adverse prognostic significance. It is also proposed that micropapillary be expanded to include a filigree, as well as classical, pattern. One of the most important needs is for pathologists to better recognize the morphologic spectrum of the micropapillary pattern which is often underestimated. Several publications suggest prognostic groupings as lepidic, acinar/papillary and solid/micropapillary as a stratification, and these have been shown to predict response to adjuvant therapy.[4] This leads into the issue of grading of resected adenocarcinomas and the presence of more aggressive histological patterns as a minor component. The histological feature termed "spread through airspaces" or STAS has been shown to be a poor prognostic factor for all major histologic types of lung cancer, including adenocarcinoma where it is frequently seen. There is considerable evidence that the presence of STAS carries prognostic significance, [5,6] in particular in relation to non-anatomic resections, but there remains a need to identify where STAS begins and artefactual dissemination of tumour due to handling and processing of specimens ends.[7] A tighter definition and evidence of international reproducibility is needed. While subtyping of histological patterns is well established in non-mucinous adenocarcinomas, mucinous adenocarcinomas are less well characterised. Various patterns of mucinous differentiation have been proposed, as well as assignment of histologic patterns in similar

fashion to non-mucinous ADCs although only invasive mucinous adenocarcinomas (IMA) and colloid adenocarcinomas currently have specific subgroupings.[2] This proposal has proved to be well founded given the specific molecular features and behaviour pattern of IMAs,[8] although again work is required to refine prognostication. More data is also required tumours with mixed mucinous and non-mucinous areas. Resections are increasingly occurring after neoadjuvant therapy, with there is already a need to assess these in a structured fashion.[9,10] Work is ongoing within the IASLC Pathology Committee to propose a method for classification in this clinical scenario. The 2015 WHO classification saw a seminal change in its structure, in that a classification system was proposed for biopsies and cytology specimens, rather than solely resections. In addition, a major theme utilized in the 2015 WHO classification was a multidisciplinary approach incorporating surgery, imaging, oncologic respiratory medicine, molecular biology as well as pathology. which needs to be maintained into the discussions of future classifications.[1] This approach must remain and will likely need to be enhanced, given the revolution in molecular and immunologic characterisation of tumours, especially adenocarcinomas, and all these new clinically relevant findings will need to be part of pathologic reporting for the ensuing decades. The relative importance and structure of morphologic, immunohistochemical, molecular and immunologic data will need to be incorporated into a system that is appropriate not just for the most advanced cancer centres where all data are available but for laboratories and diagnostic services in underserved countries where morphologic features may be the only ones available. REFERENCES 1. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. Proc Am Thorac Soc 2011;8:381-5. 2. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyons, France.: International Agency for Research on Cancer (IARC); 2015. 3. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2016;11:1204-23. 4. Tsao MS, Marguet S, Le Teuff G, et al. Subtype Classification of Lung Adenocarcinoma Predicts Benefit From Adjuvant Chemotherapy in Patients Undergoing Complete Resection. J Clin Oncol 2015;33:3439-46. 5. Chen D, Mao Y, Wen J, et al. Tumor Spread Through Air Spaces in Non-Small Cell Lung Cancer: a systematic review and meta-analysis. Ann Thorac Surg 2019. 6. Kadota K, Nitadori J, Sima CS, et al. Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences after Limited Resection for Small Stage I Lung Adenocarcinomas. J Thorac Oncol 2015;10:806-14. 7. Blaauwgeers H, Flieder D, Warth A, et al. A Prospective Study of Loose Tissue Fragments in Non-Small Cell Lung Cancer Resection Specimens: An Alternative View to "Spread Through Air Spaces". Am J Surg Pathol 2017;41:1226-30. 8. Fernandez-Cuesta L, Plenker D, Osada H, et al. CD74-NRG1 fusions in lung adenocarcinoma. Cancer Discov 2014;4:415-22. 9. Qu Y, Emoto K, Eguchi T, et al. Pathologic Assessment After Neoadjuvant Chemotherapy for NSCLC: Importance and Implications of Distinguishing Adenocarcinoma From Squamous Cell Carcinoma. J Thorac Oncol 2019;14:482-93. 10. Blumenthal GM, Bunn PA, Jr., Chaft JE, et al. Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. J Thorac Oncol 2018;13:1818-31.

Keywords: lung, classification, adenocarcinoma

GR03 PROBLEM AREAS FOR THE NEXT WHO CLASSIFICATION OF LUNG CANCERS
MONDAY, SEPTEMBER 9 15:45–17:15

GR03.03 PLEOMORPHIC CARCINOMAS

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The category of sarcomatoid carcinoma in lung cancer classification is composed of five tumor types - pleomorphic, spindle, giant cell, carcinosarcoma and blastoma. While these are all relatively rare tumors, the pleomorphic carcinoma category is the most common of this group. Pleomorphic carcinomas are defined as combinations of adenocarcinoma, squamous carcinoma or large cell carcinoma with a spindle or giant cell element. It may be that spindle or giant cell examples, while diagnostically more challenging, represent variants of similar histogenesis but with complete mesenchymal transformation. Small cell carcinoma in a pleomorphic carcinoma is exceedingly rare. These tumors are often bulky tumors at presentation, with a propensity for central necrosis. Historically, this tumor is highly aggressive and treatment refractory. The histology of this tumor type includes correct identification of a malignant spindle component morphologically, or a giant cell component. While nuclear pleomorphism is an aspect of the tumor, the degree of nuclear enlargement, multinucleation and the presence of emperipolesis all distinguish giant cells of pleomorphic carcinoma from nuclear enlargement in high grade tumors. Immunohistochemistry has be helpful in identifiable a cytokeratin positive spindle or giant cell component. The use of zinc finger E-box binding homeobox1 (ZEB1), a protein involved in epithelial-mesenchymal transition to identify spindle or giant cell component of these tumors, both in small samples and resections, is emerging. Molecular alterations have also been linked to pleomorphic carcinomas. The tumors harbor mutations in KRAS as well as a higher rate of MET exon 14 skipping mutations. This is generally confined to cases with an adenocarcinoma component. TP53 mutations are also frequent. The molecular mechanisms of pleomorphic carcinoma with a squamous only epithelial component remain to be characterized. It has been proposed that MET exon 14 mutations may be targetable using agents such as crizotinib. In addition, these tumors show an elevated rate of high positive PDL1 immunoreactivity which may offer immunotherapy option in these patients. The relationship between large cell carcinoma and new entities such as SMARCA4 deficient carcinoma/sarcoma and the category of sarcomatoid carcinoma remains unclear. Greater elucidation of the molecular underpinning of sarcomatoid carcinoma categories may help clarify the place for these entities within the classification of lung cancer.

GR03 PROBLEM AREAS FOR THE NEXT WHO CLASSIFICATION OF LUNG CANCERS
MONDAY, SEPTEMBER 9 15:45–17:15

GR03.04 MOLECULARLY-DEFINED THORACIC MALIGNANCIES (NUT, SMARCA4 AND OTHERS SARCOMAS)

A. Yoshida

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Classification of tumors has been traditionally based on clinical and histological findings, with each entity often being characterized by molecular genetic changes. However, a few recently described tumor entities are defined by specific genetic abnormalities, and three such tumors are discussed here with a particular emphasis on their nosologic controversy. [NUT carcinoma] NUT carcinoma is a poorly-differentiated aggressive carcinoma with frequent squamous differentiation. NUT carcinoma harbors *NUTM1* rearrangement by definition, with the most common fusion partner being *BRD4* (~70%) and uncommon partners including *NSD3* and *BRD3*. NUT carcinomas typically involve organs along the midline, such as the head, neck, and upper aerodigestive tract in young patients; however, a broader range of patient age and tumor sites exist. Recently, *NUTM1* rearrangement has been reported in a small number of malignant tumors that lack epithelial differentiation, some of which show an undisputable phenotype of sarcoma. Tumors with *CIC-NUTM1* fusion are the best known and their histological and transcriptomic similarities to *CIC-DUX4* sarcomas suggest their relatedness with CIC sarcomas. Other *NUTM1*-rearranged sarcomas are highly heterogeneous, both histologically and genetically, including fusion partners such as *BCORL1*, *MXD1*, *MXD4,* and *MGA*. Interestingly, *MGA-NUTM1* sarcomas have been repeatedly documented in the thoracic cavity of adults. More recently, *NUTM1* rearrangement has been discovered in benign and malignant skin adnexal tumors. *NUTM1* rearrangement is therefore no longer a signature of a single entity NUT carcinoma, and phenotypic correlation is critical for diagnosis. [SMARCA4-deficient thoracic sarcoma (DTS)] SMARCA4 is a core catalytic subunit of the SWI/SNF chromatin remodeling complex. SMARCA4 deficiency in thoracic tumors primarily occurs in association with carcinomas, accounting for 5–15% of lung adenocarcinomas and up to 30% of large cell and pleomorphic carcinomas. These carcinomas typically affect smoking men and are more common in poorly differentiated TTF1-negative tumors that are wild-type for *EGFR* and *ALK*. SMARCA4- DTS is a recently recognized sarcoma type with fewer than 60 cases reported to date. SMARCA4-DTS most commonly occurs in young to middle-aged

adult men (median, 40 years old) with heavy smoking exposure and presents as large tumors in the thoracic cavity. SMARCA4-DTSs are aggressive, and the median survival is 4–7 months. Histologically, the tumors consist of diffusely infiltrating large dyscohesive epithelioid cells with relatively monotonous nuclei and prominent nucleoli, similar to proximal-type epithelioid sarcoma. Rhabdoid cells are seen in a subset of cases. By definition, all cases are deficient in SMARCA4 immunohistochemically because of inactivating *SMARCA4* mutation. SMARCA4-DTS is different from SMARCA4-deficient lung carcinoma with respect to demographics (younger), clinical outcome (worse), histological features (more dyscohesive), immunophenotype (frequent positivity for CD34, SOX2, and/or SALL4, and negativity for claudin-4), and gene expression profiles. Interestingly, some SMARCA4-DTS tumors tested have frequent C:G/A:T transversion mutations and mutations in *TP53*, *KRAS*, *KEAP1*, and/or *NF1*, a shared profile with smoking-associated lung adenocarcinomas. The question has thus been raised whether these sarcomas might represent a dedifferentiated form of lung carcinoma. Nonetheless, an epithelial component has not been reported in any of the documented SMARCA4-DTS cases. Furthermore, most examples are not centered in the lung, and some entirely lack lung parenchymal involvement. [Primary pulmonary myxoid sarcoma (PPMS) with *EWSR1-CREB1*] PPMS is a rare low-grade lung sarcoma of young adults often presenting as an endobronchial mass. The tumor consists of multinodular myxoid growth that is populated by corded or reticular proliferation of spindle and/or epithelioid cells. These tumors often coexpress vimentin and epithelial membrane antigen and harbor *EWSR1-CREB1* fusion. Tumors with a similar histological appearance have recently been reported in various soft tissue and visceral sites, including the brain, by the names of myxoid variant of angiomatoid fibrous histiocytoma (AFH) and intracranial myxoid mesenchymal tumors, which harbor *EWSR1* fusions with genes encoding one of the CREB family transcription factors (*ATF1*, *CREB1*, or *CREM*). Primary pulmonary AFHs have been reported, with some showing myxoid features. Although PPMS is recognized in the WHO classification of the lung as a distinctive tumor, a significant overlap in histology and genetics, albeit several differences, may suggest a close relationship between PPMS and myxoid AFH.
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Keywords: Primary pulmonary myxoid sarcoma, NUT carcinoma, SMARCA4-deficient thoracic sarcoma

GR03 PROBLEM AREAS FOR THE NEXT WHO CLASSIFICATION OF LUNG CANCERS
MONDAY, SEPTEMBER 9 15:45–17:15

GR03.05 GRADING OF NSCLCS - PROBLEMS AND SOLUTIONS

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Background Tumor grading has been a traditional component of the pathologic evaluation and in many organ systems, tumor grading offers guideline to therapy and patient management. The latter has not been applied to NSCLC. However, considering the new advances in therapy modalities for NSCLC and advances in adenocarcinoma classification, it is now clear that there are different types of adenocarcinomas and these tumors should not be treated the same way. The 2015 WHO classification of pulmonary adenocarcinoma based on the predominant histological pattern has consistently been found to correlate with prognosis. There is broad agreement that the five histological patterns (lepidic, acinar, papillary, solid and micropapillary) are important prognostic indicators. Recent studies have proposed the inclusion of a number of additional pathologic features (the role of secondary patterns, non-traditional pattern such as cribriform and complex glandular patterns, nuclear grade, mitotic counts, presence of spread through alveolar space (STAS), and necrosis.) that also have prognostic value. The addition of these histological features to the predominant pattern could offer greater refinement of a grading scheme. Supplementing the classification of lung adenocarcinomas with an objective grading system will help define prognostic groups that could benefit from the changing landscape of emerging management and treatment options. Contrary to adenocarcinoma, there has been little advancements in the histological prognostic indicators in squamous cell carcinoma of the lung. Isolated reports have suggested that the presence of tumor budding into the stroma is the sole indicator of poor prognosis. Keratinization, which has been traditionally used to grade these tumors, does not appear to have prognostic value. However, a systematic evaluation of prognostic markers in these tumors have not been carried out. A summary of the current efforts in squamous cell carcinoma will be discussed. The IASLC pathology panel has proposed a systematic study to evaluate a set of histological criteria that have been described as prognostic indicators in adenocarcinoma aimed at establishing an objective grading system of invasive lung adenocarcinoma. Design A multi-institutional study involving well-annotated multiple cohorts of stage 1 adenocarcinomas with at least five years of follow up were evaluated. Annotation included an estimate of the percentage for each histological pattern present for each case; nuclear grade, cytology grade; and mitotic counts with pattern hot-spot association, presence of STAS, and necrosis. A cohort of 284 cases was used as a training set. Univariate analysis was performed to identify significant associations of histological features with recurrence-free survival and overall survival. ROC curve analysis was used to select the best model based on combinations of several features and its association with disease recurrence or death of disease. The results were validate on independent cohorts of 212 cases. Results Review of the literature showed that there are many variation in the classification and definitions on non-traditional patterns. In our cohorts, cribriform and complex glandular patterns followed similar curve as traditional high grade patterns (solid and micropapillary), therefore these non-traditional pattern were defined as patterns of high grade in the model. Another are of variation is the percentage of high grade pattern that can influence outcome. Therefore, the cut-off for a high grade pattern associated with recurrence or death of disease was also established in the training cohort and correspond to 20%. Therefore, amounts smaller than 20% of high grade pattern did not influence outcome. In the training cohort (n=284) all parameters tested, predominant patterns, mitotic count, nuclear grade, cytological grade, and STAS (but not necrosis) were found to have significant prognostic value on a univariate analysis. A Baseline Model composed of Age + Gender + Race + Type of surgery + Pathological Stage; showed an AUC of 0.673. In an attempt to improve this curve, histological parameters were added to the model. The addition of only the predominant pattern to the baseline increases the AUC to 0.698. A model based on the combination of predominant pattern paired with the second predominant pattern was found to have the highest AUC (0.765), followed by a combination of predominant pattern plus worse pattern (AUC=0.74). Addition of other histological features (nuclear grade, mitotic count, STAS etc.) did not significantly improve the model. Similar results were found in the validation set (N=212). The combination of the two

most predominant patterns showed an AUC = 0.763, followed by a combination of predominant + worse pattern with AUC = 0.766. Addition of other histological features did not show improvement of the model. There was no statistical difference between the models using the two most predominant patterns and the predominant plus worse. There was good reproducibility scores for the 2 models Conclusion Our results suggest that an objective grading system for pulmonary adenocarcinoma is possible. Considering that there is no significant differences between a model that accounts for the 2 most predominant pattern and another composed of the predominant plus worse pattern. The IASLC pathology panel proposes the later to be used, because pathologists traditionally grade tumors by the worse component. Therefore, histologic assessment of the predominant pattern and worse pattern, would represent the most parsimonious and prognostic grading system for stage I lung adenocarcinomas. The use of the model in two other independent cohorts of adenocarcinomas (stages 1-3), as well as a reproducibility study will be discussed.

Keywords: adenocarcinoma, tumor grading, prognosis

Pro Con Sessions

PC01 REINVENTING CLINICAL TRIALS
MONDAY, SEPTEMBER 9 11:00–12:30

PC01.01 SETTING THE STAGE: TENSION BETWEEN PATIENT SAFETY, SCIENTIFIC PURITY AND PATIENT INCLUSION

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Clinical trials are important to the process of better understanding the therapeutic potential of new drugs while also serving as treatment options for individuals seeking the best possible treatment. When writing protocols, we think about how best to determine the effectiveness and side effect profile of the treatment being studied. This can lead to more limited eligibility in an effort to reduce complications not related to the disease or drug. When seeing patients in clinic, we think about how best to treat each individual, which can lead to preferring less strict eligibility. These two perspectives can sometimes seem to be at odds. How do we best define eligibility in a way that both provides scientific rigor while also providing the trial as an option to as many people as possible? This session sets the stage for an in-depth discussion of these 2 important aspects of clinical trials and how to strike the ideal balance for enrollment eligibility criteria. As part of this introduction, a highlight of the process of drug development through different phases of clinical trials from "pre-clinical work" to phase 3 studies is helpful. The following is a general structure. Any prospective drug must demonstrate compelling results at one phase to then be studied in the next phase. This starts with lab studies and often treatment of mice with prospective drugs. Any studies before treatment of humans is called "pre-clinical." When results in this setting are promising, treatment in humans starts with phase 1. In this setting the focus of the study is to find the most appropriate dose, and there are often multiple diagnoses allowed for enrollment within that one study. The strategy for dose finding generally includes starting treatment for a few individuals at a low starting dose. After verifying tolerability, another group starts treatment on the study at a higher dose and so on. Less commonly, studies will allow dose increases for each individual that is tolerating the lower dose with ongoing disease control. Dose escalation often continues until finding the "maximum tolerated dose." Although the side effects of the drug often weigh heavily in determining the dose for further study, responses to the treatment are certainly considered. After determining a dose for future study, this drug may enter a phase 2 study. In this phase, many more individuals are treated at the determined dose, and the effectiveness of the treatment is studied within a specific clinical setting. Results that suggest efficacy often lead to a phase 3 study, which includes randomization to the new drug, or the standard of care treatment, within a specific clinical setting. Although placebo is sometimes utilized, all individuals should get at least the best known therapy. For example, KEYNOTE-189 enrolled individuals with metastatic nonsquamous, non-small cell lung cancer (without sensitizing EGFR or ALK mutations) to the standard of care first line chemotherapy, pemetrexed and a platinum, with randomization to also include either pembrolizumab or placebo. Although people received placebo, it was given along with the chemotherapy, as was pembrolizumab. This introduction is followed by two related session. One is focused on crafting trials to allow more broad enrollment with the acknowledgment of trials as a treatment option. The other is focused on trial development with full attention toward scientific rigor and study of the drug. A discussion of the balance of these goals follows.

Keywords: trial development, Phase

PC01 REINVENTING CLINICAL TRIALS
MONDAY, SEPTEMBER 9 11:00–12:30

PC01.02 REAL WORLD RESEARCH GROUPS - ROS1DERS

M. Hennink

Longkanker Nederland, Groningen/Netherlands

Reinventing Clinical Trials *Merel Hennink* Lung cancer research has made great progress in the last decade. Discovery of more treatable mutations have paved the way to more treatment options. We are moving away from a "one-size-fits-all" chemotherapy towards personalized medicine. (1) However, these developments require accurate diagnostics to identify the right treatment options. Furthermore, as a common cancer like lung cancer is split into rare subgroups, it also poses additional challenges. Rare mutations in NSCLC (for instance ROS1) result in small patient populations for trials and less bio-materials for research. The main question here is how to navigate this changing landscape. The ROS1ders – a community The ROS1 rearrangement was first described in 2007 and occurs in about 1% of patients with NSCLC. Of the estimated 1.5 million new cases of NSCLC worldwide each year, approximately 15,000 may be driven by oncogenic ROS1 fusions.(2) In 2015, little was known about the ROS1 rearrangement and only a single drug was available to treat the disease. Also in 2015, a group of ROS1 positive lung cancer patients formed an international community on social media, The ROS1ders, allowing them to connect with each other. Through social media, patients are becoming increasingly engaged, and discussing the diagnostic and treatment options available in their countries or hospitals. In addition, these national and global online communities, where information is shared, can highlight (inter)national disparities in treatment access. *Treatments* Crizotinib is currently the only FDA- and EMA–approved agent for the treatment of *ROS1*-rearranged NSCLC. Unfortunately several healthcare systems across the world have difficulty with reimbursing the drug due to lack of data from randomized clinical trials (UK, South Africa, Canada, New Zealand). In Canada, Real World Data from the ROS1 Facebook group helped in the approval process. "The Committee expressed that they were impressed with the patient input of 259 ROS1 positive patients and caregivers from 32 countries who supported the use of crizotinib. Overall, from the perspectives of patients with ROS1-positive NSCLC, they value a chance to extend their life and spend more time with their families by having a treatment that is effective, and improves their symptoms and outcomes."(3) Global ROS1 initiative – from advocacy to active research The ROS1ders transitioned from advocacy to active research in the past few years. Reaching out to academic cancer centers, they strove to increase the amount of cancer models available to stimulate ROS1 research. The Global ROS1 Initiative is a partnership connecting researchers, patients, caregivers, and physicians worldwide. Patients who have an upcoming biopsy contact the national study nurse, and can choose to donate extra material to generate a cell line, a patient-derived xenograft (PDX) mouse model, or both. The goal is to create models and data accessible to all researchers. All models and characterization data will be made available as an open access database to researchers and collaborators. The Global ROS1 initiative has already generated four cell lines at the University of Colorado, and three PDX mouse models are in development. Patients are in the driver seat!(4) Europe *Diagnostics* Testing is essential to select the right treatment. Nevertheless, systematic diagnostic testing for ROS1 in metastatic NSCLC is not yet included in the European Society of Medical Oncology recommendation, but only suggested. (5) In Europe, access to molecular testing and new medicines differs between individual countries, even within the same country. In the Netherlands, a retrospective study in all patients that tested negative for EGFR and KRAS, showed an increase in ROS1 testing between 2013 (10%) and 2017 (61%) (6). Given the demonstrated added value of patient-driven organizations, both for patients and research, we need a more systematic testing for ROS1, in order to offer effective treatment to more ROS1 patients and strengthen our international community. *ROS1 patients as research partners in Europe* The Global ROS1 Initiative requires streamlined protocols to be successful. Currently, European ROS1ders cannot donate tissue for a variety of reasons. Therefore, a pan-European collaboration should be implemented, that centralizes expertise on the small number of potential tissue donations. In this network, tissue processing should be centralized in a single lab, and the resulting data and models could be distributed to collaborating partners. However, the setup of such network is very difficult, in part due to national differences in legislation. Furthermore, although we are a European Union, patients are not really united, and bringing together the European ROS1ders

is not an easy task. We deal with language, boundary and policy issues. Due to European public health systems, all responsibility is given to doctors. Most patients see less benefit in getting informed and organized. Data protection laws and less use of social media make it more difficult to connect patients. Next, the number of non-governmental organizations supporting lung cancer patients is small - in particular in Europe. And finally, fundraising activities are rather uncommon in Europe. Overall these aspects make it harder for patient advocates to make a difference. As such, international networking and solidarity become even more important. In the Netherlands, www.stichtingmerelswereld.nl was founded to raise awareness and accelerate research. As a result, research on drug resistance has been initiated in cell lines and PDX mouse models. In parallel, drug resistance is also studied in France and Germany. Combining these individual studies might result in a 1+1 equals 3 scenario. We strive to unite our national voices to influence European policies and use our European voices to connect national studies. *Understanding the role of personalized medicine* https://www.lungcancer.org Jessica J. Lin MD & Alice T. Shaw (2017) *"Recent Advances in Targeting ROS1 in Lung Cancer"* in Journal of Thoratic Oncology. https://doi.org/10.1016/j.jtho.2017.08.002 Xalkori for ROS1 positive advanced lungcancer. 2019 (4) https://ros1cancer.com/ros1-patient-driven-research D. Planchard et al. (2018) "*Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*." Annals of Oncology 29 (Supplement 4): iv192–iv237, 2018 doi:10.1093/annonc/mdy275 Kuijpers Chantal C.H.J. et al (2018). "*National variation in molecular diagnostics in metastatic lung cancer.* " Nederlands Tijdschrift voor Geneeskunde 162:D1607

Keywords: paradigmshift, research, ROS1ders

PC01 REINVENTING CLINICAL TRIALS
MONDAY, SEPTEMBER 9 11:00–12:30

PC01.03 REAL WORLD RESEARCH GROUPS - ALK+ GROUP

L. Olson

www.outlivinglungcancer.com, Lowell/United States of America

There is a natural tension inherent to clinical trials—between scientific rigor and a participant's hope that an experimental therapy shall prove effective. However, it is important to never lose track of the reason for clinical trials. To quote Dr. Richard Pazdur, Director of the FDA's Oncology Center of Excellence, 'We have to understand that the clinical trials are here to serve the patients. The patients are not here to serve the clinical trials.' (1) The decision to enroll in a clinical trial—particularly phase I where both maximum tolerable dose and the safety profile are being ascertained—is not a casual one. Generally the prospective participant has exhausted traditional therapies. With the emergence of actionable mutations and targeted therapies, the paradigm for participation is evolving. It is foreseeable that a participant can have a response to a therapy measured not only in months but in years. And when progression does occur, that same participant may enroll in yet another clinical trial. For many patients with advanced lung cancer, clinical trials now offer the best option for therapeutic treatment. It is critically important to find the balance between advancing medical research and extending individual lives. To this end, exclusion criteria need to be reevaluated. A patient who is desperately ill is often willing to tolerate a far higher degree of risk. Arguments for exclusion criteria fail to take into account the fact that this is a representative population; should the drug receive FDA approval, this will be the consumer profile. (2,3) It is also vital to understand the burden that clinical trial participants take on. First, financial. There is an overriding misperception that participation in a clinical trial is cost free. In reality, it is often only the experimental therapeutic that is provided free of charge. Clinical trials are procedure rich—from pharmacokinetics to additional scans/MRIs/EKGs/biopsies. In most cases a participant's insurance is billed for these procedures, resulting in quickly maxed out deductibles and added copays. More frequent visits to the site of the trial require additional time and travel on the part of the participant. Transportation, lodging and meals are often the responsibility of the patient. There are lost wages, for either the patient or their caregiver or both. Often there is also the burden of childcare. The financial toll adds to the high degree of stress that a patient and their families are already living under. It also means that clinical trials are an option only for those with both the financial means and a solid support system in place. As economically distressed families are unevenly distributed among minorities, the clinical trial population is not representative. Not only does this mean there is an inherent disparity in access to clinical trials, it also impacts the science, as clinical trial participants in an ethically diverse country such as the US are overwhelmingly caucasian. In addition, it is important to point out that healthy volunteers to clinical trials are almost always compensated for both their time and even small things that are typically not covered in a clinical trial for oncology patients—such as parking. (4,5,) And then there is the physical toll upon a patient. Excessive scanning, multiple biopsies, exhaustion associated with additional visits to the site. "When you begin to look at a trial from the patient's perspective and consider the complexity of the trial and what we are asking them to do, is it any wonder that so many patients are refusing to participate? And is it any wonder why so many patients choose to withdraw from a clinical trial?" (6) As accrual is an ongoing issue in clinical trials, it is imperative for both the sake of patients as well as medical science, that the voice of the patient be heard. Patient reported outcomes (7) often fail to capture the actual experience of a trial participant. Rather than being the one size fits all that is commonly handed to participants at each visit now, why not write the PRO with the assistance of actual participants? Humans, unlike their rodent counterparts in the lab, are sentient beings. Potentially a wealth of anecdotal information is being lost simply because no one thinks to ask. Clinical trials cannot happen without the cooperation of human participants. That cooperation is referred to as compliance. A patient who is noncompliant risks ejection from a trial. This creates a relationship that is inherently unbalanced. It is possible to address both accrual and the needs of the participant if clinical trials become truly patient centric. To do so one must consider the burden of participation. A clinical trial should be viewed as an opportunity, albeit one that is not risk free. Lessening the burden and removing some of the barriers to participation will better address the needs of both patients and the field of medical research. 1. NCCS Celebrates "Focus on the Care" Reception in Honor of Dr. Richard Pazdur and Ellen Goodman Oct 22 2015 https://www.canceradvocacy.org/news/nccs-celebrates-focus-on-the-care-reception-in-honor-of-dr-richard-pazdur-and-ellen-goodman/ 2. Clinical Trial Patient Inclusion and Exclusion Criteria Need an Overhaul, Say Experts April 23, 2018 Redfearn, S https://www.centerwatch.com/cwweekly/2018/04/23/clinical-trial-patient-inclusion-and-exclusion-criteria-need-an-overhaul-say-experts/ 3. 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Patient involvement in clinical research: why, when and how Apr 27, 2016 Sacristán, JA; Aguarón, A; Avendaño-Solá, C; Garrido, P; Carrión, J; Carrión, A; Kroes, R; Flores, A; NCBI PMC https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854260/

Keywords: Patients, Partners, Trials

PC01 REINVENTING CLINICAL TRIALS
MONDAY, SEPTEMBER 9 11:00–12:30

PC01.04 LUNG CANCER PATIENTS SHOULD HAVE BETTER ACCESS TO CLINICAL RESEARCH: RELAX THE ELIGIBILITY CRITERIA

J. Freeman-Daily[1,2]

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Clinical trials are essential for improving treatment of cancer patients. However, only 2%-3% of adult cancer patients participate in clinical trials, and many trials close because they do not enroll enough patients. Others are slow to accrue patients, which prolongs the time required to obtain results. Those trials that meet accrual goals often have cohorts that don't reflect the demographics or performance status of the real-world population of patients who have the disease. Why do trials have trouble enrolling enough patients? Some of the significant barriers to clinical trial participation stem from over-

restrictive trial eligibility criteria. Unger et al (2019) found 21.5% of patients did not enroll in a clinical trial because they were not eligible. A Kaiser Permanente study of non-small cell lung cancer patients found 80% of the patients were not eligible for two NSCLC treatment studies. Trial eligibility must balance opposing factors. It must be narrow enough to ensure the effect of the treatment can be determined, yet broad enough that the population of patients is meaningful. Researchers often use "common" eligibility criteria without giving due consideration to how those criteria may impact trial recruitment and the real-world applicability of their study. A population of younger patients with no health issues other than lung cancer might make it easier to identify the effect of the experimental treatment, but this population gives no real insight into how the treatment affects the typical population of lung cancer patients (which has an average age of 71). Recommendations to modernize eligibility criteria have been recently published by a joint effort of the American Society for Clinical Oncology and Friends of Cancer Research, as well as the US Food and Drug Administration and the National Cancer Institute. The recommendations include relaxing restrictions on brain metastases, minimum age, HIV/AIDS, organ dysfunction, and prior and concurrent malignancies while ensuring patient safety. Other aspects of a trial may cause patients to decide not to enroll even if they meet the eligibility requirements. Locations of trial sites might require the patient to travel, yet the patient might not be able to afford time or cost of travel, or their insurance might not cover treatment at any trial site. The trial protocol may prohibit certain previous treatments, or require weeks of washout from previous tyrosine kinase inhibitor (TKI) treatments (which raises the possibility of TKI flare). Preliminary evidence shows that relaxing trial eligibility requirements could result in a greater number of patients becoming eligible for clinical trials. Harvey et al (2019) conducted a retrospective study of 10,500 CancerLinq records of patients with lung adenocarcinoma. They found 47.7% of patients were excluded from clinical trials by traditional exclusion criteria (no brain metastases, no other malignancies, and creatinine clearance greater than 60 mL/minute), while only 1.5% of patients were excluded by the ASCO-Friends recommended expanded criteria that removed these restrictions. Relaxing clinical trial eligibility while maintaining safety is in the best interest of the patient. Patients are not for clinical trials. Clinical trials are for the patient. References: Gore, L, et al. (2017). "Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group." Journal of Clinical Oncology 35(33): 3781-3787 Harvey RD, et al. (June 2019). "Impact of broadening clinical trial eligibility criteria for advanced non-small cell lung cancer patients: Real-world analysis." Presentation at ASCO Annual Meeting 2019, Chicago, IL. https://meetinglibrary.asco.org/record/178360/abstract Jin, S, et al. (2017). "Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015." Journal of Clinical Oncology 35(33): 3745-3752. Lichtman, SM, et al. (2017). "Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group." Journal of Clinical Oncology 35(33): 3753-3759. Lin, NU, et al. (2017). "Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group." Journal of Clinical Oncology 35(33): 3760-3773. Sharpless NE, Doroshow JH. "Modernizing Clinical Trials for Patients With Cancer." JAMA. Published online January 23, 2019. 321(5):447–448. doi:10.1001/jama.2018.18938 Uldrick, TS, et al. (2017). "Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group." Journal of Clinical Oncology 35(33): 3774-3780. Unger JM, Hershman DL, Fleury ME, Vaidya R. "Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation." JAMA Oncol. Published online January 10, 2019 5(3):326–333. Doi:10.1001/jamaoncol.2018.5953

Keywords: eligibility criteria, trial accrual, clinical trials

PC02 COMBINING WITH CHEMO: OLD SCHOOL IS NEW AGAIN
MONDAY, SEPTEMBER 9 14:00–15:30

PC02.02 TKIS SHOULD BE GIVEN WITH CHEMO

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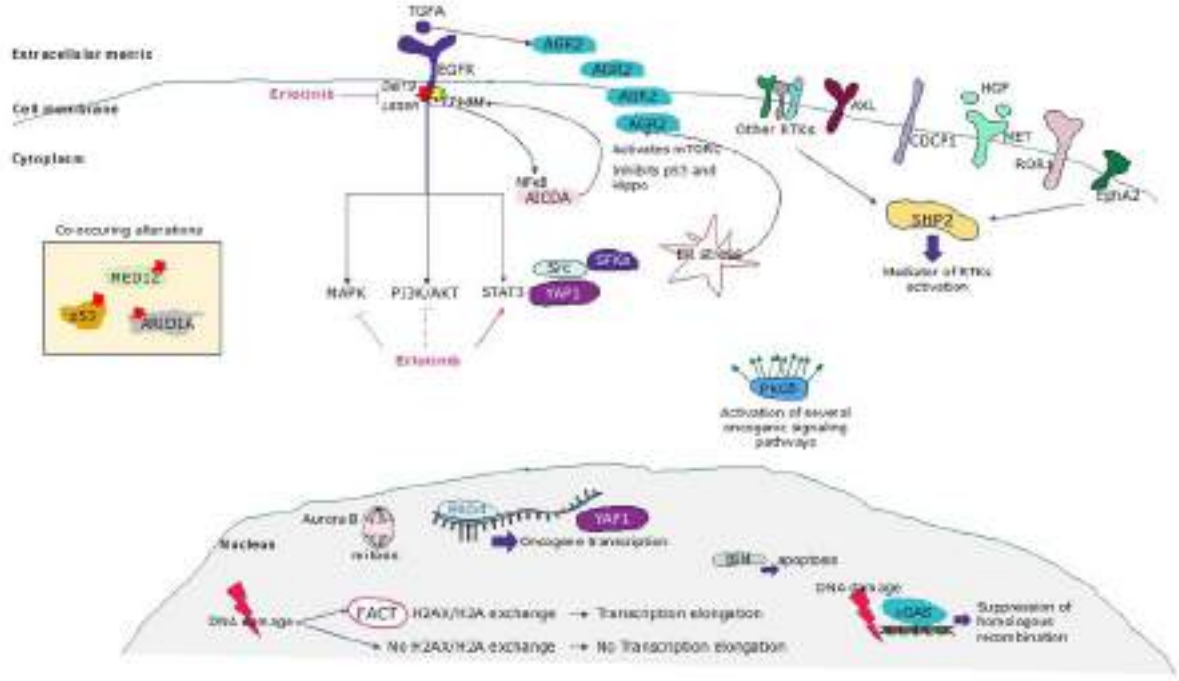
TKIs Should Be Given with Chemotherapy. This is an open question, with some pros and cons, mainly due to the complexities of chemotherapy activity regarding genetic alterations. However, there are several promising hints that the combination could be useful, but not all chemotherapeutic drugs prove beneficial. This information will be provided in the presentation. Resistance to erlotinib and, in general, to any generation of EGFR TKIs, is heterogeneous and requires the comprehensive dynamic molecular profiling of the tumor with either tissue, liquid biopsies, or both. Before the development of the third-generation EGFR TKIs, at the time of progression to erlotinib or gefitinib, patients were successfully treated with chemotherapy [Sequist et al Sci Trans Med 2011]. The alternation of chemotherapy and EGFR TKIs merits revisiting. The intercalation of erlotinib with chemotherapy has shown a median PFS of 16.8 months in EGFR-mutant NSCLC patients [Wu et al Lanect Oncol 2013]. The most salient biological concept to re-address the contribution of chemotherapy in EGFR-mutant NSCLC is the fact that nuclear cyclic GMP-AMP (cGAMP) synthase (cGAS) expression suppresses DNA repair and, therefore, can enhance the activity of EGFR TKIs. Preclinical data strongly favors this model, showing that etoposide or other chemotherapeutic drugs can promote the translocation of cGAS to the nucleus by phosphorylation of cGAS on the tyrosine residue 215. In the nucleus, cGAS is recruited to double stranded breaks, interacting with PARP1. The cGAS-PARP1 interaction jeopardizes the generation of the PARP1-Timeless complex and suppresses homologous recombination [Liu et al Nature 2018]. The fact that cGAS transcripts are increased in NSCLC is of clinical interest, indicating that cGAS could be a new biomarker involved in the response to immune checkpoint inhibitors [Gui et al Nature 2019]. Multilayer research sheds light on potential safe and active combinatory therapies in EGFR-mutant NSCLC and many therapeutic approaches converge in the complex signaling pathway crosstalk. Perhaps tumor heterogeneity is not the major difficulty and the mechanisms of resistance are more dependent on the capacity of tumor cells to re-wire and re-program the signaling pathways that they use to grow and migrate [Karachaliou et al EBioMedicine 2018]. Epi-transcriptomics are also involved in resistance to EGFR TKIs (Figure) [Zanconato et al Nat Med 2018]. Several chromatin regulators have emerged as druggable targets, including bromodomain-containing protein 4 (BRD4). BRD4 interacts with YAP1, and Bromodomain and Extra-Terminal motif (BET) inhibitors impair the expression of YAP1 direct target genes, including AXL, FST1 and aurora A [Zanconato et al Nat Med 2018]. We have recently reported that the combination of EGFR TKIs with barasertib, an aurora kinase B inhibitor, illustrates a strong antiproliferative activity in a broad panel of EGFR-mutant resistant cell lines [Bertran-Alamillo Nat Comm 2019]. DNA repair modulators may be associated with resistance to EGFR TKIs. In our original study of erlotinib in EGFR-mutant NSCLC [Rosell et al NEJM 2009], we explored the role of DNA repair genes on the treatment outcome. Among several transcripts examined, breast cancer type 1 susceptibility (BRCA1) gene mRNA surfaced as relevant in the repair of erlotinib-induced DNA damage through an H2A histone family member X (H2AX)-independent pathway [Rosell et al Clin Cancer Res 2011]. Normally, DNA damage repair involves a homologous recommendation, through H2AX [Wang et al Science 2007]. Patients with low BRCA1 mRNA expression had significantly longer PFS than patients with high BRCA1 mRNA levels, and BRCA1 levels were an independent predictor of PFS in the Cox-multivariate regression analysis. Finally, turning off the DNA damage checkpoint after DNA repair involves the removal of phosphorylated H2AX from the chromatin, followed by its replacement with canonical H2A. This exchange of phosphorylated H2AX for H2A is mediated by facilitates of chromatin transcription (FACT) (Figure). The ability of FACT to remove phosphorylated H2AX from the chromatin is inhibited by PARP1 [Rosell et al Clin Cancer Res 2011]. A novel class of drugs, curaxins, act as a chromatin trapping of the FACT, suppressing simultaneously NF-κB signaling and promoting activation of p53 [Gasparian et al Sci Trans Med 2011]. The combination of erlotinib with curaxins, or FACT inhibitors, like CBL0137 [Lindner et al Cancer Res 2018], may be a significant advance in the field of EGFR-mutant NSCLC therapy.



Keywords: NSCLC, TKIs, erlotinib

PC02 COMBINING WITH CHEMO: OLD SCHOOL IS NEW AGAIN
MONDAY, SEPTEMBER 9 14:00–15:30

PC02.03 IO SHOULD BE GIVEN AS A SINGLE AGENT

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Programmed cell death 1 (PD-1) checkpoint pathway inhibitors have greatly changed the treatment paradigm for advanced stage non-small cell lung cancer (NSCLC). Durvalumab is approved for use as a single agent after chemotherapy combined with radiation for stage 3 NSCLC.(1) Pembrolizumab is approved for use in the first line treatment setting for advanced NSCLC not amenable to radiation for patients whose tumor has a tumor proportion score (TPS) of 1% or greater in the United States.(2) For patients whose tumor has a TPS of ≥ 50%, it is approved for use in the first-line treatment setting in multiple countries throughout the world.(3) However, PD-1 checkpoint blockade combinations, either anti-PD1 or anti-PD-L1 antibodies, with chemotherapy regardless of PD-L1 status have shown benefit as well. (4,5,6) Single agent immunotherapy (IO) has several advantages. Cost of combination therapy is an issue. While these PD-1 pathway blocking antibodies are expensive as single agents, combining them with chemotherapy adds to the cost, time in infusion, and adds chemotherapy related side effects. So, if patients can, single agent immunotherapy is still preferred, particularly in a population i.e. TPS ≥ 50% who is more likely to benefit compared to chemotherapy. Some would say the same is true for patients with TPS ≥ 1, but here the data for single agent IO compared to combinations with chemotherapy is mixed. While trials comparing this scenario, i.e. comparing single agent PD-1 antibody compared to chemotherapy plus IO, head to head have not yet been done, it is hard not to do cross trial comparisons as seen in table 1. Clearly though, chemotherapy and IO combinations have increased objective response rates regardless of PD-L1 TPS status where response rates range from 57.9%-62.1%.(4,5,6,7,10) While combinations with chemotherapy show increased response rate regardless of PD-L1 TPS, chemotherapy can have deleterious effects on the immune system. (8) Chemotherapy can alter immune function by causing lymphopenia. Steroids, added to chemotherapy regimens to prevent allergic reactions and control nausea, can suppress pro-inflammatory cytokines and impair Natural Killer (NK) cell function and dendritic cell differentiation or activation. Taxanes specifically can cause inhibition of T-cell and NK-cell activation. Thus, these combinations may prevent immune activation and suppress immune memory. Duration of response in single agent IO in the first line treatment setting is 16.8-20.2+ month.(9,2,3) The duration of response in the IO plus chemotherapy patient population is 7.7-11.2 months.(4,5,6) The data from the chemotherapy IO combinations is too immature to know what the potential five-year survival is compared to the impressive 23.2% 5 year survival rate of the initial trial of pembrolizumab in the treatment-naïve setting(Keynote 001).(9) Immunotherapy, particularly PD-1 pathway checkpoint antibodies, have drastically changed the treatment landscape for advanced stage lung cancer patients. Single agent pembrolizumab particularly in patients with TPS ≥ 50% lung cancer results in an impressive long term survival that is not seen with chemotherapy alone. Combining immunotherapy agents with chemotherapy increases disease response but long term survival outcome data and duration of response is immature. Table 1 – Overview of Results in NSCLC PD-L1 TPS ≥ 50% patient population

	KeyNote 0243	KeyNote 0422	KeyNote 1894,10	KeyNote 4076
ORR	44.8%	39.5%	62.1%	60.3%
DOR (mo)	NR (1.9-14.5+)	20.2	15.1	Not reported
mPFS (mo)	10.3 HR 0.5 (0.37-0.68), p<0.001	7.1 HR 0.81 (0.67-0.99), p=0.017	11.1 HR 0.36 (0.26-0.51)	8 HR 0.37 (0.24-0.58)
mOS (mo)	30 HR 0.63 (0.47-0.86), p=0.002	20 HR 0.69 (0.56-0.85), p=0.0003	NR HR 0.59 (0.39-0.88)	NR HR 0.64 (0.37-1.10)
2 year OS	51.5%	44.7%	51.9%	Not reported

NR=not reached, ORR=overall response rate, DOR=duration of response, mPFS=median progression free survival, mo=months, mOS=median overall survival, OS=overall survival 1-Antonia SJ, Villegas A, Daniel D et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018 Dec 13;379(24):2342-2350. 2-Mok TSK, Wu YL, Kubaba I et al. Pembrolizumab versus Chemotherapy for Previously Untreated,

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Keywords: metastatic, Immunotherapy, Non-Small Cell Lung Cancer

PC02 COMBINING WITH CHEMO: OLD SCHOOL IS NEW AGAIN
MONDAY, SEPTEMBER 9 14:00–15:30

PC02.04 IO SHOULD BE GIVEN WITH CHEMO

L. Paz-Ares

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Lung cancer is the leading cause of cancer death worldwide. Non-small-cell lung cancer (NSCLC) accounts for almost 85% of all cases. The prognosis of NSCLC patients remains quite unsatisfactory due to the frequent advanced disease stage at diagnosis and the relatively low efficacy of the available systemic treatments. Of note, over the las few years significant progress as inhibitors of programmed death-1 (PD-1) and its ligand PD-L1 have proven to be effective therapies in metastatic NSCLC lacking sensitizing *EGFR* or *ALK* mutations, initially in pretreated patients. Subsequently, in metastatic NSCLC patients with PD-L1 expression of at least 50% on tumor cells, upfront pembrolizumab improved median progression-free survival (PFS) and overall survival (OS) compared to standard platinum-based chemotherapy. However, patients with a tumor proportion score (TPS) of 50% or greater represent only some 30% of those with NSCLC, and progression during the first three months is frequent in one third of the cases. To enhance the immune response through PD-1 inhibition, several studies have combined the potential immunogenic effects of cytotoxic chemotherapy with immune checkpoint inhibitors (ICPI), particularly of some chemotherapy regimens such as those pemetrexed-based. The first study that gave some important information regarding the efficacy of combining IO and chemotherapy was Keynote 021, randomized phase II trial of carboplatin plus pemetrexed with and without pembrolizumab. It showed significantly better response rates (RR) and longer PFS with the addition of pembrolizumab to chemotherapy. Over the last two years at least 6 other phase III clinical trials with pembrolizumab (KN 189 and KN 407) have showed the benefits of combined chemotherapy plus IO therapy in terms of PFS and OS (HR 0.49-0.64). Consistent data have been achieved on atezolizumab trials, although the magnitude of the OS benefit (HR 0.78-0.93) have been somehow lower. Randomized studies with nivolumab, durvalumab and avelumab are expected to be reported in the near future. Chemo-immunotherapy combinations are associated with the expected toxicities of chemotherapy and IO on their own. At present, for patients with tumors with TPS >50%, there are no comparative trials of IO monotherapy (e.g. pembrolizumab) as compared to chemotherapy. Across trial comparisons may support the use of IO monotherapy for most of cases. Chemo-IO regimens may be considered for patients requiring rapid responses (e.g. symptomatic patients) or those with aggressive disease. In patients, whose tumors express PD-L1 in 1-49% of cells, chemo-IO combinations are seen as the best treatment options. Of note, in the IMPOWER 150 trial, patients with EGFR/ALK aberrations also benefitted from the addition of atezolizumab to the paclitaxel/carboplatin/bevacizumab regimen. In patients with tumors with negative expression of PD-L1 the benefits on PFS were more debatable but the pembrolizumab-based combos, and to some extend those with atezolizumab, resulted in prolonged survival. The value of certain genomic aberrations (e.g. Keap or LKB1) or low tumor mutational burden (TMB) as a predictive tool in this setting needs further validation. In addition, the results of several ongoing combination studies (CheckMate-9LA, POSEIDON) investigating two and four drug regimens of PD-(L)1 plus CTLA-4 inhibition with/without chemotherapy are eagerly awaited and will reveal further knowledge of efficacy and tolerability in this setting. 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Keywords: PD-1/PD-L1 inhibitors, TMB, PD-1/PD-L1 and chemotherapy combinations

PC03 ADJUVANT THERAPY FOR RESECTED NSCLC HARBORING EGFR MUTATION, CHEMOTHERAPY OR TARGETED THERAPY
MONDAY, SEPTEMBER 9 15:45–17:15

PC03.01 PROS

W.-Z. Zhong

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Lung cancer is so far the leading cause of cancer death worldwide. Complete surgical resection remains the most effective approach for patients with early-stage non-small cell lung cancer (NSCLC). Patients with completely resected stage I NSCLC could have a 5-year survival of ~80%, whereas it fails to ~30%. Since 2003, adjuvant chemotherapy became the standard of care showing 4% absolute 5-year survival benefit compared to surgery alone [1]. Following randomized control trials revealed similar results [2-4], yet limited survival benefit, low therapeutic completed rate plus high toxicities rate may somehow hinder its clinical applicability. In the past decade, targeted therapies had achieved tremendous success in oncogene-driven advanced NSCLC showing both high efficacy and low toxicities [5]. As a matter of course, targeted therapy had its baby steps in early-stage NSCLC. However, no positive results were found in these trials which should probably be blame for large proportion of stage IB patients and incorrect detection methods for *EGFR*mutation. Besides, conservative trial design without head to head comparison could not fully address toxicities issues caused by chemotherapy. Precise target population seemed to be an essential key point to adjuvant targeted therapies and ADJUVANT as well as EVAN trial came into being [6, 7]. Although overall survival (OS) was not mature enough to measure, significantly prolonged disease-free survival (DFS) was observed in both trials along with better tolerability. Indeed, questioning around adjuvant targeted therapy has never been adjourned such as the optimal duration of targeted therapies, study design and lack of OS data. Ross et al brought up with an informative comment for ADJUVANT trial bringing the concept of MRD (molecular residual disease) into adjuvant treatment [8]. Based on the ctDNA testing after standard of care adjuvant chemotherapy, patients of high risk of recurrence will be given further treatments while observation for the others. It highlighted the significant role of discriminating beneficiaries from adjuvant targeted therapies instead of simply providing more efficient treatment modalities. Previous biomarker-based studies regarding adjuvant treatment among different tumor types [9, 10] had provided inspirational examples, and as well shown clinical feasibility and urgent need for personalized adjuvant treatment after complete surgical resection. For ADJUVANT trial, we established a comprehensive signature of genetic-features (MEDUSA) to guide personalized adjuvant treatment in EGFR-mutant stage II-III NSCLC. Results would be unleashed in upcoming ESMO meeting. Through utilizing multi-omics data, we could predict whether additional treatments, adjuvant chemotherapy only or observation would be adequate for each individual and provide optimal sequential treatments. Further translational researches and corresponding trials regarding resectable NSCLC should decipher the issues. Fortunately, several trials regarding dynamic monitoring postoperative ctDNA or genomic profile of primary cancer to guide sequential treatments are ongoing and the results should be expected.

	Study	Regimen	Sample size	Population	IB ratio	Median follow-up	DFS	5-year DFS	OS	5-year OS	complete rate
Adjuvant Chemotherapy	JBR.10	• Vinorelbine plus cisplatin • Observation	482	IB-II NSCLC	45.9%	9.3 years	• NR • 3.8 years (P<0.001)	• 61.0% • 49.0%	• 7.8 years • 5.1 years (P=0.05)	• 67.0% • 56.0%	69%
	IALT	• Cisplatin based CT (not specify) • Observation	1867	I-III NSCLC	36.5%	7.5 years	• 3.2 years • 2.5 years (P=0.02)	• 40.7% • 36.4%	• 54 months • 45 months (P=0.13)	• 45.8% • 41.9%	NA
	CALGB9633	• Paclitaxel plus carboplatin • Observation	304	IB NSCLC	100%	9.0 years	• 7.4 years • 4.7 years (P=0.084)	• 52.0% • 46.0%	• 8.2 years • 6.6 years (P=0.084)	• 60.0% • 58.0%	80%
	ANITA	• Vinorelbine plus cisplatin • Observation	840	IB-IIIA NSCLC	39%	76 months	• 36.3 months • 20.7 months (P=0.002)	• 43.5% • 34.9%	• 65.7 months • 43.1 months (P=0.017)	• 50.8% • 42.2%	49%
Adjuvant Targeted Therapy	BR19	• Gefitinib • Observation	503	IB-IIIA NSCLC	52%	4.7 years	• 4.2 years • NR (P=0.15)	• 49.2% • 56.6%	• 9.1 years • NR (P=0.14)	• 52.5% • 59.3%	NA
	SELECT	• Erlotinib	200	IA-IIIA NSCLC with sensitizing EGFR mutation	21%	5.2 years	NR	88.5% (2-year)	NR	NR	NA
	RADIANT	• Erlotinib • Placebo	973	IB-IIIA NSCLC with EGFR positive*	51%	47 months	• 50.5 months • 48.2 months (P=0.324)	• 46.0% • 43.4%	• NR • NR (P=0.335)	• 63.5% • 65.1%	68.7% (2 year)
	ADJUVANT	• Gefitinib • Vinorelbine plus cisplatin	222	II-IIIA EGFR mutant N1-N2 NSCLC	0%	35.5 months	• 28.7 months • 18 months (P=0.0054)	• 31.0% • 20.0% (3 year)	NA	NA	75% (1 year)
	EVAN	• Erlotinib • Vinorelbine plus cisplatin	202	IIA EGFR- mutant NSCLC	0%	33.0 months	• 42.4 mo#s • 21 months (P<0.0001)	• 64.2% • 19.8% (3 year)	NA	NA	80% (1 year)
	E1505	• Cisplatin based CT plus bevacizumab • Cisplatin based CT	1501	IB-IIIA NSCLC	26%	50.3 months	• 42.9 mo#s • 40.6 months (P=0.96)	• 44.2% • 39.0%	• NR • 85.8 months (P=0.9)	• 62.5% • 62.3%	37%

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Keywords: Adjuvant therapy, EGFR-TKI, Lung cancer

PC03 ADJUVANT THERAPY FOR RESECTED NSCLC HARBORING EGFR MUTATION, CHEMOTHERAPY OR TARGETED THERAPY
MONDAY, SEPTEMBER 9 15:45–17:15

PC03.02 CONS

J. Patel

University of Chicago, Chicago/United States of America

Surgery remains the cornerstone of treatment for early-stage non-small cell lung cancer (NSCLC). However, despite undergoing potentially curative surgery, patients with stage I, II, or IIIA NSCLC are at substantial risk for recurrence and death from lung cancer. Adjuvant cisplatin-based systemic therapy has conclusively been proven to decrease the risk of recurrence and improve overall survival outcomes. EGFR tyrosine kinase inhibitors have been proven to be the superior first-line treatment for EGFR-mutant advanced NSCLC. Several trials have shown superior progression-free survival and fewer side effects compared with doublet chemotherapy in advanced disease. Given that EGFR-TKIs are more active than platinum-based doublet chemotherapy in patients with advanced EGFR mutant lung cancer, there has been substantial interest in bringing these agents to earlier disease states.There are several clinical trials evaluating the effect of EGFR-TKIs as adjuvant treatment. Despite improvements in disease free survival, to date, none have demonstrated statistically significant improvements in overall survival. Moreover, multiple questions regarding duration of therapy and appropriate TKI remain unanswered. More survival data are needed before one can recommend adjuvant TKIs for all.

Keywords: adjuvant EGFR-TKI

PC03 ADJUVANT THERAPY FOR RESECTED NSCLC HARBORING EGFR MUTATION, CHEMOTHERAPY OR TARGETED THERAPY
MONDAY, SEPTEMBER 9 15:45–17:15

PC03.03 FUTURE STRATEGIES IN EARLY STAGE EGFR-MUT NSCLC

V. Papadimitrakopoulou

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EGFR tyrosine kinase mutations occur in approximately 10% of advanced non-small cell lung cancer (NSCLC) Western patients and in 30% of Asian patients. *EGFR* tyrosine kinase inhibitors (i.e., gefitinib, erlotinib, afatinib, icotinib, dacomitinib and, recently, osimertinib) are superior to chemotherapy in patients with advanced *EGFR*+ lung cancers and have become the standard first-line treatment for NSCLC patients harbouring those specific mutations (1-5). Despite this, definitive trials of EGFR-TKIs as adjuvant treatment of EGFR-mutant early stage NSCLC are few and controversial. Improving outcomes with targeted adjuvant therapy and specifically overall survival remains a challenge in the management of radically resected NSCLC. As shown by the addition of the antiangiogenic agent, bevacizumab to adjuvant chemotherapy in the E1505 trial (6). The first prospective data to suggest that adjuvant targeted therapy may indeed alter the disease course for early-stage NSCLC were from the SELECT and RADIANT trials (7, 8), in addition retrospective analyses also showed promising results in improving DFS in stage I-III EGFR mut+ NSCLC and a potential OS benefit. The results of the ADJUVANT/CTONG1104 study (9), a randomized open-label phase III trial in completely resected (R0) stage II–IIIA (N1-N2) EGFR-mutant NSCLC (defined as exon 19 deletion or exon 21 Leu858Arg) comparing 4 cycles of standard adjuvant Cisplatin and Vinorelbine or 24 months of the EGFR-tyrosine kinase inhibitor (TKI), gefitinib revealed significantly longer median DFS in the gefitinib arm than in chemotherapy arm, while OS was not mature. Several questions remain including: A) the patient subset with early stage disease that may derive the most benefit B) the optimal duration of adjuvant TKI therapy C) the degree of toxicity and associated adherence to therapy over long periods of time and finally D) the cost of therapy. Phase 3 prospective trials remain necessary and several are under way, including the ALCHEMIST study, using erlotinib and the ADAURA study using Osimertinib. Finally use of neoadjuvant targeted therapy (10) and chemotherapy may offer distinct advantages in eliminating micrometastatic disease prior to surgery and clinical trials using this approach are planned or ongoing and will be discussed. References 1.Shi YK, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol 2017;28:2443-50. 2.Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 2015;16:830-8. 3.Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8. 4.Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25. 5.Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66. 6.Wakelee HA, Dahlberg SE, Keller SM, et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2017;18:1610-23. 7.Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2015;33:4007-14. 8.Neal JW, Pennell NA, Govindan R, et al. The SELECT study: a multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). J Clin Oncol 2012;30:abstr 7010. 9. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/ CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48. 10.Zhong WZ et al., Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment for stage IIIA-N2 EGFR.-mutation positive non-small-cell lung cancer (EMERGING-CTONG 1103): multicentre phase 2 randomized study. ESMO 2018, abstract LBA48_PR

Keywords: EGFR mutation, adjuvant therapy

PC04 IS CHEMOTHERAPY NECESSARY FOR ADVANCED NSCLC PATIENTS WITH PD-L1 50% OR MORE?
TUESDAY, SEPTEMBER 10 11:30–13:00

PC04.01 PRO: CHEMOTHERAPY IS NECESSARY

M. Garassino

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan/Italy

As first-line therapy single agent pembrolizumab showed better outcomes than chemotherapy (CT) in patients with NSCLC and PD-L1 expression ≥50% [1]. Recently has been published another phase 3 trial in which patients with aNSCLC with an expression of PD-L1 ≥1%, treated with pembrolizumab as single agent, results in better overall survival (OS) than CT in first-line, mainly in subgroup with PD-L1 ≥50% [2]. After the approval and subsequent use of pembrolizumab as single agent in first-line in NSCLC with PD-L1 ≥50%, in 2018 several phase III trials explored the combination of immunotherapy agents (pembrolizumab and atezolizumab), with no regards of PD-L1 status, in association with standard CT, gaining better outcomes than CT alone in first-line NSCLC [3-8]. A matter of debate is what we have to do in patients with PD-L1 ≥50% due to the absent comparison between combination therapy and ICI as single agent and similar results in 1-year OS among these treatments [1,3-4]. So, why should we suggest the use of combination over ICIs as single agent in patients with PD-L1 ≥50% in first-line? First of all, we can see that trials of combination therapy report benefit with CT plus ICI across all PD-L1 subgroups, with a greater magnitude of benefit in patients with PD-L1 ≥50% with no regards of kind of drugs used (either CT and ICI) and histology (squamous or non-squamous) [3-8]. This magnitude of benefit is supported from an higher objective-response rate (ORR) in patients treated with combination therapy over ICI as single agent in subgroups of patients with PD-L1 ≥50% [1-4], suggesting combination therapy as best choice even in patients with highly symptomatic disease with the purpose of obtaining a fast shrinkage of tumor. Analyzing Kaplan-Meyer curves of single agent trials [1,2], you can observe that there is a violation of proportional hazard assumptions. We can see a crossing of the curves within first 3-6 months suggesting us that there's a subgroup of patients who have a worse prognosis when treated with single agent immunotherapy over CT. This worse prognosis could be

possibly partially due to a phenomenon called hyperprogressive disease [9], a quicken tumor growth during treatment with ICIs in NSCLC irrespectively of the line of therapy. If we look at Kaplan-Meyer curves of all combination studies, we can see that the combination of CT plus ICI abrogates the crossing curves [3,4,6,8], probably overcoming hyperprogessive disease with the addiction of CT by modulating tumor microenvironment. In subgroups of patients with liver and/or brain metastases, generally considered at worse prognosis, combination therapy demonstrates a benefit. In a retrospective analysis of KEYNOTE189 [10] were evaluated outcomes of patients with brain and/or liver metastases. In this analysis the addiction of pembrolizumab to CT grants a benefit over CT alone either in progression-free survival, OS and ORR in patients with liver and/or brain metastases. Another evidence of benefit in patients with liver metastases in combination therapy was seen in IMpower150, in which the addiction of atezolizumab to bevacizumab plus CT seemed to add something even though there's a bias due to the use of bevacizumab [5]. In advanced NSCLC treated with ICI as single agent [1,2] we see a lower benefit in non-smoker than in current or former smoker patients, whilst in combination studies this difference isn't seen regardless kind of drug and histology [3,6-8]. Even gender may be a possible reason to choose combination instead of ICI as single agent. As we previously do for smoking habit, we indirectly compare trials with single agent and with combination. We can see that in KEYNOTE024 there's a stronger benefit using pembrolizumab in males over females. This reported benefit for male patients is lost in combination treatment, with slight better outcomes in women instead, with no regards of drugs used and histology [3,4,6-8]. Finally, basing on preclinical evidences, we know that the combination between CT and ICIs may enhance the immune system activity due to immunological effect of cytotoxic agents through the expression of PD-L1 on the surface of tumor cells, the depletion of myeloid-derived suppressor cells and T-regulatory cells and the augmentation of the presentation of antigens by cancer cells [10]. At the state of the art the aim of our discussion remains an unanswered question but based on what we previously said, at least in patients with high tumor burden, in never smokers, we suggest CT plus ICI as first-line in aNSCLC with PD-L1 ≥50%.This could allow us not to lose patients in the first six months of treatment. [1] Reck M et al.Pembrolizumab versus chemotherapy for PD-L1 positive non-small cell lung cancer. NEJM 2016; 375: 1822-1833 [2] Mok TSK et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic non-small cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019; 393: 1819-1830 [3] Gandhi L et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. NEJM 2018; 378: 2078-2092 [4] Paz-Ares L et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. NEJM 2018; 379: 2040-2051 [5] Socinski MA et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. NEJM 2018; 378(24): 2288-2301 [6] Cappuzzo F et al. IMpower130: efficacy and safety from a randomise phase 3 study of carboplatin and nab-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC. Presented at ESMO 2018 [7] Jotte R et al. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. Presented at ASCO 2018 [8] Papadimitrakopoulou VA et al. IMpower132: PFS and safety results with 1L atezolizumab + carboplatin/cisplatin + pemetrexed in stage IV non-squamous NSCLC. Presented at WCLC 2019 [9] Proto C et al. Choosing wisely first line immunotherapy in non-small cell lung cancer (NSCLC): what to add and what to leave out. Cancer Treat Rev 2019; 75:39-51 [10] Garassino MC et al. Outcomes among patients with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab plus pemetrexed-platinum: results from the KEYNOTE-189 study. Presented at AACR 2019

Keywords: Chemotherapy, Immunotherapy, first line

PC04 IS CHEMOTHERAPY NECESSARY FOR ADVANCED NSCLC PATIENTS WITH PD-L1 50% OR MORE?
TUESDAY, SEPTEMBER 10 11:30–13:00

PC04.02 CON: ICI IS ENOUGH

M. Reck

Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), Member of the German Center for Lung Research (DZL), Grosshansdorf/Germany

The implementation of anti PD-1 / anti PD-L1 checkpoint inhibitors has completely changed management of patients with advanced non-small-cell lung cancer (NSCLC). On the way to an individualized use of these agents a correlation between the PD-L1 expression on tumor cells and immune cells and efficacy of immunotherapies could be demonstrated across different agents and treatment lines. In particular a clear correlation between survival and PD-L1 expression on tumor cells (TPS-score) has prospectively been evaluated and validated for the anti-PD1 antibody pembrolizumab defining a TPS score of =/> 50% as a predictor for enhanced outcome by pembrolizumab and showing impressive 4 and 5 year overall survival rates for untreated patients with a TPS-Score of =/> 50% of 48% and 29.6% respectively (1,2). Two prospectively randomized phase III trials confirmed the superior efficacy of pembrolizumab monotherapy with a significant prolongation of overall survival compared to platinum based chemotherapy in untreated patients with a TPS-score of =/> 50% (3,4). Recently the concept of combining immunotherapies with chemotherapies has demonstrated superior efficacy compared to chemotherapy patients with advanced NSCLC independent from the PD-L1 expression and the question appears, whether such a combination would also be the preferred treatment for the selected group of patients with a TPS-score of =/>50%. Analysing this question a couple of points need to be addressed: First of all this important question has never been addressed appropriately in a prospective trial and in none of the combination trials a immunotherapy monotherapy arm was part of investigated schedule. Therefore all assumptions remain subjective and exploratory. Second: We have seen a dramatic improvement of survival expectation together with a relevant prolongation of treatment duration by the adaption of immunotherapies in management of advanced NSCLC. Therefore tolerability, symptom control and quality of life become essential parameters for feasibility of treatment. Across all chemo-immunotherapy combination trials the frequency of CTC grade 3-5 treatment related adverse events (TRAEs) was substantially higher compared to the pembrolizumab monotherapy arms. In particular in an updated report of the Keynote 189 trial the frequency of TRAEs grade 3-5 was 71.9% for the combination of pembrolizumab and chemotherapy compared to 17.8% in the Keynote 42 trial and 31.2% in the Keynote 24 trial leading to a treatment discontinuation rate of 33.6% compared to 9% and 13.6% in the Keynote 42 and 24 trial (4,5,6). Considering the symptomatic efficacy ICI monotherapy has shown a clinical relevant improvement of symptoms during treatment compared to chemotherapy assessed by the QLA-C30 GHS/QOL score together with a substantial prolongation of time to symptom deterioration in the Keynote-24 (7). This unique pattern of symptomatic efficacy, which clearly reflects the patient related impact of anti tumor therapy has so far not been to that extent for the combination trials. Third: Besides the impressive activity demonstrated by the use of first line chemo-immunotherapy combinations we are confronted with the rapidly emerging clinical problem, that we suffering effective and tolerable post progression treatment opportunities. So far no specific treatment approaches are available and mostly we are ending up with the use of limited effective docetaxel +/- an antiangiogenic agent. In contrast a first line ICI monotherapy offers the opportunity of a post progression full dosed platinum based combination treatment with clearly higher efficacy compared to docetaxel alone. Fourth: Currently the most appropriate endpoint to assess efficacy of immunotherapies remains to be determined and we have seen in various trials that response and PFS might not be the optimal endpoints. In contrast it is general accepted the survival represents the most eminent and meaningful endpoint. Looking on the survival results of the different trials the differences in follow up periods need to be taken into account leading potential differences in the assessment of survival times. However respecting the lack of prospective randomised trials it appears that no benefit in survival in particular long term survival could be generated by the addition of chemotherapy to immunotherapy in the group of patients with a TPS-score =/> 50%. In an exploratory analysis of the Keynote 189 trial the 2 year OS rate for patients with a TPS-score =/> 50% was 51.9% for the combination of chemotherapy and pembrolizumab

compared to 51.5% and 44.7% for pembrolizumab monotherapy in the Keynote-24 and -42 trial. Furthermore also the Hazard ratios were comparable across the trials (HR 0.59 for Keynote-189 compared to HR 0.63 and 0.69 in Keynote-24 and -42). In summary ICI monotherapy represents the preferred new highly effective and well tolerable first-line treatment opportunity in untreated patients with a TPS-score of =/> 50%. Addition of chemotherapy is associated with poorer tolerability and in particular long-term tolerability. Ongoing research might define the few patients, where tumor control cannot be achieved by ICI monotherapy. 1. Garon EB, Rizvi NA, Rui R, et al: Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372 (2015): 2018-2018 2. Garon EB, Hellmann MD, Rizvi NA et al: Five-Year Overall Survival for patients with advanced non-small-cell lung cancer treated with pembrolizumab: results from the phase I Keynote-001 studay. J Clin Oncol (2019): e-published June 2, 2019-06-01 3. Reck M, Rodriguez-Abreu D, Robinson AG et al: Pembrolizumab versus chemotherapy for PD-L1 positive non-small-cell lung cancer. N Engl J Med (2016): 1823-1833. 4. Mok TSK, Wu Y-L, Kudaba I et al: Pembrolizumab versus chemotherapy for previously untreated PD-L1-expressing locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. Lancet (2019): 1819-1830. 5. Gadgeel S, Garrassino MC, Esteban E, et al: Keynote-189: Updated overall survival and progression after the next line of therapy with pembrolizumab plus chemotherapy with pemetrexed and platinum vs placebo plus chemotherapy for metastatic nonsquamous NSCLC: ASCO 2019, abstract 9013 6. Reck M, Rodriguez-Abreu D, Robinson AC et al: Updated analysis of Keynote-024: Pembrolizumab vers platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 Tumor Poportion Score of 50% or greater: J Clin Oncol 37 (2019): 537-546 7- Brahmer J, Radriguez-Abreu D, Robinson AG et al: Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (Keynote-024): a multicentre, intenational, randomised, open-label phase 3 trial. Lancet Oncology 18 (2017): 1600-1609.

Keywords: ICI, Monotherapy, first-line treatment

PC05 IMMUNE CHEKPOINT INHIBITORS IN REAL WORLD - HOW DO WE TREAT NSCLC "SPECIAL POPULATIONS"
TUESDAY, SEPTEMBER 10 14:30–16:00

PC05.01 ICIS FOR PATIENTS WITH INTERSTITIAL PNEUMONIA

T. Kato

Kanagawa Cancer Center, Yokohama/Japan

Interstitial pneumonia (IP) or pulmonary fibrosis (PF) is one of the most common and poor prognostic comorbidities with lung cancer, and also known as a risk factor of treatment related pneumonitis. Around 10% of patients are diagnosed concomitant IP/PF at the time of cancer diagnosis. The prognosis of lung cancer patients with IP/PF has been reported to be poor, because 5-20% of those receiving chemotherapy experienced exacerbation of IP/PF, and some of them are mortal. Median overall survival time of these patients with stage IV non-small cell lung cancer is around 10 months, which is 2 months shorter than patients without IP/PF. In spite of risk of acute exacerbation, chemotherapy including platinum doublet or monotherapy are considered as the standard treatment for the patient with IP/PF because of a certain level of efficacy. Not only chemotherapy, other types of cancer treatment including radiotherapy, surgical resection, and targeted drug also induce acute exacerbation of pre-existing IP/PF occasionally. Targeted small molecules including EGFR-TKIs are reported to have higher risk of acute exacerbation of pre-existing IP/PF, and some surveillance reports that existence of IP/PF is a most significant risk factor related to emergence of treatment related pneumonitis. Immuno-checkpoint inhibitors (ICI) now play an important role in lung cancer treatment, and as immune related adverse event, immune mediated pneumonitis is considered that should be paid most attention because of its high frequency and potential lethality. Regarding to ICI, relation between pre-existing IP/PF and treatment related pneumonitis is not clear, so far. Because of relationship to smoking history, higher level of microsatellite instability (MSI), and tumor mutation burden (TMB), these are associated with favorable efficacy, ICI also may have some role in treatment strategy for the lung cancer patients comorbid with IP/PF. A phase II trial of nivolumab for pretreated NSCLC patients with IP/PF, in 18 pretreated NSCLC patients with mild idiopathic IP, showed 36% of response rate and a 56% of 6-months progression-free survival rate in mild idiopathic IP. Two grade 2 pneumonitis were observed, and both are improved by corticosteroid treatment. In this session I will try to review ICI treatment for patients with IP/PF and also discuss about their clinical adaptation for clinical practice.

Keywords: immune checkpoint inhibitor, pulmonary fibrosis, interstitial pneumonia

PC05 IMMUNE CHEKPOINT INHIBITORS IN REAL WORLD - HOW DO WE TREAT NSCLC "SPECIAL POPULATIONS"
TUESDAY, SEPTEMBER 10 14:30–16:00

PC05.02 ARE ICIS EFFECTIVE FOR POOR PERFORMANCE STATUS PATIENTS WITH ADVANCED NSCLC?

F. Grossi[1], C. Genova[2]

[1]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano/Italy,* [2]*IRCCS Ospedale Policlinico San Martino, Genoa/Italy*

The management of non-small cell lung cancer (NSCLC) in patients with poor performance status (PS) has always been a challenging task. Until the last decade, platinum-based chemotherapy has been the main therapeutic approach to NSCLC, and is retaining a major role in patients without actionable oncogenic drivers and low expression of programmed death protein ligand 1 (PD-L1). However, patients with poor PS are generally excluded from combination-based regimens and from enrollment in novel clinical trials [1]. While immunotherapy with immune checkpoint inhibitors (ICIs) has become a cornerstone in the management of advanced NSCLC, data regarding its role in ECOG PS=2 patients are generally limited; indeed, the most relevant phase III randomized controlled trials involving ICIs in advanced NSCLC have excluded ECOG PS=2 patients, resulting in a general lack of recommendations from international guide-lines [2]. The currently available information on this specific population has been collected from a handful of clinical studies, all of them involving patients receiving ICIs in second or further lines. In the phase II CheckMate 171 trial, 98 ECOG PS= 2 previously treated patients with squamous NSCLC received single-agent nivolumab; in the preliminary data, the safety profile of nivolumab and the objective response rate (ORR) in ECOG PS=2 patients were globally similar to the overall population, while median overall survival (mOS) was lower, as expected due to the prognostic effect of PS [3]. The phase III-IV CheckMate 153 trial, designed to assess safety of nivolumab in pre-treated NSCLC patients, showed similar results, but notably, in patients with ECOG PS=2, a significant improvement in symptom burden was observed [4]. An additional source of data for unfit NSCLC patients treated with ICIs is represented by expanded access programs (EAPs), in which real-life patients received nivolumab before its registration. In the largest EAP (Italian nivolumab non-squamous NSCLC cohort), 108 pre-treated ECOG PS=2 patients received nivolumab; the independent negative prognostic role of ECOG PS on survival was confirmed, while no safety issues were observed [5]. In contrast with the previous studies, the PEPS2 trial was specifically designed to assess the role of pembrolizumab in a population of previously treated NSCLC patients with ECOG PS=2. The study is currently ongoing, although the data reported so far encourage the use of pembrolizumab in this population; moreover, PD-L1 tumor proportion score appeared to be associated with survival [6]. In conclusion, while the well-known prognostic effect of poor performance status is observed during administration of ICIs, the safety profile and the activity of these agents make immunotherapy a feasible strategy for treating unfit NSCLC patients, especially when single-agent ICIs are administered, although limited outcomes in terms of survival are to be taken into account when choosing whether to offer active antineoplastic treatment to unfit patients or not; since ECOG PS=2 represents a wide range of patients, this choice needs to be made on an individual basis. Notably, a limit of the aforementioned data is represented by the lack of comparison with chemotherapy in controlled randomized studies; to fill this gap, some ongoing trials are being conducted: more specifically, the IPSOS trial is designed to enroll patients who are unfit for platinum-based chemotherapy and randomize them to atezolizumab vs. single-agent chemotherapy [7], while another trial (NCT02581943) is designed to compare pembrolizumab alone or in combination with low-dose carboplatin-paclitaxel [8]; finally, the eNERGY trial is designed to compare ipilimumab-nivolumab with a carboplatin-based doublet in ECOG PS=2 patients [9]. The availability of data from these and similar studies will provide additional insights on the role of ICI in unfit NSCLC patients.

Study	Regimen	ECOG PS=2 patients (% of global population)	Results in ECOG PS=2 (results in global population)
CheckMate 171 (phase II)	Nivolumab	98 (12%)	TRAEs= 46% (50%) Grade 3-4 TRAEs= 6% (12%) mOS= 5.4 months (9.9) ORR= 11% (14%)
CheckMate 153 (phase III-IV)	Nivolumab	128 (9%)	TRAEs= 48% (62%) Grade 3-4 TRAEs= 11% (12%) mOS= 4.0 months (9.1)
Italian non-squmous EAP	Nivolumab	108 (7%)	Compared to PS=0-1: increased risk of OS < 3 months (odds ratio at multivariate analysis= 0.29 (0.19-0.44)
PEPS2 (phase II)	Pembrolizumab	60 (100%)	Grade 3-4 TRAEs= 12% mPFS= 5.4 months mOS= 11.7 months ORR= 28%

Table 1. Studies involving ICIs in ECOG PS=2 patients with NSCLC.
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Keywords: Immunotherapy, advanced NSCLC, Poor Performance Status

PC05 IMMUNE CHEKPOINT INHIBITORS IN REAL WORLD - HOW DO WE TREAT NSCLC "SPECIAL POPULATIONS"
TUESDAY, SEPTEMBER 10 14:30–16:00

PC05.03 ICIS FOR PATIENTS WITH IMMUNE-RELATED COMORBIDITY

R. Pirker

Medical University of Vienna, Vienna/Austria

Immune checkpoint inhibitors have recently been established as standard therapy for patients with advanced NSCLC. However, data on immune checkpoint inhibitors are limited for special patient populations such as elderly patients, patients with poor performance status and patients with immune-related comorbidity (1). Major clinical trials excluded patients with active autoimmune diseases requiring systemic steroids, patients with systemic immunosuppressive treatment, patients with interstitial lung disease or history of pneumonitis requiring systemic steroids, and patients with chronic viral infections (e.g. hepatitis, HIV). Patients with immune-related comorbidity include patients with autoimmune diseases, patients with organ transplants, patients with end-stage renal disease and patients with chronic viral infections. Data on the efficacy and safety of immune checkpoint inhibitors are limited for these patients and mainly based on patients with melanomas and only few patients with lung cancers. Immune checkpoint inhibitors could result in unacceptable immune activation in patients with pre-existing autoimmune diseases (1). Based on a literature report, exacerbations of autoimmune symptoms occurred in about 1/3 of patients who had been treated with these drugs (1). Therefore, great caution with regard to the use of these drugs in patients with autoimmune diseases is mandated. Patients with organ transplants have been excluded from clinical trials because of the concern of potential organ rejections. Nevertheless, few reports are available on immune checkpoint inhibitors in patients who had undergone prior organ transplantations (2-8). A recent overview (4) reported on 19 patients with the following characteristics: median age 59 (14-77) years, 74% males, melanoma (n=11), cutaneous squamous cell carcinoma (n=3), NSCLC (2) and hepatocellular ca (n=2), and duodenal cancer (n=1). Median time to start of checkpoint inhibitors after organ transplantation was 11 (range 1-25) years. Patients were treated with nivolumab (53%), ipilimumab (26%) or pembrolizumab (21%). Most patients received low dose prednisone. Graft rejections occurred in ten patients (7/12 kidney, 2/5 liver, and 1/2 heart transplants), particularly among patients who had been treated with anti PD-1 antibodies. Median time to rejection was 21 (range 5-60) days. Among nine patients without rejections, four had immune-related adverse events (hepatitis, colitis, pneumonitis, and dermatitis). A clinical benefit was seen in 57% of patients. This overview indicated that treatment with immune checkpoint inhibitors is associated with a high rate of transplant rejections. A high rejection rate was also reported by others (5). A retrospective analysis of patients with liver transplants indicated transplant rejections in two out of seven patients undergoing treatment with PD-1 inhibitors for hepatocellular carcinomas (n=5) and melanomas (n=2) (8). Taken together, patients with solid organ transplants have a clinically relevant risk of transplant rejection when treated with immune checkpoint inhibitors. Little information is available for patients with impaired renal function including end-stage renal disease (1, 9). In a report on three patients undergoing hemodialysis, immune checkpoint inhibitors resulted in a partial response in one patient and in stable disease in two patients (9). The toxicity was acceptable except grade 2 pneumonitis in one patient. Based on a literature review, 10 out of 13 patients undergoing hemodialysis responded to immune checkpoint inhibitors. Grade 3-4 immune-related adverse events occurred in three patients. The authors concluded that immune checkpoint inhibitors may not be contra-indicated in patients undergoing hemodialysis but may result in significant toxicity (9). Patients with chronic viral infections, especially hepatitis C, appear to have little risk of treatment-related increases in adverse events and, therefore, may be treated with immune chekpoint inhibitors under careful monitoring (1). Although our knowledge on immune checkpoint inhibitors in patients with cancers is rapidly expanding, we still need more information on the efficacy and safety of these drugs in patients with immune-mediated diseases. Data in the real-world setting would be of particular interest. The gathering of these data could be facilitated by establishing registries on national and international levels. Until further information on the safety of these drugs will become available, immune checkpoint inhibitors should be administered with great caution and only after a careful risk benefit assessment in patients with immune-related comorbidity.

References 1. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer 2017; 123: 1904-1911. 2. Kittai AS, Oldham H, Cetnar J, Taylor M. Immune checkpoint inhibitors in organ transplant patients. J Immunother 2017; 40: 277-281. 3. Chae YK, Galvez C, Anker JF, et al. Cancer immunotherapy in a neglected population: The current use and future of T-cell-mediated checkpoint inhibitors in organ transplant patients. Cancer Treat Rev 2018; 63: 116-121. 4. Hassan NA, Abudayyeh A, Shah M, et al. The outcome of checkpoint inhibitor therapy in patients with cancer and solid organ transplant: A systematic review of the literature. J Clin Oncol 2018; 36: 5 suppl, 41. 5. Abdel-Wahab N, Safa H, Abudayyeh A, et al. Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature. J ImmunoTher Cancer 2019; 7: 106. 6. Owonikoko TK, Kumar M, Yang S, et al. Cardiac allograft rejection as a complication of PD-1 checkpoint blockade for cancer immunotherapy: a case report. Cancer Immunol Immunother 2017; 66: 45-50. 7. Charles J, Giovannini D, Terzi N, et al. Multi-organ failure induced by nivolumab in the context of allo-stem cell transplantation. Exp Hematol Oncol 2019; 8: 8. 8. DeLeon TT, Salomao MA, Aqel BA, et al. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience. J Gastrointest Oncol 2018; 9: 1054-1062. 9. Cheun H, Kim M, Lee H, et al. Safety and efficacy of immune checkpoint inhibitors for end-stage renal disease patients undergoing dialysis: a retrospective case series and literature review. Invest New Drugs 2019; 37: 579-583.

Keywords: Immune Checkpoint Inhibitors, Organ transplants, Autoimmune diseases

PC05 IMMUNE CHEKPOINT INHIBITORS IN REAL WORLD - HOW DO WE TREAT NSCLC "SPECIAL POPULATIONS"
TUESDAY, SEPTEMBER 10 14:30–16:00

PC05.04 ICIS FOR ELDERLY PATIENTS WITH ADVANCED NSCLC

H. Borghaei

Fox Chase Cancer Center, Philadelphia/United States of America

Immunotherapy with checkpoint inhibitors has changed the treatment landscape of many cancers. In the management of patients with non-small cell lung cancer the introduction of immunotherapy as a single agent or in combination with chemotherapy has led to significant improvement in survival and response rates in many patients but not all. I will discuss the role of this approach in the treatment of the elderly patient population with non-small cell lung cancer. I will examine the available data related to clinical efficacy and toxicity of these treatments and hope to delineate a potential role for the continued use of checkpoint inhibitors in the elderly patient population.

Keywords: chekpoint inhibitors, Eldelry patient, Non small cell lung cancer

Mini Symposia

MS01 IMMUNOTHERAPY RESISTANCE
SUNDAY, SEPTEMBER 8 10:30–12:00

MS01.01 BIOLOGICAL MECHANISMS OF RESISTANCE

J. Gainor

Massachusetts General Hospital, Boston/United States of America

Immune checkpoint inhibitors targeting the programmed cell death 1 (PD-1) axis have transformed the management of non-small cell lung cancer (NSCLC). Despite the dramatic and sometimes durable activity of these agents, a majority of patients will progress on therapy.[1] Patients who experience a de novo lack of response to initial therapy are deemed as having primary (intrinsic) resistance. By contrast, acquired resistance refers to patients who initially achieve an objective response to therapy but eventually progress over time. The mechanistic basis for primary versus acquired resistance to immune checkpoint inhibitors is still poorly defined. To date, studies into the biological mechanisms of resistance to immunotherapies have centered around preclinical studies and analyses of repeat biopsies obtained from patients at the time of disease progression.[2] These efforts have been complemented by similar studies in other immuno-oncology settings (e.g., melanoma),[3,4] since there is potential for shared biology underlying immunotherapy resistance across malignancies. Both tumor cell-intrinsic and tumor cell-extrinsic factors have been implicated in mediating resistance to immunotherapies.2 In the setting of primary resistance, disease progression is commonly driven by a lack of neoantigens sufficient to illicit an initial immune response, commonly due to a low tumor mutation burden.5 Alternatively, tumors may actually harbor antigens capable of generating an immune response, but defects in antigen processing may ultimately limit the presentation of these antigens on the cell surface via MHC. Defective antigen presentation may be due to loss of beta-2 microglobulin (B2M), elimination of transporters associated with antigen processing (TAP) proteins, or downregulation of HLA.2,3 In addition, intrinsic resistance to immune checkpoint inhibitors may be due to altered oncogenic cell signaling (e.g., WNT/B-catenin pathway) and/or tumor de-differentiation with impaired antigen expression. Molecular mechanisms of acquired resistance to checkpoint blockade likely include many of the same processes as those implicated in intrinsice resistance. Indeed, homozygous loss of B2M, which is required for stabilization of HLA on the cell surface, has been described in NSCLC at the time of acquired resistance to PD-1 pathway blockade.6 Additionally, neoantigen loss through elimination of specific tumor subclones (i.e., immunoediting), genetic alterations in interferon gamma (IFN) signaling, and upregulation of alternative checkpoints (e.g., TIM3) have also been purported to confer acquired resistance to checkpoint inhibitors.4,7,8 At present, the relative frequencies of these processes and the interplay among them within NSCLC and other malignancies remains to be defined. Moving forward, it will be critical to pursue more in-depth preclinical and clinical studies of resistance to PD-1 pathway blockade in NSCLC. Just as insights into the molecular mechanisms of resistance to targeted therapy have transformed the therapeutic landscape for oncogene-driven tumors, it will be imperative for immuno-oncology to develop a framework for understanding resistance to checkpoint inhibitors and apply this framework to clinical development of next-generation immuno-onclogy agents. This is especially critical due to the sheer number of immuno-oncology combinations currently in clinical testing. Ultimately, knowledge of the mechanisms of resistance to immune checkpoint inhibitors may help better inform the rationale design of trials evaluating PD-1 inhibitor combinations. 1. Garon EB, et al. J Clin Oncol 2019 Jun 2 [Epub ahead of print]. 2. Sharma P, et al. Cell 2017;168(4):707-23. 3. Sade-Feldman M, et al. Nat Commun 2017;8(1):1136. 4. Zaretsky JM, et al. NEJM 2016;375:819-29. 5. Rizvi NA, et al. Science 2015;348(6230):124-128. 6. Gettinger S, et al. Cancer Discov 2017:7:1420-35. 7. Anagnostou V, et al. Cancer Discov 2017;7(3):264-76. 8. Koyama S, et al. Nat Commun 2016;7:10501.

Keywords: PD-1 blockade, Immunotherapy, resistance

MS01 IMMUNOTHERAPY RESISTANCE
SUNDAY, SEPTEMBER 8 10:30–12:00

MS01.02 TREATMENT DETERMINING MARKERS - WHAT HAVE WE ACHIEVED SO FAR?

N. Rizvi

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Progress has been made selecting patients for immune checkpoint blockade employing expression of PD-L1 however limitations exist with this approach. Increasing use of genetic markers has been incorporated into clinical trials and clinical practice. Beyond MSI testing, tumor mutation burden has gained increasing traction and prospective trials employing TMB are under way and will be reviewed. Additional unique sensitivity and resistance mutations are emerging and may be incorporated into our genetic analysis paradigm. Additionally genetic studies are now being performed with success on plasma ctDNA and emerging ctDNA analyses will be discussed.

MS01 IMMUNOTHERAPY RESISTANCE
SUNDAY, SEPTEMBER 8 10:30–12:00

MS01.03 OVERCOMING RESISTANCE - CLINICAL RESULTS?

R. Soo

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The management of oncogene negative advancednon-small cell lunghas been transformed with the use of immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1) and programmed death receptor ligand-1 (PD-L1). However, in a significant number of patients, either primary or acquired resistance has been observed. Primary resistance, usually defined as disease progression upon the first radiologic evaluation, represents an important clinical problem and has been reported in up to 20% of patients. Acquired resistance, defined as tumors with initial response following treatment but eventually develop disease progression, has been reported in approximately 20-40% of patients. The mechanisms of primary and acquired resistance to immunotherapy are complex and are interdependent, involving alterations in immune cells, cytokines, metabolic and oncogene signaling pathways in the tumor cell and the tumor microenvironment. The usual treatment following progression on first line immune checkpoint inhibitor with or without a platinum doublet is single agent docetaxel or a platinum doublet +/- bevacizumab. With an improvement in the understanding of the mechanisms of resistance to immune checkpoint inhibitors, to improve patients' outcomes following resistance, strategies have been devised to tailor subsequent therapy according to the mechanism of resistance, including the use of therapies to increase antigenicity, enhance immune cell function, and modulate the tumor microenvironment.

Keywords: Immune Checkpoint Inhibitors, Resistance mechanisms, overcome of resistance

MS01 IMMUNOTHERAPY RESISTANCE
SUNDAY, SEPTEMBER 8 10:30–12:00

MS01.04 SMOKING AND IMMUNOTHERAPY

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Smoking disrupts the homeostasis of the innate and the adaptive immune system. Carcinogenic and pro-inflammation compounds of tobacco leaves and other chemicals present in cigarette interfere with the regulation of immunity in two opposing ways. Some compounds trigger chronic inflammation inducing cell damage and transformation; others inhibit apoptosis, a protective strategy against transformed cell proliferation. Smoking attenuates response by dendritic cells (DC), natural killer cells (NK), macrophages against transformed cells[1]. Smoking affects as well the adaptive immune cells, B lymphocytes, T helper cells, CD4+ / CD25+ regulatory T cells, and CD8+ T cells.[1] Patients with NSCLC had low levels of serum bilirubin

correlated with tumor progression and poor response to platinum-based chemotherapy[2]. Studies found that high normal levels of serum bilirubin indicated favorable prognosis in NSCLC and colorectal tumor.[3],[4] Bilirubin has anti-inflammatory, anti-oxidative, and anti-proliferative effects[5] and smoking decreased bilirubin in a cohort study using metabolomics profiling.[6] Zhang et al. reported that pretreatment with bilirubin correlated with overall survival (OS) in NSCLC patients with EGFR mutations.[7] Epithelial to mesenchymal transition (EMT) is an important process of cell-transformation that facilitates metastases and smoking induced hypoxia, inflammation, and oxidative stress, culminating in malignancy and EMT.[8],[9] The effect of smoking on EMT also occurs in other cancer histologies. A study showed that the HDAC inhibitor MS-275 restores E-cadherin expression, reversing EMT, metastases, and invasion induced by smoking.[10], [11],[8] Smoking impairs lung cancer chemotherapy, requiring increased doses for patients who smoke. The polycyclic aromatic hydrocarbons (PAH) of smoke increases the synthesis of enzymes that metabolize many antineoplastic drugs. PAH increase clearance, requiring dose adjustments to reach toxicity levels of efficacy.[12] Smokers receiving irinotecan had increased clearance and lower exposure to therapeutic metabolites; and treatments with paclitaxel, docetaxel, irinotecan, and gemcitabine showed lesser neutropenia in smokers than in nonsmokers.[12] Nicotine-derived nitrosamine ketones antagonizes cisplatin and carboplatin regimens by blocking apoptosis.[13],[14],[15] Erlotinib blocks the receptor for tyrosine-inhibiting epidermal growth activation (EGFR) and is metabolized by CYP3A4 and, by CYP1A2 and CYP1A1.[16] Smoking accelerates drug catabolism, decreasing erlotinib plasma concentrations and survival rates in NSCLC. Retrospective analysis of 88 patients NSCLC receiving erlotinib or pemetrexed showed better progression-free survival (PFS) with erlotinib in never smokers than in former smokers (3.5 versus 2.7 months, p = 0.005) [17] and smokers with squamous histology receiving erlotinib lived longer than former smokers.[18] A study on the efficacy of second-line docetaxel and erlotinib in NSCLC patients with smoking history versus never smokers shoed decreased overall survival (hazard ration [HR] 3.61 [1.77–7.4], p = 0.0005) in the erlotinib arm.[19] Nicotine affected *EGFR/AKT/ERK* pathways, preventing/decreasing erlotinib action in NSCLC, promoting tumor growth in the PC9 xenograft model. [20] [1] Qiu F. et al. (2016) Impacts of cigarette smoking on immune responsiveness: up and down or upside down? Oncotarget, 2017, Vol. 8, (No. 1), pp: 268-284. [2] Song Y-J. et al. (2018) Direct bilirubin levels are prognostic in non-small cell lung cancer. Oncotarget, 2018, Vol. 9, (No. 1), pp: 892-900. 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Keywords: smoking, immunotherapy, treatment efficacy

MS02 WHAT MOLECULAR SCREENING FOR WHICH PATIENTS?
SUNDAY, SEPTEMBER 8 10:30–12:00

MS02.01 PLATFORM SELECTION IN AN ERA OF INCREASING NUMBERS AND TYPES OF RELEVANT BIOMARKERS

D. Carbone

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30 years ago, the selection of therapy for lung cancer patients was simple, with only a few choices available, and very little personalization beyond that which can be defined by standard light microscopy and physical exam. The treatment of lung cancer patients today has greatly improved with the discovery of features of tumors and patients that enable the selection of specific targeted and immunotherapy approaches resulting in substantially improved quality and quantity of life. Selection of the appropriate therapeutic based on these features makes huge differences in the lives of these patients, and many studies are now showing that starting with the matched therapy improves survival over switching to it after trying "one size fits all" therapy. Scientific advances are introducing more and more of these markers every year, and while this is undoubtedly a good thing for our patients, each of them has sensitivity, specificity, and platform issues that need to be defined, and adds a level of complexity to lung cancer management that is unprecedented. Individually, many of these features are rare so that the vast majority of individual assays performed are negative, further adding to clinical frustration. Technology has advanced to allow the testing of hundreds or thousands of gene sequences in a single analysis, but other markers are not simple gene sequence alterations, but rather gene rearrangements, protein expression alterations, and some RNA expression profiles that require testing on different platforms. As a result, optimal tumor profiling can involve several different analyses, can cost a significant amount of money, and take a significant amount of time to return a result in a disease where both time and resources available are scarce. Biopsy adequacy also becomes an issue with multi-platform testing, and the availability of blood-based testing lessens this issue for certain types of testing, but introduces issues of limited sensitivity and scope of analyses. Layered upon this are the different health care systems and availability of testing platforms found worldwide, each of which has to make hard decisions about doing the best thing for their patients within these local constraints. However, the impact on patient outcomes and the health care system of missing a key tumor feature and the selection of inappropriate and potentially toxic therapy, in a world where a single dose of a drug costs several times the cost of the testing makes cost of testing less of an issue than sample adequacy, speed of results availability, accuracy of results interpretation, and availability of matching drugs. In this section, the clinical and technical features of the currently available platforms in use and their advantages and disadvantages will be reviewed and compared.

MS02 WHAT MOLECULAR SCREENING FOR WHICH PATIENTS?
SUNDAY, SEPTEMBER 8 10:30–12:00

MS02.02 LIQUID BIOPSY: WHO, WHEN, WHAT AND HOW

C. Rolfo

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Liquid biopsy (LB) refers to a multitude of biomarkers that can be isolated with minimally invasive methods from human body fluids (blood, saliva, urine, ascites, pleural effusion, etc.) that include cell free DNA (cfDNA), circulating tumor cells (CTCs), microRNAs (miRNAs), long non coding RNAs (lncRNAs), and exosomes ( ). Plasma genotyping of cfDNA entered clinical practice in non-small cell lung cancer (NSCLC) for detection of *EGFR*mutations in both treatment-naïve and EGFR-mutated NSCLC after progression to EGFR tyrosine kinase inhibitors (TKIs) as an alternative source to tissue when histological samples are insufficient or when a biopsy is not feasible. Indeed according to the LB IASLC statement[1], plasma cfDNA analysis should be offered to the same population candidate for molecular testing using DNA isolated from tissue (all non-squamous NSCLC subjects, or adenosquamous or in patients with clinical features suggestive of the presence of a molecular driver) in cases with insufficient tumor tissue specimens or where tissue specimens are not obtainable. Moreover, LB is indicated for the identification of acquired resistance mutations in EGFR-mutated NSCLCs progressing during treatment with first- or second-generation EGFR TKIs, reserving tissue re-biopsy in case of negative or inconclusive results. The PCR-based cobas EGFR Mutation Test v2 was the first FDA approved LB test for NSCLC, although several limitations on sensitivity of this technique. Fortunately, LB is a rapidly evolving field and several commercial and *"in house"*NGS platforms have been developed, allowing a more comprehensive plasma genotyping that include genetic rearrangements (such as ALK, ROS1, RET, and NTRK) as well as other relevant oncogene drivers, including mutations of BRAF, HER2, MET, and KRAS. Some of the vendors have a Medicare reimbursement in United States. Recently, the multicenter prospective Noninvasive versus Invasive Lung Evaluation (NILE) study demonstrated that a validated and highly sensitive plasma 73-gene NGS test (Guardant360) used at the time of diagnosis of NSCLC was non-inferior to standard-of-care tissue genotyping in identifying guideline-recommended genomic biomarkers, allowing a guideline-complete genotyping in a higher proportion of patients with a shorter median turnaround time[2]. These results support the rationale for a *"blood-first"* approach, reserving tissue for PD-L1 immunohistochemistry or in case of negative liquid biopsy testing. In addition to cfDNA, cfRNA is a novel approach to enhance the comprehensive analysis of circulating biormakers. Furthermore, the increasing use of more sensitive detection methods, such as NGS, poses novel technical and biological challenges in our clinical practice, including the identification of non tumor-related mutations due to clonal hematopoiesis (CH), increased risk of false positive in presence of low variation allelic fraction (VAF), need for standardization and validation of the analytical methods, definition of requirements for appropriate report and interpretation of the results. Novel technologies such as CH-filtering ultradeep NGS have been tested with promising results[3]. Moreover, the adoption of molecular tumor board is essential for helping oncologists in interpreting NGS testing results[4], using evidence-based scales, such as OncoKB and ESCAT tiers[5,6]. Recently, LB use has been advocated in immunotherapy-treated patients as a minimally invasive method that can allow a real time monitoring of treatment response and interpretation of challenging radiographic situations, overcoming the limits of conventional radiological assessment methods[7,8]. Further prospective studies are needed to better clarify the role of cfDNA as a predictive biomarker for immune checkpoint blockage in NSCLC. LB can also allow the estimation of tumor mutational burden (TMB) in plasma, proving a valuable alternative to tissue. Exploratory analyses of two large randomized phase III studies explored the potential utility of blood TMB (bTMB) as predictive biomarker for immunotherapy, using two different platforms (Foundation Medicine and GuardantOMNI)[9,10]. The results of these studies support bTMB as potential biomarker for immunotherapy in NSCLC. Further prospective studies will clarify the role of bTMB in treatment selection of patient candidate for immunotherapy, as well as the optimal cut-off value, the minimum number of genes necessary for TMB estimation, and the specific mutations useful. Rolfo C, et al. J Thorac Oncol 2018 Leighl N, et al. Clin Cancer Res 2019 Li BT, et al. Ann Oncol 2019 Rolfo C, et al. ESMO Open 2018 Chakravarty D, et al. JCO Precis Oncol 2017 Mateo J, et al. Ann Oncol 2018 Anagnostou V, et al. Cancer Res. 2019 Guibert N, et al. ASCO-SITC 2019 Peters S, et al. AACR Annual meeting 2019 Gandara DR, et al. Nat Med 2018

Figure 1Liquid biopsy in NSCLC – Who, When, What and How? (*Credit: created with BioRender*)

Keywords: Liquid Biopsy, cfDNA, NGS

MS02 WHAT MOLECULAR SCREENING FOR WHICH PATIENTS?
SUNDAY, SEPTEMBER 8 10:30–12:00

MS02.03 ACHIEVING EFFECTIVE LUNG CANCER GENOTYPING WHILE BALANCING CONSTRAINED RESOURCES

L. Sholl

Brigham and Women's Hospital, Boston/United States of America

Modern oncologic practice for patients with non-small cell lung carcinoma (NSCLC) demands real time data for an increasing numbers of tumor biomarkers. As a result, laboratories are embracing panel-based approaches to tumor molecular profiling, a trend that is facilitated by the adoption of next generation sequencing (NGS) assays. NGS assays may be designed for highly sensitive and focused detection of hotspot mutations (typically by amplicon sequencing) or broader, more comprehensive profiling for detection of a wide variety of alterations in oncogenes and tumor suppressor genes (typically by hybrid capture technology). There are benefits and drawbacks to both approaches. In general, amplicon sequencing offers speed and sensitivity but limited scope and a propensity for PCR-related artifacts that may adversely affect detection of certain mutation types. In contrast, hybrid capture techniques offer tremendous breadth, enabling capture of 100s of genes to whole genomes, but are limited by sensitivity and longer turnaround time.[1] Preanalytic steps including sample acquisition, pathologist review to confirm sample adequacy, and nucleic acid extraction often comprise the majority of the turnaround time required to complete focused tumor tissue molecular profiling. Some assays have been optimized for turnaround times of just a few hours- these assays bypass the separate nucleic acid extraction step, [2] but are limited by the few number of mutational targets detected, ultimately requiring the use of multiple simultaneous or sequential focused panels.[3] This practice, while perhaps the optimal current model from the standpoint of patient care, may be financially prohibitive for many laboratories. This approach additionally requires careful stewardship of patient tissues, as the use of multiple competing assays and may lead to exhaustion of tumor tissue and incomplete tumor molecular profiling. For patients with limited tissue, a considered plan incorporating input from the treating physician, surgical pathologist, and molecular laboratorian should developed early in order to guide assay priority and ensure adequate tissue is available to confirm any unexpected or contradictory results. When the turnaround time for comprehensive large panel testing is clinically acceptable, this approach may be theoretically more cost effective and in most cases will deliver information for essential and emerging biomarkers.[4] It is important to keep in mind, however, that even comprehensive DNA-based assays may lack optimal sensitivity for certain structural variants (fusions, large insertion-deletion events), and it may be necessary to couple these tests with focused RNA-based panels optimized for transcript fusion detection.[5] 1. Rizzo JM, Buck MJ. Key principles and clinical applications of "next-generation" DNA sequencing. Cancer Prev Res (Phila). 2012;5(7):887-900. 2. Ilie M, Butori C, Lassalle S, et al. Optimization of EGFR mutation detection by the fully-automated qPCR-based Idylla system on tumor tissue from patients with non-small cell lung cancer. Oncotarget. 2017;8(61):103055-103062. 3. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing

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Keywords: amplicon sequencing, hybrid capture, turnaround time

MS02 WHAT MOLECULAR SCREENING FOR WHICH PATIENTS?
SUNDAY, SEPTEMBER 8 10:30–12:00

MS02.04 THE ROLE OF MOLECULAR BOARD

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The Role of Molecular Board Lung Tumor Board is a multidisciplinary group of specialists who are responsible for diagnosing and deciding the best treatment for a patient with lung cancer. In cancers with little to no metastatic evidence, the case is handed over to surgeons or sometimes to radiotherapists for local and curative treatment. But in cases of locally advanced or metastatic stages, the patient visits the oncologist alone or in conjunction with the radiotherapists for a more systemic approach. A few years ago, the patient was presented to tumor board immediately, but now because we are in the age of precision medicine, the oncologist can gather more information about the tumour itself to initiate the best personalized treatment for each patient's cancer. In fact, the oncologist requires 3 types of information: accurate histological diagnosis, molecular characteristics of the tumor, and PD-L1 expression. Prior to the creation of this molecular tumor board, this information could be given by mail, mobile phone messaging, phone call or in person, since all the information usually arrives a few days after the patient is presented at Lung Tumor Board. If all this information is presented in a room with all the specialists involved in obtaining it, the data can be better analysed and the therapeutic decision making will be much more precise. Hence the idea of creating a MTB with oncologists, pathologists, biologists, bioinformatics, technicians, palliative care, and residents to review the different results for a lung cancer patient. The type of patients to present in this type of Molecular Tumour Board is widely variable, but usually fall into one of these 6 categories: 1) Newly diagnosed patients with metastatic disease. The MTB would reaffirm that there is sufficient material and that all the molecular or immunohistochemical techniques are underway (EGFR, BRAF, ALK, ROS1, and PD-L1). Oncologists re-assign the patient for the next MTB to review final results. The pathologist also comments on the percentage of tumour cellularity, so that technicians and biologists can make optimized calculations of the cuts and the type of sample that the biologist has to work with (biopsy and/or cell block and/or cytological smears). 2) Patients with progressive disease with a known molecular marker. They can be patients where the oncologist repeats sampling. Usually the patient is more familiar to the biologist because he receives liquid biopsies to monitor the disease and the pathologist only knows the patient if he has a re-biopsy. 3) Patients with possible disease progression, pseudoprogression or hyperprogression after immunotherapy. 4) Patients with molecular results received from outside (FM, FOne, clinical trials) The patient is more familiar to the oncologist who treats him and who has decided to send a sample for a clinical trial or external platform. They are presented in the MTB in order to reaffirm the mutation or translocation found with technology available in the center or maybe it can be consulted outside. 5) Surgical patients with multiple adenocarcinomas that require definitive staging. The patient is most familiar to the pathologist who diagnosed the surgical tumor. They are presented in order to know molecular details of multiple synchronous tumours. 6) Patients that wish to utilize stored material for new diagnostic studies/techniques For reasons of disease progression, the patient may enter a clinical trial or has the option of systemic treatment, so some studies that were not previously performed in are required.

Keywords: Molecular Tumor Board, Pathologist, biomarkers

MS03 WORKUP AND MANAGEMENT OF SMALL ANTERIOR MEDIASTINAL MASSES/LESIONS
SUNDAY, SEPTEMBER 8 13:30–15:00

MS03.01 DIFFERENTIATION OF SMALL ANTERIOR MEDIASTINAL LESIONS USING IMAGING

E. Marom

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Mediastinal masses are relatively uncommon in the general population and no specific algorithm exists for the evaluation and diagnosis of these lesions. Most mediastinal masses occur in the anterior, or prevascular compartment and these lesions demonstrate tremendous heterogeneity in clinical and pathologic features. The selection of laboratory tests, whether to perform a biopsy, immediate surgery, follow-up imaging or order further imaging investigation varies between medical disciplines, and patients' clinical features. The use of CT has grown exponentially over the last decade. This has led to an increasing amount of incidental prevasscular mediastinal lesions encountered, often smaller than those encountered in symptomatic patients. There is no agreement as to what defines a mediastinal lesion as 'small'. For the radiologist, this usually constitutes a lesion, which is too small to characterize, perhaps smaller than 1cm. For the surgeon, this may be a lesion, which could be approached with minimally invasive surgery, or perhaps a lesion which one may suspect is benign. When dealing with the incidental prevascular lesion, the most important role for the radiologist is to correctly identify a "no touch lesion": a benign lesion or normal variant that should not be treated. The second task the radiologist must face is diagnose correctly a lesion or at least narrow the differential to tailor the diagnostic approach causing minimal harm in the process. The imaging modality of choice for identifying, localizing, and characterizing most mediastinal masses is CT. Most clinicians and radiologists are most familiar with this imaging modality and it has the ability to accurately locate, identify densities such as fat, bone, calcification and fluid. There are some prevascular mediastinal lesions that have a pathognomonic appearance on CT, which may obviate the need for a biopsy, such as goiter, mature teratoma or thymolipoma. However, CT has two major drawbacks: it does expose individuals to a relatively large amount of ionizing radiation, and it is not as good as MRI in tissue characterization. Thus, when a prevascular lesion measures as fluid, it is sometimes difficult to identify nodular thickening within the fluid to distinguish a benign cyst for example, from a cystic thymoma. Similarly, cysts may seem solid on CT. Proteinaceous cyst, when measured by CT, have Hounsefield Units, which measure as soft tissue rather than fluid. MRI overcomes these issues, with its better contrast resolution. MR imaging is not routinely performed to evaluate all mediastinal masses; however, it is the best modality for distinguishing cystic from solid masses (e.g., thymic cysts from solid tumors), identifying cystic and/or necrotic components within solid lesions, demonstrating septations and/or soft tissue within cystic lesions, and distinguishing thymic hyperplasia and normal thymus from soft tissue tumors. Tissue characterization, whether using CT or MRI, relies on visible assessment or measuring the density/intensity of the lesion. When a tissue is measured, a region of interest (ROI) is placed in the lesion. For the measurement to be accurate, the ROI should include more pixels, should be about 1cm in diameter and not include soft tissue around the lesion. It is because of this, that in small lesions, smaller than 1cm, the density/intensity cannot be accurately measured. Another example is the use of MRI to distinguish thymic hyperplasia from a soft tissue malignancy. The MRI chemical shift sequence shows a signal drop when fat and soft tissue abut each other. This causes the fat-soft tissue interface to appear as a dark linear outline on this sequence. Since thymic hyperplasia contains a combination of fat and soft tissue, there is a signal drop in thymic hyperplasia using this sequence, not seen with other masses in the prevascular mediastinum. However, when a soft tissue lesion in the prevascular mediastinum is too small, chemical shift imaging is not useful. The periphery will drop out due to the soft tissue interface with the surrounding mediastinal fat, leaving insufficient amount of tissue centrally for investigation. Positorn emission tomography (PET) integrated with CT using fluorodeoxyglucose as the isotope, is commonly used in staging different malignancies. Its role however in differentiating benign from malignant masses is limited. That is because some benign entities, such as thymic hyperplasia may be FDG avid, whereas some malignancies, such as some types of thymoma, are sometimes not FDG avid. Also, the FDG uptake of commonly encountered malignancies in the prevascular mediastinum is high, so that it is impossible to distinguish between them. For example thymic carcinoma, paraganglioma and non-seminomatous germ cell tumor show similar FDG uptake. In addition, the spatial resolution of PET is

low, much lower than CT or MRI so that small lesions, those smaller than 1cm, are not accurately assessed by this modality. We will review the imaging approach to the incidentally discovered, usually small, prevascular mass. How to identify the 'no touch lesion', when to order additional imaging and which imaging modality to select in order to prevent futile surgery.

MS03 WORKUP AND MANAGEMENT OF SMALL ANTERIOR MEDIASTINAL MASSES/LESIONS
SUNDAY, SEPTEMBER 8 13:30–15:00

MS03.02 RESECTION, BIOPSY OR OBSERVATION OF SMALL ANTERIOR MEDIASTINAL LESIONS

F. Detterbeck

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With greater prevalence of CT scanning for many reasons, the incidental detection of a prevascular lesions has increased markedly. 3 sources of data show the incidence to be around 0.5-1% in asymptomatic adults. There is no accepted standard for how to manage these patients, and until recently there was little data to base an approach on. Recently, examination of scans done for lung cancer screening provide some answers. The majority of these lesions have CT characteristics that are consistent with a thymic epithelial tumor (TET). However, the vast majority are stable over a median follow-up of approximately 5 years. While a minority exhibit growth, on further observation most of these do not continue to grow or decrease in size. It is well documented that thymic cysts and other benign lesions sometimes grow slightly. The overall incidence of a malignancy is around 2%. Even after a prolonged period of observation, when resection is undertaken for a TET, the vast majority are stage I (8th edition of TNM) and there have been no recurrences over a median follow up of approximately 5 years. This has been the case even with thymic carcinoma. In summary, simple observation of incidentally discovered prevascular lesions appears to be safe, without losing a window for intervention in the small percentage of patients that need this.

Keywords: thymic epithelial tumor, prevascular lesion, TET

MS03 WORKUP AND MANAGEMENT OF SMALL ANTERIOR MEDIASTINAL MASSES/LESIONS
SUNDAY, SEPTEMBER 8 13:30–15:00

MS03.03 MINIMALLY INVASIVE SURGICAL STRATEGIES AND CONSIDERATIONS FOR SMALL ANTERIOR MEDIASTINAL LESIONS

B. Weksler

Allegheny Health Network, Pittsburgh/United States of America

Minimally Invasive Surgical Strategies and Considerations for Small Anterior Mediastinal Lesions Thymomas are the most common anterior mediastinal masses. These are slow growing relatively indolent tumors that are often curable with surgical resection. Thymomas are often detected in asymptomatic patients who had a computed tomography of the chest for other reasons. Until recently, the surgical standard of care for curative surgery was resection of the thymus en-bloc with the mass through an open sternotomy. Advances in video surgery have allowed resection of the thymus and the anterior mediastinal masses through small incisions. Currently, there are multiple minimally invasive approaches to the anterior mediastinum, including thoracoscopy though the chest wall, thoracoscopy through a subxiphoid incision, and robotic assisted thoracoscopy. Although data comparing the techniques is sparse, there is no reason to believe that one has oncologic or survival advantages over the other. Data comparing minimally invasive approaches with open approaches have shown better short-term outcomes such as postoperative complications and blood loss, and similar long-term survival. Several authors have questioned the need for a complete thymectomy in patients with small anterior mediastinal lesions, hence the term thymomectomy. Thymomectomy involves the removal of the thymoma only, with margins around it, but without a formal complete thymectomy. Data comparing complete thymectomy with thymomectomy is sketchy and likely unreliable. Another area of intense investigation is the role of nodal dissection or sampling in the surgical management of thymomas. Data from multiinstitutional database suggests that the incidence of nodal metastases is higher than previously thought. Although data is lacking, removal of enlarged nodes, or sampling of nodes in the anterior mediastinum is likely indicated. In summary, small anterior mediastinal masses can be removed using minimally invasive techniques. The need for complete thymectomy, and nodal sampling are areas of investigation. Until more data is available, complete thymectomy with nodal sampling appears prudent.

Keywords: THYMOMA, minimally invasive surgery, Robotic Surgery

MS03 WORKUP AND MANAGEMENT OF SMALL ANTERIOR MEDIASTINAL MASSES/LESIONS
SUNDAY, SEPTEMBER 8 13:30–15:00

MS03.04 FOLLOWUP/SURVEILLANCE OF SMALL ANTERIOR MEDIASTINAL LESIONS

W. Fang

Shanghai Chest Hospital, Shanghai/China

With increasing popularity of CT screening for early stage lung cancers, there is a tendency toward increased detection of small anterior mediastinal nodules. However, work-up and management strategy for such incidentally found small mediastinal lesions remains to be established. During 2013-2018, 415 patients with incidentally found small anterior mediastinal mass less than 3 cm in diameter were retrieved from a prospectively kept database at the Division of Mediastinal Surgery, Shanghai Chest Hospital. A marked increase was seen in the annual number of such cases detected (Figure 1). MRI was used in addition to CT scan for differential diagnosis in 413 cases. The other 2 patients could not receive MRI because of metal implantation at previous surgery. Eight-nine patients received surgery, 82 (92.1%) of them turned out to have thymic epithelial tumors (Table). Among thymic tumor patients, 36 had a follow-up history for a median of 18 months, and 27 (75%) of the lesions increased in size. Thymic carcinomas and neuroendocrine tumors enlarged more rapidly than type B2/B3 thymomas, and the latter more rapidly than type A/AB/B1 tumors (Figure 2). Two of the seven thymic carcinomas were upstaged to UICC T3 lesions, and nodal involvement was found in two thymic carcinoma and one atypical carcinoid patients. The other 33 tumors were all in UICC stage Ia. Seven patients turned out to have bronchogenic cysts (3) or thymic cysts (4). None of them had follow-up history and 5 of them received surgery because of MR suspected thymomas. Thus the accuracy of MRI for diagnosing thymic tumors was 94.1% (80/85). Three-hundred-twenty-six patients are still under follow-up, 311 of them were diagnosed of having benign lesions (cysts, hyperplasia, lymph nodes) by MRI. With a median follow-up of 33 months, none but one MRI diagnosed cyst increased by 0.3 cm after 3 years. Two MRI diagnosed cystic and two hyperplasic lesions decreased in size during follow-up. Thirteen patients with MRI diagnosed clinical stage I thymomas refused surgery. Only two of the lesions increased in size by 0.2-0.3 cm after 2 years (Table). In conclusion, MRI is highly useful in differential diagnosis of small anterior mediastinal lesions. Follow-up could be safely recommended for those MRI diagnosed benign lesions. Table. Change in size during follow-up for small anterior mediastinal lesions.

Diagnosis	Patient (Number)	Size (Mean, cm)	Follow-up (Median, month)	Size (+) (Number)	Size (-) (Number)
Surgery (TET)	36	2.4	18	27	0
AB	11	2.4	36	2	0
B	11	2.5	12	4	0
Ca	7	2.3	24	6	0
NETT	3	2.3	15	3	0
Metaplastic	2	1.1	36	2	0
Micronodular	2	2.1	5	0	0
No surgery	326	2.2	33	3	4
TET	13	1.5	18	2	0
Cyst	267	2.3	36	1	2
LN	24	1.2	24	0	0
Hyperplasia	22	2.4	24	0	2

Figure 1. Increasing incidence of incidentally detected small anterior mediastinal lesions at Shanghai Chest Hospital.

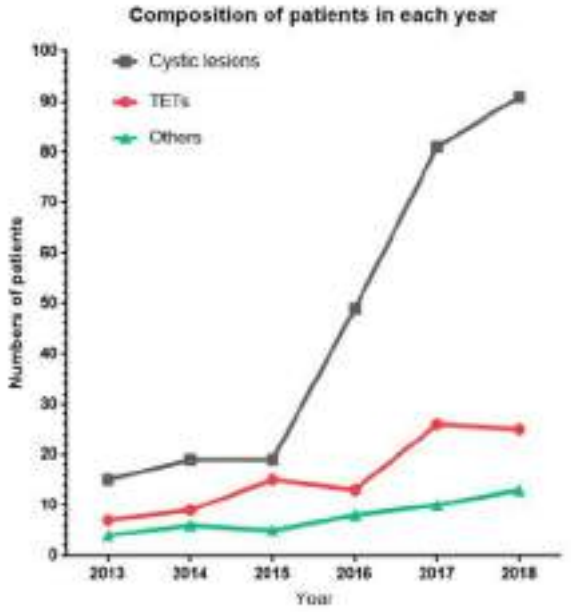
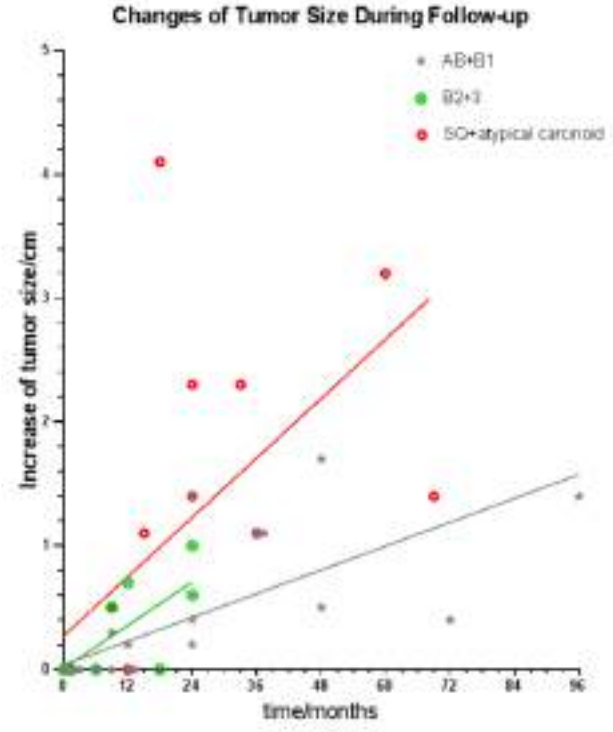


Figure 2. Trends of increase in size during follow-up in different subtypes of thymic epithelial tumors.



Keywords: MRI, mediastinum, Follow-up

MS03.05 RELEVANCE OF NODAL INVOLVEMENT AND THE THYMIC LYMPH NODE MAP

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Thymic epithelial tumors (TET) including thymoma, thymic carcinoma, and thymic neuroendocrine tumors are rare cancers, accounting for less than 1% of all tumors. No official staging system was defined by the Union Internationale Contre le Cancer and the American Joint Commission on Cancer (AJCC) until 2017. This led to several proposals being published over the years, but few received clinical validation. Unlike lung cancer, where regional spread through the lymphatics has been proved, most common patterns of recurrence in TET are local failure, or dissemination into the pleural or pericardial spaces. Therefore, the role of additional intraoperative nodal assessment is uncertain in TET, for which total thymectomy is the standard procedure. Lymph node metastasis in TET is more common with thymic carcinoma. Kondo et al. reported in their retrospective study (n=1320) that lymphogenous spread with or without distant metastasis was found in 3.2% of thymomas, and more commonly in 33% of thymic carcinomas.[1] In particular, anterior mediastinal lymph nodes were thought to be the primary drainage location for TET. Anterior mediastinal lymph nodes were involved in approximately 90% of thymomas, 70% of thymic carcinomas, and 90% of thymic neuroendocrine tumors with lymph node metastasis. Furthermore, a cadaveric study found that the anterior mediastinal nodes are the primary drainage basin and the intrathoracic lymph node group are secondary.[2] In 2017, the first TNM classification of TET was announced in the 8thedition of the AJCC Cancer Staging Manual, based on proposals made through a collaboration between IASLC and ITMIG.[3] A new N category was presented based on the lymph node drainage pattern found in anatomic studies and international databases. Prominent nodes defined by anatomic studies are included as regional nodes in the lymph node map (Table 1).[2] In addition, the IASLC lymph node map of lung cancer and AAO-HNS/ASHNS node map were referenced to define boundaries. This new N category classifies the node involvement into three groups according to a region-based system: N0, N1 (anterior region: anterior mediastinal and anterior cervical nodes), and N2 (deep region: middle mediastinal and deep cervical nodes) (Fig. 1). However, this classification is limited by the fact that the amount of data included was too limited to determine statistical significance.[2,4,5] Although the first official N category has been published, controversy still remains over the lymph node involvement in TET. The prognosis with nodal metastasis is clearly poor, but the clinical significance of the criterion dividing the current N1, and N2 groups is uncertain. Moreover, the treatment strategy according to each stage is not yet fully defined. ITMIG recommends removal of anterior mediastinal nodes at the time of resection for thymoma.[6] This fits into the generally accepted definition of an extended thymectomy which includes anterior mediastinal nodes. For locally advanced thymomas (Masaoka stage III or IVA) and thymic carcinoma, a systematic removal of intrathoracic nodes is encouraged (i.e., those corresponding to the deep region). However, for minimally invasive surgery, which is currently in widespread use, the extent and level of lymph node removal should be discussed further. It also remains to be determined whether different treatment strategies should be adopted according to the histological classification of thymomas, as well as whether it is appropriate to apply the same staging for the different TET pathological entities (i.e. thymoma, thymic carcinoma, and thymic neuroendocrine tumor). Therefore, the current official staging system will play a major role in settling these debates through collection from appropriate databases under uniform definitions. Further research is needed to establish the relevance of the node map, the prognostic role of nodal involvement, and the clinical implications of node dissection. Reference 1. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. *Ann Thorac Surg.* 2003;76(6):1859–64 2. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol.* 2014;9(9):S88–S96. 3. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York:*Springer*; 2017 4. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for

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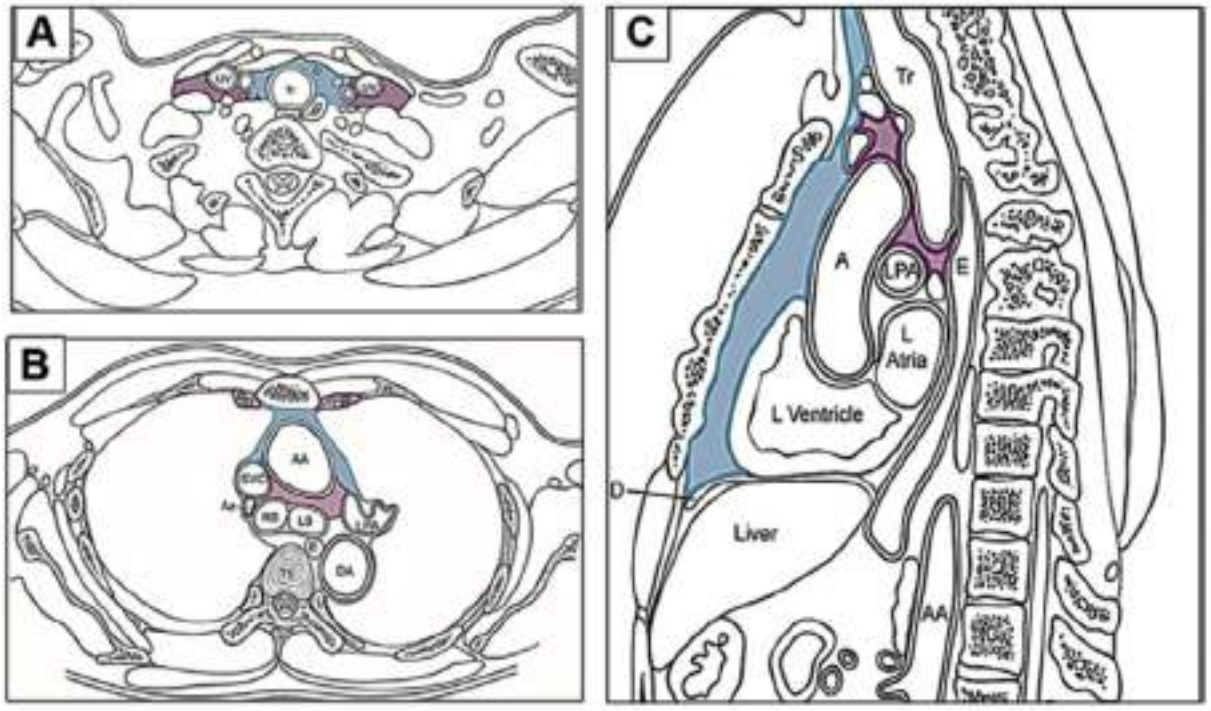

	Region Boundaries	Node Groups*
N1: Anterior Region	*Superior:* hyoid bone *Lateral (neck):* medial border of carotid sheaths *Lateral (chest):* mediastinal pleura *Anterior:* Sternum *Posterior (medially):* great vessels, pericardium *Posterior (laterally):* phrenic nerve *Inferior:* Xiphoid, diaphragm	Low anterior cervical: pretracheal, paratracheal, peri-thyroid, precricoid/delphian Peri-Thymic Prevascular Para-aortic, Ascending Aorta, Superior Phrenics Supradiaphragmatic / Inferior Phrenics / Pericardial
N2: Deep Region	*Superior:* Level of lower border of cricoid cartilage *Anteromedial (neck):* lateral border of sternohyoid, medial border of carotid sheath *Posterolateral (neck):* anterior border of trapezius *Anterior (chest): Right* – Anterior Border of SVC; *Left* – aortic arch, aortopulmonary window *Posterior (Chest):* Esophagus *Lateral (chest):* pulmonary hila *Inferior:* Diaphragm	Lower Jugular Supraclavicular/venous angle: confluence of internal jugular & subclavian vein Internal Mammary nodes Upper Paratracheal Lower Paratracheal Subaortic / Aortopulmonary Window Subcarinal Hilar

*Region and node group boundaries match those established by the American Academy of Otolaryngology - Head and Neck Surgery, American Society for Head and Neck Surgery, and the International Association for the Study of Lung Cancer where applicable.
SVC, superior vena cava

Keywords: staging, lymph node, THYMOMA

MS04 NEW SYSTEMIC ADJUVANT/NEO-ADJUVANT STRATEGIES IN EARLY STAGE LUNG CANCER: TARGETED THERAPY AND I/O
SUNDAY, SEPTEMBER 8 15:15–16:45

MS04.01 EGFR TKIS FOR RESECTED EGFRMUT NSCLC

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Adjuvant chemotherapy became the standard treatment for resected stage 2-3 non-small cell lung cancer (NSCLC). It increased overall survival (OS) by 5% at 5 years, and resected NSCLC was considered "curable disease." Stage II to IIIA resected NSCLC is heterogeneous. The 5-year survival was only 40% -50%. There is a huge medical need to improve the long-term survival for these patients whose cancers are destined to recur after surgery. BR.19, the first trial to evaluate an EGFR TKI (gefinitib) in the adjuvant setting, and the subsequent RADIANT trial, which compared erlotinib to placebo, were not designed specifically for patients with *EGFR* mutations. Thus, these two adjuvant TKIs failed to show meaningful benefits.[1,2] The ADJUVANT trial, first randomized phase 3 trial compared gefitinib with doublet chemotherapy for stage 2 and 3 (N1N2) resected EGFR mutant NSCLC. The results showed that adjuvant gefitinib significant improved disease-free survival (DFS). HR for recurrence was 0.60 with 28.7 months in gefitinib vs 18.0 months in chemotherapy[3]. Subsequently the EVAN -- another Chinese phase 2 trial confirmed that adjuvant erlotinib was superior to chemotherapy in DFS[4]. SELLECT trial from American once again confirmed that adjuvant EGFR TKI improved DFS[5]. The both Chinese adjuvant trials targeted the patients with the highest risk of recurrence and are more likely to respond to EGFR TKIs in patients harboring an *EGFR* mutation. Unlike BR.31 and RADIAN EGFR TKIs were used following adjuvant chemotherapy. the ADJUVANT trial was a direct comparison of adjuvant TKIs with Vinorelbine plus cisplatin instead of comparing TKIs with placebo after chemotherapy, as evaluated in the BR.19 and RADIANT trials. Compliance with adjuvant TKIs (95.5%) was better than that with chemotherapy (78.4%) in ADJUVANT trial. This means that patients receiving adjuvant TKIs were more likely to complete treatment than patients receiving standard chemotherapy. The design of ADJUVANT is different from RADIANT, and the hypothesis of the two trials designs is different. The ADJUVANT study was created to test whether an EGFR TKI might be a viable treatment alternative to chemotherapy in the adjuvant setting, specifically in EGFR mutant (+) NSCLC. In this situation, using DFS as the primary endpoint was rational. The U.S. Food and Drug Administration has stated that a prolonged delay in the development of metastatic disease is an objective and a clinically relevant outcome and that agents can be approved based on metastasis-free survival (MFS) if substantial effects on this endpoint are demonstrated and the safety profile is acceptable.[6] In addition, after adjuvant gefitinib or erlotinib, patients with disease recurrence still have the opportunity to be re-challenged with TKIs. And the median duration of treatment approximates the DFS in a de novo advanced *EGFR*-mutant population.[7] Recently Zhong et al reported a phase 2 trial on neo-adjuvant setting for EGFR mutant stage 3A resectable NSCLC. Of 386 patients screened, 72 were randomized to treatment. The ORR for neoadjuvant erlotinib versus GC chemotherapy was 54·1% versus 34·3% (p=0·092). pCR was 10·7% vs 0. Median DFS was significantly longer with erlotinib (21·5 months) versus GC chemotherapy (11·9 months; HR 0·42; 95% CI, 0·23–0·76; p=0·003)[8]. The results of neo-adjuvant EGFR TKI treatment in CTONG 1103 was similar to adjuvant EGFR TKI in CTONG 1104. The difference of DFS comparing with chemotherapy in both trials are 10 months. Definitely EGFR TKIs could be safely and effectively used in early resected NSCLC. The treatment paradigm for early resectable NSCLC is evolving. Similar to advanced NSCLC early stage NSCLC should be divided to driver mutation or wild type NSCLC. For wild NSCLC check point blockade should be tested in peri-operation. For driver mutation NSCLC TKIs including EGFRi or ALKi even other rare mutation should be tested. Some issues should be evaluated. One issue is how to select populations more precisely for adjuvant or neo-adjuvant treatment. Whether circulating tumor DNA (ctDNA) could serve as biomarker of minimal residual disease (MRD) and how to monitor it[9]? Second issue is what is the primary endpoint for neo-adjuvant or adjuvant treatment in NSCLC? Apparent OS is rational but the trial will last a long time even beyond 10 years. The third issue is how to choose neo-adjuvant or adjuvant treatment for recectable NSCLC either clinical trial or clinical practice. For personalized adjuvant treatment in the future, we need to identify patients precisely and match the appropriate treatment with appropriate patient. 1. Goss GD, O'Callaghan C, Lorimer I, et al. 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MS04 NEW SYSTEMIC ADJUVANT/NEO-ADJUVANT STRATEGIES IN EARLY STAGE LUNG CANCER: TARGETED THERAPY AND I/O
SUNDAY, SEPTEMBER 8 15:15–16:45

MS04.02 NEO-ADJUVANT PD-(L)1 CHECKPOINT INHIBITORS

L. Raez

Memorial Cancer Institute/Florida International University, Pembroke Pines/ United States of America

Neoadjuvant chemotherapy never made to become standard of care for non-small cell lung cancer (NSCLC) and until today it is being used in special circumstances. However neoadjuvant immunotherapy as single agent or in combination with chemotherapy has become a very promissory intervention. In 2018 we had the publication from Forde et al in the NEJM showing that using nivolumab as neoadjuvant approach did not delay surgery in any of the treated patients (pts) and there were no unexpected safety signals were seen. Very interesting 45% of resected tumors demonstrated a major pathologic response (MPR) that correlated with mutational burden. MPR was defined as less than 10% viable tumor in the resected specimen [1]. Following these results there were also several presentations at ASCO 2018: The LCMC study Rusch et al [2] (treats pts with atezolizumab for 2 cycles follow by surgery then standard of care chemotherapy follow by immunotherapy for 1 year) showed 4/19 (21%) pts had MPR after 2 doses of atezolizumab. Shu et al (Abstract 8532) showed that 4 cycles carboplatin/nab-paclitaxel/atezolizumab had 7/14 (50%) pts with MPR and 3/14 (21%) had pCR. [3] Later at the 2018 World lung Cancer Conference in Toronto in September, we have had the Spanish Lung Cancer Group presenting the study NADIM by Provencio-Pulla that was briefly presented before at ASCO 2018 [4,5]. They had a phase II open label study for patients with stage IIIA NSCLC that received carboplatin/paclitaxel/nivolumab for 3 cycles follow by surgery and adjuvant immunotherapy for 1 year. The CR was 10%, PR 60% and SD 30% for a DCR of 100%. MPR was 80% and complete response 75%. The toxicity profile was tolerable and not unexpected. During the same meeting Rusch [6] did an updated of the LCMC study this time with 45 pts: the ORR was 10% and the DCR 100%. 22% of the pts had MPR. There was no observable correlation between pathologic and radiographic responses. Neoadjuvant atezolizumab did not cause major delays to surgery or interfere with surgical resection, and there were no unexpected safety findings. There was also a poster presentation of the CheckMate 816 [7]: Phase 3 Neoadjuvant Trial of Chemotherapy with and without nivolumab for stage I-IIIA NSCLC presented by Enriqueta Felip with 21 pts in the nivolumab arm that have 10% CR and 45% MPR. Following this success from 2018 at this year in ASCO 2019 there will be 2 important presentations

Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): the NEOSTAR study for pts with stage I-IIIA [8] and another updated of the LCMC study that is expected to showed data with larger number of pts [9]. There are also several studies with targeted agents for NSCLC that will be presented at 2019 World Lung Cancer Conference where we will have the opportunity to review the updates of some of the studies mentioned before and new ones. References: 1) Forde PM1, Chaft JE1, Smith KN1, et al. 1. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer.N Engl J Med. 2018 May 24; 378(21):1976-1986. doi: 10.1056/NEJMoa1716078. Epub 2018 Apr 16. 2) Rusch, Valerie et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Initial results from a multicenter study (LCMC3) J Clin Oncol 36, 2018 (suppl; abstr 8541) 3) Catherine A. Shu, Claud Grigg, Codruta Chiuzan, Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). J Clin Oncol 36, 2018 (suppl; abstr 8532) 4) Provencio-pulla et al. Neoadjuvant chemo/immunotherapy for the treatment of stages IIIA resectable non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study—NADIM study-SLCG. J Clin Oncol 36, 2018 (suppl; abstr 8521) 5) M. Provencio, E. Nadal, A. Insa, R. et al. OA01.05 Phase II Study of Neo-adjuvant hemo/Immunotherapy for Resectable Stages IIIA Non-Small Cell Lung Cancer- Nadim Study-SLCG Journal of Thoracic Oncology, Vol. 13, Issue 10, S320 6) V. Rusch, J. Chaft, B. Johnson, et al. MA04.09 Neoadjuvant Atezolizumab in Resectable Non-Small Cell Lung Cancer (NSCLC): Updated Results from a Multicenter Study (LCMC3) Journal of Thoracic Oncology, Vol. 13, Issue 10, S369 7) E. Felip, J. Brahmer, S. Broderick, et al. P2.16-03 CheckMate 816: A Phase 3 Trial of Neoadjuvant Nivolumab Plus Ipilimumab or Chemotherapy vs Chemotherapy in Early-Stage NSCLC 8) Tina Cascone et al., Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study.J Clin Oncol 37, 2019 (suppl; abstr 8504)8) 9) Rusch V et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 37, 2019 (suppl; abstr 8503)

Keywords: neoadjuvant, Immunotherapy, Lung cancer

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MS04 NEW SYSTEMIC ADJUVANT/NEO-ADJUVANT STRATEGIES IN EARLY STAGE LUNG CANCER: TARGETED THERAPY AND I/O
SUNDAY, SEPTEMBER 8 15:15–16:45

MS04.03 ADJUVANT PD-(L)1 CHECKPOINT INHIBITORS

J. Hellyer, H. Wakelee

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Advances in adjuvant therapy for early stage, resectable, non-small cell lung cancer (NSCLC) have been slow for many years. Four cycles of post-operative platinum-based chemotherapy remains the standard of care in most of the world, yet this confers a survival benefit of only ~5% at 5 years.[1] Early efforts to stimulate adaptive immunity to prevent tumor recurrence via several immunologic interventions including antigen specific cancer vaccines, Bacillus Calmette-Guerin (BCG), adoptive cell transfer and tumor-infiltrating lymphocytes failed to show a benefit in overall survival in a meta analysis of the early trials[2,3] In 2018 though positive results from the PACIFIC trial ushered in a new era of immunotherapy with PD-L1 checkpoint blockade in non-operable, stage III non-small cell lung cancer (NSCLC) and established consolidation durvalumab following chemoradiation as the new standard of care.[4] These data provided further enthusiasm for ongoing trials of checkpoint inhibitors in early stage, surgically resectable disease. Promising preliminary data has been presented from ongoing neoadjuvant PD-(L)1 checkpoint inhibitor trials, many of which contain an adjuvant component. The most exciting results to date have come from the NADIM trial of neoadjuvant carboplatin/paclitaxel/nivolumab followed by adjuvant nivolumab for one year after surgical resection. Analysis of the first 41 patients following surgical resection showed 35 (86%) of patients with a major pathologic response (MPR) (defined as <10% viable tumor cells present) and of those, 25 (71%) had a complete pathologic response (CR).[5] The NEOSTAR study of induction nivolumab or nivolumab/ipilumumab and the LCMC trial with neoadjuvant followed by adjuvant atezolizumab in resectable NSCLC patients were both updated at ASCO 2019 with reported MPR in 17%, 33%, and 19% (with 5% CR) of the nivolumab and nivolumab/ipilumumab and atezolizumab intent to treat populations, respectively.[6,7] However, immune toxicity was reported in all of these trials and there were some patients who were not able to complete definitive surgery. We also do not know how MPR with immune therapy correlates with disease free survival (DFS) and overall survival (OS). Thus there is still a lot of enthusiasm for the post-operative (adjuvant) use of checkpoint inhibitors. There are multiple adjuvant immunotherapy trials currently underway although there are no results reported to date. A branch of the US coopertive network (NCTN) ALCHEMIST trial, ANVIL, is currently enrolling patients with stage IB (>4cm)-IIIA NSCLC who test negative for EGFR and ALK mutations. After completion of surgical resection and standard of care adjuvant therapy (chemotherapy or radiation therapy if indicated), patients are randomized to up to a year of adjuvant nivolumab or observation. These patients are further stratified by stage, histology, adjuvant treatment received and PD-L1 status (≥1% or <1%). Co-primary endpoints are disease free and overall survival.[8] IMpower 010 is a randomized, phase III trial of adjuvant atezolizumab vs supportive care in stage IB (>4cm) - IIIA NSCLC patients following surgical resection and cisplatin-based adjuvant chemotherapy with enrollment of 1280 patients. This study does not allow for radiation therapy and mandates that the adjuvant chemotherapy contain cisplatin plus vinorelbine, gemcitabine, docetaxel or pemetrexed. Following completion of 4 cycles of adjuvant chemotherapy, patients are randomized 1:1 to a year of atezolizumab or observation. Primary outcome is disease free survival.[9] In KEYNOTE-091 patients with IB/II-IIIA surgically resected NSCLC who have completed standard of care adjuvant therapy will be randomized to one year of pembrolizumab vs supportive care. The target enrollment is 1080 patients. Primary endpoint is disease free survival. Finally, adjuvant durvalumab is being examined in a randomized, phase III prospective, triple-blind, placebo controlled trial of patients with stage IB (>4cm)-IIIA resected NSCLC being lead by the Canadian Cancer Trials Group. Standard adjuvant chemotherapy is permitted, but post-operative radiation is only allowed for N2 disease. Primary endpoint is disease free survival in PD-L1 positive patients and in all randomized patients. The study stratifies across PD-L1 subgroups (≤1%, 1-49% and ≥50%). Target enrollment is 1360 patients.[10] Checkpoint inhibitor therapy has been established as the new standard of care in unresectable and metastatic NSCLC. Many trials are underway with adjuvant and neoadjuvant immunotherapy for early stage lung cancer and preliminary data from the neoadjuvant trials are promising. In a setting where patients have only modestly benefited from chemotherapy, we eagerly await the results of the ongoing adjuvant immunotherapy studies with the hopes of improving outcomes for surgically resectable NSCLC. References 1. Pignon JP, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008;26(21):3552-3559. 2. Somasundaram A, Burns TF. 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Keywords: Checkpoint inhibitor, Adjuvant, Early Stage Lung Cancer

MS04.04 OPTIMAL CLINICAL TRIAL DESIGN FOR ADJUVANT SYSTEMIC THERAPY

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Surgery is the gold standard local therapy for medically operable patients with stage I or II NSCLC. Adjuvant chemotherapy is indicated for high risk patients with stage IB disease as well as those with stage II disease. While cytotoxic chemotherapy remains the standard of care in the adjuvant setting, the modest benefits offered leave much room to advance therapy and improve survival in patients with early stage NSCLC (1). One particular area of enthusiasm surrounds the potential role of novel agents such as immunotherapies in the treatment of early NSCLC, given the benefits seen in the advanced NSCLC setting (2). Select ongoing studies addressing novel adjuvant therapeutic regimens in NSCLC are summarized in Table 1. This presentation examines issues surrounding advancement of knowledge in systemic therapy in the adjuvant setting. First, clinical trials must identify and address questions of relevance to both care providers and patients. These include optimal biomarker testing, the use of biomarkers as predictive and prognostic factors, the role of targeted and immunotherapies, novel and combination regimens, optimal duration of therapy and the role of maintenance therapy. Second, outcomes with clinical relevance which are also of interest to cancer patients should be prioritized such as prolongation of survival and improvement in quality of life. Third, studies should be designed in a robust manner focusing on improved efficiency and generalizability. Novel trial designs such as platform studies employing umbrella and basket protocols, driven by biomarkers with flexible objectives should be considered to accelerate clinical development and generate enthusiasm in the community of practitioners treating NSCLC. In platform studies, a single master protocol is employed in which multiple treatments are evaluated simultaneously. Platform designs can be implemented in an adaptive fashion, allowing treatments to be added as they become available, dropped for futility, or declared superior during the course of a trial (3). Inclusion and exclusion criteria, which are often quite restrictive in explanatory trial designs such as conventional randomized controlled trials, limit generalizability and are often not reflective of the real world setting. Consideration of a more pragmatic approach with broadened inclusion criteria may increase both enrollment and applicability in the broader clinical context. Other novel study designs focused on precision medicine such as co-clinical trials provide an attractive alternative to traditional early phase clinical trials. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) trial is reviewed as an example of a biomarker driven platform study with the potential to provide actionable molecular targets, guide personalized approaches to the care of patients with early NSCLC, and establish standard of practice in those without defined genetic targets (4). Finally, in this post surgical setting, involvement of surgeons in the design and implementation of trials should be encouraged. This could serve to maximize identification and enrollment of patients. Also the integration of surgical questions with those of medical therapy will allow further advancement in the personalized care of patients. In conclusion, the ongoing challenge will be to efficiently and robustly answer questions that matter to researchers, clinicians and patients in a rapidly changing treatment landscape, keeping in mind the ultimate goals of improved survival and quality of life. References (1) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. Pignon et al. 2008 Jul 20;26(21):3552-9. (2) Antonia et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. 2018 Dec 13;379(24):2342-2350 (3) Saville and Berry. Efficiencies of platform clinical trials: A vision of the future. Clin Trials. 2016 Jun;13(3):358-66. (4) The ALCHEMIST Lung Cancer Trials [website]. National Cancer Institute. Updated July 24, 2017. https://www.cancer.gov/types/lung/research/alchemist. Accessed July 27, 2017. 3. Cancer Research Institute [website]. Clinical trials. 2017.

Table 1. Select ongoing studies examining novel adjuvant therapeutic regimens in NSCLC.

NCT Trial Number	Agent(s)	Phase	Setting	No. of Patients	Primary Endpoints
CANOPY-A NCT03447769	Canakinumab vs placebo	III	Stage II-IIIA and IIIB (T>5cm N2) post-surgery +/- chemo	1500	DFS
EVIDENCE NCT02448797	Icotinib vs standard chemo	III	Stage II-IIIA post-surgery, with EGFR mutation	320	DFS
PEARLS NCT02504372	Pembrolizumab vs placebo	III	Stage IB-IIIA post-surgery +/- chemo	1080	DFS
ICWIP NCT02125240	Icotinib vs placebo	III	Stage II-IIIA post-surgery post chemo, with EGFR mutation	124	DFS
ICTAN NCT01996098	6 vs 12 months icotinib vs chemo alone	III	Stage IIA-IIIA post-surgery and chemo, with EGFR mutation	318	DFS
NCT03456076	Alectinib vs chemo	III	Stage IB-IIIA post-surgery	255	DFS
NCT02273375	MEDI4736 vs placebo	III	Stage IB-IIIA and IIIB (T>5cm N2) post-surgery	1360	DFS
ANVIL NCT02595944	Nivolumab vs observation	III	Stage IB-IIIA post-surgery	903	DFS OS
RCTACSCNSCLC NCT03656393	Gefitinib vs chemo	III	Stage II-IIIA post-surgery, with EGFR mutation	48	DFS

Keywords: Lung cancer, Adjuvant therapy, study design

MINI SYMPOSIA

MS05.01 EPIGENETIC THERAPEUTICS IN LUNG CANCER

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Epigenetic Targets and Drugs to enhance immune response in Lung Cancer Kwok-Kin Wong Effective therapies for non–small cell lung cancer (NSCLC) remain challenging despite an increasingly comprehensive understanding of somatically altered oncogenic pathways. It is now clear that therapeutic agents with ability to impact the tumor immune microenvironment potentiate immune-orchestrated therapeutic benefit. We have previously demonstrated the immunoregulatory properties of histone deacetylase (HDAC) and bromodomain inhibitors, two classes of drugs that modulate the epigenome, with a focus on key cell subsets that are engaged in an immune response. By evaluating human peripheral blood and NSCLC tumors, we have shown that the selective HDAC6 inhibitor ricolinostat promotes phenotypic changes that support enhanced T-cell activation and improved function of antigen-presenting cells. The pan-bromodomain inhibitor JQ1 attenuated $CD4^{+}FOXP3^{+}$ T regulatory cell suppressive function and synergized with ricolinostat to facilitate immune-mediated tumor growth arrest, leading to prolonged survival of mice with lung adenocarcinomas. Finally, we have recently performed in vivo CRISPR screens to identify additional novel epigenetic targets that would synergize with PD1 blockade in KRAS driven NSCLC.

Keywords: Epigenetics, Tumor Immune Microenvironment, therapeutics targets

MS05.02 GENETICS ABNORMALITIES IN CHROMATIN MODIFIERS: CONNECTION WITH MYC PATHWAY AND EXPLORATION FOR THERAPEUTICS

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The understanding about the complexity of the molecular networks that regulate the epigenetic control of gene expression is boosting. Moreover, it is accepted that an abnormal function of these networks, due to genetic alterations of its components, play an essential role during tumorigenesis. Among the networks involved in this epigenetic control, there is the SWI/SNF-chromatin remodeling complex, a regulator of the accessibility of the chromatin to DNA-binding proteins (1-2). Inactivating mutations at different members of the complex have been found to be inherent to most human cancers. Our team had pioneered these investigations, being the first to report inactivating mutations at BRG1 (also SMARCA4) which codes for the ATPase of the SWI/SNF complex (3-4). In lung cancer (LC), alterations at any member of this complex affect about half of the tumors and occur in a background of wild type MYC (either C, L or N) (3). In the lasts years, inactivating mutations at other members of the complex (e.g. SNF5, PRBM, ARID1A, ARID2) have been shown to evolve in most human cancers (2,5). More recently, our laboratory also pioneered the identification of tumor-specific inactivation of the MYC-associated factor X gene, MAX, in small cell lung cancers, where it is present in tumors that are wild type for MYC and BRG1 (6). Altogether, the genetic observations indicate the existence of an important network, involving SWI/SNF and MAX/MYC, which is critical to LC development. Using LC as a model, we have scrutinized genomic data, whole exome sequencing (WES) and RNA-sequencing, collected from patient-derived xenografts (PDXs), from patient-derived cells (PDCs) and from public databases (Sanger-COSMIC and CCLE), to delineate the gene alteration profile at epigenetic controllers (including already known drivers and novel candidates) in LC. Combined, all the alterations at epigenetic controllers include different members of the SWI/SNF complex (SMARCA4/BRG1, ARID1A, PBRM1) as well as interesting candidates such as the MAX-binding protein, MGA, or the histone-modifying enzymes (KMT2D/MLL2, KMT2G/SETD1B), among others. Some of these alterations appeared in a mutually exclusive pattern, suggesting a functional connection We have also integrated this information to search for cancer vulnerabilities.Components of the SWI/SNF complex are known to bind to various nuclear receptors, such as those of estrogens, progesterone, androgens, glucocorticoids (GCs) and retinoic acid (RA), thereby adapting the gene expression programs to the demands of the cell environmental requirements (7-9). We found that the restitution of BRG1 in LC cells restores the gene expression signature of normal lung and that cells lacking BRG1 did not respond to RA or GCs, while restoration of BRG1 restored sensitivity (10). The co-administration of the epigenetic compounds azacitidine (demethylating agent) and SAHA (inhibitor of histone deacetylases) enhanced all these effects, both in cell cultures and *in vivo,* accompanied by sustained reductions in genome-wide DNA methylation. Together, these data support the notion that an inactive BRG1 confers resistance to RA and GCs, which prevents cancer cell differentiation. In contrast, the observations also indicate that RA/GC-based treatments could be designed to treat LC patients with MYC-amplified tumours. On the other hand, recent investigations have searched for vulnerabilities of BRG1-mutant cells that may be therapeutically approachable and have found that the inhibition of cyclin-dependent kinase 4/6 (CDK4/6) appear to be synthetic lethal in BRG1-deficient tumours (10). In my presentation I will be showing our last and novel observations of epigenetic-related compounds that promote cell growth inhibition specifically in BRG1-mutant lung cancers. In parallel, gene alterations at other epigenetic-related components have also been reported in cancer. Some of these include the methyltransferase EZH2, a transcriptional repressor, the transcriptional co-activator protein p300, a histone acetyltransferase that regulates transcription via chromatin remodelling or the histone acetyltransferase CREBBP, which also acts as a scaffold to stabilize additional protein interactions with the transcription complex. In LC these alterations are more common in small cell lung cancer (SCLC). In SCLC, there is also recurrent inactivation of MAX and of MGA, proteins directly linked to the MYC trans-activation activities. Here, we found that the gene expression profile of MAX-mutant SCLC cells cluster to that of the ASCL1-transcription factor dependent group of SCLCs, which also includes NMYC- and LMYC-activated but not with MYC or BRG1-mutant SCLC cells. MGA, is an extraordinary large protein that is also recurrently inactivated in NSCLC. The MYC-MAX and MADs/MGA-MAX complexes have opposed functions in transcription, being MAX a central player in this network. MAX and MGA have shown to also act as part of the Polycomb Repression Complex 1 (PRC1), specifically the non-canonical PRC1 complex designated as ncPRC1. I will also present our data on the functional characterization of the role of MYC and of MGA in the MAX-deficient SCLC cells. References: 1.Peterson CL et al. Five SWI/SNF gene products are components of a large multisubunit complex required for transcriptional enhancement. Proc Natl Acad Sci USA. 1994; 91: 2905-8. 2.Wilson GB, Roberts CWM. SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer 2011; 11: 481-92. 3.Medina PP et al. Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines. Hum Mut. 2008; 29: 617-22a. 4.Rodriguez-Nieto S et al. Massive parallel DNA pyrosequencing analysis of the tumor suppressor BRG1/SMARCA4 in lung primary tumors. 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Xue Y, et al.SMARCA4 loss is synthetic lethal with CDK4/6 inhibition in non-small cell lung cancer. Nat Commun. 2019;10:557.

Keywords: BRG1/SMARC4, MYC/MAX, epigenetic therapies,

MS05.03 NOTCH SIGNALLING

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The Notch signaling pathway is a highly conserved pathway that has a vital role in embryonic development and post-embryonic functions such as hematopoiesis, neural cell development and angiogenesis (1). The signaling pathway is activated by the interaction of 4 Notch receptors and their interactions with 5 different ligands. Signaling is characterized by juxtacrine interaction between ligands and receptors on neighboring cells or within the same cell. Alterations in this pathway have been detected in several tumors both as tumor promoter and tumor suppressor. Notch signaling does appear to have relevance in non-small cell lung cancers (NSCLC) (2). In approximately 30% of NSCLCs loss of Numb, a negative regulator of Notch1, leads to increased Notch activity and about 10% of NSCLCs have gain of function mutations in Notch1. A meta-analysis demonstrated that higher expression of Notch1 was correlated with more advanced tumors (3). In addition, higher expressions of both Notch1 and Notch3 were associated with poor prognosis (4,5). In pre-clinical studies inhibition of Notch3 signaling has reduced growth of lung cancers. In addition, it has been demonstrated that there is cross talk between Notch3 and EGFR pathways and inhibition of both pathways can induce expression of anti-apoptotic protein BIM. Finally, Notch signaling may have a role in induction of the epithelial to mesenchymal phenotype (EMT) in cancers (6). EMT is known to be associated with resistance to both cytotoxic agents and targeted agents and inhibition of Notch signaling can not only reverse EMT but also can enhance the anti-tumor activity of cytotoxic agents such as cisplatin and targeted agents such as erlotinib. The EMT phenotype is frequently observed in a sub-population of cancer cells with self-renewal capacity or cancer stem cells. Notch signaling may be crucial to survival of cancer stem cells and persistence of this population may contribute to resistance to therapeutic agents. In squamous cell lung cancers Notch signaling may have tumor suppressive properties (7). Loss of function mutations in Notch family of genes, predominantly in Notch receptors, are frequently identified in several squamous cell cancers including squamous cell cancer of the lung. Similarly, loss of function mutations in Notch genes, particularly Notch1 have been identified in small cell lung cancer (SCLC). Expression of Notch receptor in a mouse model of SCLC reduced tumor burden, suggesting its tumor suppressive properties. The expression of DLL3, one of the Notch ligands is induced in SCLC by a key transcription factor ASCL1.DLL3 is shown to downregulate Notch signaling in SCLCs and enhance the carcinogenic phenotype. All the above data suggest that Notch signaling is highly contextual. In some tumors this pathway may have tumor suppressive properties but in others tumor promoting properties. Defining the role of this pathway in tumor types may guide development of therapeutic strategies targeting the Notch signaling pathway. References Bigas A, Espinosa L. The multiple usages of Notch signaling in development, cell differentiation and cancer. Curr Opin Cell Biol 2018;55:1-7. Westhoff B, Colaluca IN, D'Ario G, et al. Alterations of the Notch pathway in lung cancer. Proc Natl Acad Sci 2009;106:22293-8. Yuan X, Wu H, Xu H, et al. Meta-analysis reveals the correlation of Notch signaling with non-small cell lung cancer progression and prognosis. Sci Rep 2015;5:10338. Donnem T, Andersen S, Al-shibili K, et al. Prognostic impact of Notch ligands and receptors in nonsmall cell lung cancer: coexpression of Notch-1 and vascular endothelial growth factor-A predicts poor survival. Cancer 2010:116:5674-85. Hassan WA, Yoshida R, Kudoh S, et al. Evaluation of role of Notch3 signaling pathway in human lung cancer cells. J Cancer Res Clin Oncol 2016;142:981-93. Yuan X, Wu H, Han N, et al. Notch signaling and EMT in non-small cell lung cancer: biological significance and therapeutic application. J Hematol Oncol 2014;7:87. Nowell CS, Radtke F. Notch as a tumor suppressor. Nat Rev Cancer 2017;17:145-159.

Keywords: Tumor suppressor, NOTCH, squamous

MS05.04 INNATE IMMUNE MEDIATORS IN LUNG CANCER

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Non-small-cell lung cancer (NSCLC) accounts for about 85% of total lung cancer cases. The major types of NSCLC—squamous cell carcinoma and adenocarcinoma—harbor distinct histopathologies, biomarker expression, genomic alterations, and response to therapy [1,2]. Recent studies have shown that there are also differences in their tumor immune microenvironments [3–6]. Specifically, adenocarcinomas have increased infiltration of tumor-associated macrophages, while squamous lung tumors exhibit an enrichment in tumor-associated neutrophils (TANs) in both mouse and human lung tumors. The two major subtypes of NSCLC are also associated with distinct lineage-specific master regulators: SOX2 is commonly amplified and up-regulated in the vast majority of squamous tumors anddrives the squamous fate, whereas NKX2-1 is highly expressed in adenocarcinoma and governs adenocarcinoma fate [2]. We developed novel genetically engineered mouse models (GEMMs) of squamous lung cancer on the basis of overexpression of the transcription factor Sox2 and loss of the tumor suppressor Lkb1 (SL mice) (Mukhopadhyay et al, *Cell Rep*, 2014 [7]). SL tumors recapitulated gene expression and immune infiltrate features of human squamous NSCLC, including an enrichment of TANs and a decrease in expression of NKX2-1. Deletion of *Nkx2-1*in SL mice (SNL) revealed that NKX2-1 suppresses SOX2-driven squamous tumorigenesis by repressing adeno-to-squamous transdifferentiation. We further employed multiple GEMMs to elucidate the role of SOX2 and NKX2-1 in tumor cell fate and TAN recruitment. In Kras-driven adenocarcinomas,mis-expression of Sox2 or loss of Nkx2-1 led to TANrecruitment. SOX2 recruits, whereas NKX2-1 suppresses, TANs at least partly through inverse regulation of the chemokine*Cxcl5*. Tumor-derived CXCL5 is sufficient to recruit TANs. Single cell RNA sequencing (scRNA-seq) revealed that TANs exhibit tumor-promoting features, including production of reactive oxygen species (ROS), and distinct gene expression profiles compared to blood neutrophils (Mollaoglu et al, *Immunity*, 2018 [8]). Depletion of TANs through LY6G blocking antibodies or CXCR2 inhibitors in SNL mice reduced squamous tumors, suggesting that TANs foster squamous cell fate. Furthermore, TAN depletion coupled with scRNA-seq suggests that TANs regulate distinct aspects of tumor cell fate. Together, these data suggest that lineage-defining transcription factors determine the tumor immune microenvironment, which in turn can impact the nature of the tumor. References 1 Langer, C.J. *et al.* (2016) Incremental Innovation and Progress in Advanced Squamous Cell Lung Cancer: Current Status and Future Impact of Treatment. *J. Thorac. Oncol.*11, 2066–2081. 2 Campbell, J.D.*et al.* (2016) Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet.*48, 607–616. 3 Kargl, J. *et al.* (2017) Neutrophils dominate the immune cell composition in non-small cell lung cancer. *Nat. Commun.*8, 14381 4 Nagaraj, A.S. *et al.* (2017) Cell of Origin Links Histotype Spectrum to Immune Microenvironment Diversity in Non-small-Cell Lung Cancer Driven by Mutant Kras and Loss of Lkb1. *Cell Reports* 18, 673–684. 5 Xu, C. *et al.* (2014) Loss of Lkb1 and Pten Leads to Lung Squamous Cell Carcinoma with Elevated PD-L1 Expression. *Cancer Cell* 25, 590–604. 6 Ferone G., *et al.* SOX2 Is the Determining Oncogenic Switch in Promoting Lung Squamous Cell Carcinoma from Different Cells of Origin. *Cancer Cell*. 2016;30(4):519-532. doi:10.1016/J.CCELL.2016.09.001. 7 Mukhopadhyay, A. *et al.* (2014) Sox2 Cooperates with Lkb1 Loss in a Mouse Model of Squamous Cell Lung Cancer. *Cell Reports* 8, 40–49. 8 Mollaoglu, G. *et al.* (2018) The Lineage-Defining Transcription Factors SOX2 and NKX2-1 Determine Lung Cancer Cell Fate and Shape the Tumor Immune Microenvironment. *Immunity* 49, 764-779.e9.

Keywords: squamous, neutrophil, SOX2

MS05 NOVEL BIOLOGICAL PATHWAYS AND DRUGGABLE TARGETS
MONDAY, SEPTEMBER 9 11:00–12:30

MS05.05 HARNESSING ONCOGENE DEPENDENCIES IN LUNG CANCER

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The introduction of precision medicine had a dramatic impact on the overall survival of genomically selected lung cancer patients. This is primarily true for lung adenocarcinomas in which druggable targets like mutant EGFR or rearranged ALK are frequently oncogenically activated. The major challenge in these patients is the inevitable emergence of drug resistant clones that abrogate the effects of selected tyrosine kinase inhibitors. Through a detailed characterization of patients that relapse under osimertinib treatment we identified novel routes to overcome individual resistance mutations in EGFR. At the same time, the majority of lung lacks directly druggbale targets and thus remains largely unaffected by this therapeutic revolution. The induction of programmed cell death by perturbing the pro- and anti-apoptotic members of the BCL-2 family may represent an attractive strategy to circumvent this medical need. We sought to explore dependencies on individual BCL-2 family members with different therapeutic strategies to identify therapeutically relevant pathways in lung cancer models.

Keywords: resistance, BCL-2 family

MS06 AN INTERDISCIPLINARY APPROACH TO OPTIMAL NODAL STAGING
MONDAY, SEPTEMBER 9 11:00–12:30

MS06.01 RADIOLOGIC STAGING

J.M. Goo

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Current definitions of borders for lymph node stations based on a few anatomic landmarks have limitations to explain the three-dimensional location of lymph nodes. Variability in the classification of lymph node stations (especially N1 vs N2 and N2 vs N3 categories) inevitably results in different management and also has an impact on database for the future revision of staging. Several articles have dealt with the ambiguity of the IASLC map and proposed recommendations. The Japan Lung Cancer Society and the Japanese Society for Radiation Oncology map provided more detailed description about the borders of lymph node stations (1). 1. Station 1 and 2 - Proposal: Changing the lower border of #1 station (upper border of #2 station) to the thoracic inlet: upper border of the 1st ribs (anterior border of the 1st ribs on axial CT) (2) and manubrium 2. Station 3a - Potential problem: Absence of sideness - Proposal: Split 3a to 3aR and 3aL with a left lateral border of the SVC (3) OR No change (like subcarinal lymph node) 3. Station 3p Current border - Potential problem: Absence of sideness - Proposal: Right-sided lymph node OR No change (like subcarinal lymph node) 4. Precarianl area (below the lower border of the azygos vein in the right side and upper rim of the left main pulmonary artery in the left side) - Current border: Lymph nodes located in the precarinal area is currently #10, hilar lymph nodes, but there is no description for the border between the right and left. - Proposal: Midline of the trachea In the current IASLC lymph node map, the pleural reflection no longer serves as the border between nodal stations. However, still many physicians regard N2 lymph nodes as mediastinal lymph nodes, and a survey also support this trend (3). Therefore, if the IASLC abandons the notion that N2 lymph nodes are mediastinal lymph nodes, the current map needs only a minor modification. Instead, a clear announcement should be provided to avoid confusion from other researchers (2). If the IASLC regards N2 lymph nodes as mediastinal lymph nodes, major modifications are required. 5. Station 4 and 10 - Problematic area: Anterior aspect of the lower trachea and carina below the lower border of #4 lymph nodes are located in the mediastinum. 6. Station 5 and 10 - Problem: Pulmonary arteries are curved structures craniocaudally, and different interpretation of this border results in differeces among altases. The intersection of the left superior pumonary vein branch and left main pulmonary artery may serve as a clear border. If # 10 lymph nodes are classified as non-mediastinal lymph nodes, the border definition should also be modified. 1. Itazawa T, Tamaki Y, Komiyama T, et al. The Japan Lung Cancer Society-Japanese Society for Radiation Oncology consensus-based computed tomographic atlas for defining regional lymph node stations in radiotherapy for lung cancer. J Radiat Res 2017; 58:86-105. 2. El-Sherief AH, Lau CT, Wu CC, Drake RL, Abbott GF, Rice TW. International association for the study of lung cancer (IASLC) lymph node map: radiologic review with CT illustration. Radiographics 2014; 34:1680-1691. 3. El-Sherief AH, Lau CT, Obuchowski NA, Mehta AC, Rice TW, Blackstone EH. Cross-Disciplinary Analysis of Lymph Node Classification in Lung Cancer on CT Scanning. Chest 2017; 151:776-785.

Keywords: CT, Lung cancer, lymph node staging

MS06 AN INTERDISCIPLINARY APPROACH TO OPTIMAL NODAL STAGING
MONDAY, SEPTEMBER 9 11:00–12:30

MS06.02 ENDOSCOPIC NODAL STAGING

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Endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) were first described in the early 1980's and 1990's respectively. However, their incorporation into clinical practice began some years later, after the development of echoendoscopes and echobronchoscopes. EBUS-TBNA allows the sampling of retrotracheal (3P), upper paratracheal (2L,2R), lower paratracheal (4L/4R) and subcarinal (7) nodal stations. Moreover, EBUS-TBNA can access hilar (10L/10R) and interlobar nodal stations (11L/11R). EUS-FNA can access stations 2 and 4, subaortic (5), 7, paraesophageal (8L/8R) and pulmonary ligament (9L/9R). EBUS-TBNA/EUS-FNA is usually performed under conscious sedation or general anaesthesia in an outpatient setting. The reported complications rate for EBUS and EUS is < 1%. The current international guidelines for preoperative mediastinal staging of lung cancer[1] recommends, for an endoscopy-based mediastinal staging procedure, as a minimum requirement, sampling the largest LN in 4R, 4L and 7 stations, as well as positron emission tomography (PET) positive LNs within each of these stations. Thus, 3 nodes is the minimum sampling requirement for an endoscopy-based staging procedure. Overall, the reported pooled sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of EUS-FNA for lung cancer staging is 0.83, 0.97, 0.78 and 0.98 respectively[2]. Two meta-analysis focussed on EBUS-TBNA in lung cancer staging were published ten years ago[3,4]. Most of the studies included patients with abnormal mediastinum on CT and/or PET/CT and thereby a high prevalence of disease. The reported pooled sensitivity was 0.9 and 0.93, respectively, ranging from 0.69 to 0.99. More recently, two meta-analysis[5,6] have analysed the usefulness of EBUS-TBNA in lung cancer staging in patients with radiologically normal mediastinum. Both have shown similar pooled results for sensitivity (0.49, 0.495) and NPV (0.99, 0.93) with a similar median prevalence of N2/N3 disease (15.2%, 12.8%). EBUS and EUS are complementary techniques that can access to different nodal stations. Thus, combination of both techniques may result in an increase of the sensitivity. A meta-analysis that included 2395 patients[7] reported a mean sensitivity of the combined approach of 0.86 with a mean NPV of 0.92. Depending on the order of both techniques, the addition of EUS(B) to EBUS increased sensitivity by 0.12, and addition of EBUS to EUS(B) increased sensitivity by 0.22. However, no differences in sensitivity and NPV were shown between studies that performed EBUS first and studies that performed EUS first. Combining EBUS with EUS has several limitations: usually needs to be performed by two different operators (pulmonologist/thoracic surgeon or gastroenterologist), in different settings, increasing the cost and waiting time of the procedure. These problems can be solved using a single scope (EBUS), in the same setting, by the same operator, by introducing the EBUS scope into the esophagus (EUS(B)). Several studies have demonstrated that EUS(B) combined with EBUS-TBNA results in an increase of the sensitivity compared with EBUS-TBNA alone[8]. On the last years, several lung-sparing treatments for lung cancer have been developed. To select candidates for these techniques, accurate staging not only of the mediastinal nodes but also of the hilar nodes is crucial. One of the advantages of EBUS-TBNA is the ability to access N1 nodes. A study conducted by Yasufuku et al.[9] that included patients with clinically N0/N1 disease eligible for surgical resection demonstrated that EBUS-TBNA can accurately access the hilar and interlobar LNs with a reported sensitivity, specificity, diagnostic accuracy and NPV of 0.76, 1, 0.96,

and 0.96 respectively. Currently there are two questions that have to be answered: As mentioned before[7], EUS (B) needs to be added to EBUS in 25 patients and EBUS to EUS (B) in 14 patients to detect one additional patient with mediastinal nodal disease that would not have been detected if only one test had been performed. One recent meta-analysis[10] studied the rate of unforeseen N2 disease in patients with lung cancer with or without mediastinoscopy after negative endosonography. In patients with EBUS and or EUS alone, the rate of unforeseen N2 was 9.3% for EBUS, and 13.4% for EUS. In patients with confirmatory mediastinoscopy the rate of unforeseen N2 disease after negative findings of EBUS (plus mediastinoscopy) was 11.2%, and after negative EUS (plus mediastinoscopy) was 14.9%. 1.De Leyn, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg. 2014 May;45(5):787-98. 2.Micanes CG, et al. Endoscopic ultrasound-guided fine-needel aspiration for non-small cell lung cancer staging. A systematic review and metaanalysis. Chest 2007;131:539-548. 3.Gu P, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer. 2009 May;45(8):1389-9. 4.Dong X, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the mediastinal staging of non-small cell lung cancer: a meta-analysis. Ann Thorac Surg 2013;96:1502-07. 5.Leong TL, et al. Preoperative staging by EBUS in cN0/N1 lung cancer systematic review and meta-analysis. J Bronchol Intervent Pulmonol [Epub ahead of print] 6.El-Osta H, et al. Endobronchial ultrasound for nodal staging of patients with non-small-cell lung cáncer with radiologically normal mediastinum a meta-analyisis. Ann Am Thorac Soc 2018;15:864-874. 7.Korevaar DA, et al. Added value of combined endobronchial and oesophagueal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. Lancet Respir Med 2016;4:960-68. 8.Dhooria S, et al. Utility and safety of endoscopic ultrasound with bronchoscope-guided fine-needle aspiration in mediastinal lymph node sampling: systematic review and meta-analysis. Respir Care 2015;60(7):1040-1050. 9.Yasufuku K, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for differentiating N0 versus N1 lung cancer. Ann Thorac Surg 2013;96:1756-60. 10.Bousema JE, et al. Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2019 Jun;14(6):979-992

Keywords: Endobronchial ultrasound; Endoscopic ultrasound; Staging

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MONDAY, SEPTEMBER 9 11:00–12:30

MS06.03 PATHOLOGIC STAGING: OPERATIVE EVENTS

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Accurate pathologic nodal staging, a powerful prognostic factor after resection of lung cancer, requires thorough examination of the mediastinal lymph nodes. Accurate pathologic staging of lung cancer requires effective collaboration between the surgery and pathology teams. There is a quality gap in pathologic nodal staging from three sources: poor surgical lymph node examination practice (failure to collect nodes), problems in the pathologic transfer of specimens (loss in transit or improper communication of the source of specimens), and poor pathology examination practice (incomplete examination or inaccurate and inconsistent reporting). Adequacy of mediastinal lymph node dissection (MLND) during resection for lung is an important quality measure that is not universally met in the US. For most patients with lung cancer, mediastinal lymph node dissection or systematic sampling is recommended at the time of resection, but it is only infrequently performed. For example, 62% of pathologic N0 and N1 non-small cell lung cancer resections in the US SEER database have no mediastinal lymph nodes examined. There is also significant discordance between surgeon claims of the extent of mediastinal lymphadenectomy and verifiable lymph node examination from pathology reports. Review of pathology reports in one study suggested that only 8% of all resections meet systematic sampling criteria, 50% have random sampling, and 42% have no mediastinal lymph nodes examined. However, a blinded independent audit of the surgeons' operation notes suggested that 29% of cases had described a mediastinal lymph node dissection procedure. Some surgeons utilize a strategy of using several pathologic variables to determine the need for MLND during resection for non-small cell lung cancer. The premise is that it is an important goal to "minimize surgical trauma". However, most surgeons would agree that there is not significant trauma related to the dissection of clinically negative lymph nodes, and that the incremental trauma related to MLND is itself minimal. Other strategies to obviate MLND have been suggested. Sentinel lymph node identification has been proved unsuccessful for lung cancer; sentinel technologies do not reliably identify a single lymph node, and N2 disease may still be present even when the sentinel node is negative. In any case, that strategy was tested in an era when only N2 patients could receive adjuvant chemothererapy, and the strategy was based on finding micromestastic disease, not limiting surgical trauma. In an era where N1 disease and tumor size both direct adjuvant therapy, the effort to limit lymphadenectomy is even less useful and this practice should be scrutinized. Even in major cancer centers, the targets of ten lymph nodes and three N2 stations is not universally met. In summary, patients with cT2 or > N0 lung cancer should undergo pre-resectional staging with either endobronchial ultrasound or mediastinoscopy. At the time of anatomic resection, adequate management of mediastinal lymph nodes should also be performed, either complete mediastinal lymph node dissection (favored) or rigorous systematic mediastinal lymph node sampling, with the goal of at least 3 N2 stations, and at least 10 lymph nodes.

Keywords: Lung cancer, staging, surgery

MS06 AN INTERDISCIPLINARY APPROACH TO OPTIMAL NODAL STAGING
MONDAY, SEPTEMBER 9 11:00–12:30

MS06.04 APPROACHES TO OVERCOMING THE NODAL STAGING QUALITY GAP

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The importance of pathologic nodal staging. Surgical resection remains the most important curative-intent treatment modality for non-small cell lung cancer (NSCLC), with 75-85% of 5 year survivors having undergone resection. For such patients, the status of nodal involvement is the most important prognostic factor, which also has implications for subsequent management, since patients with any nodal involvement (pN1-3) benefit from adjuvant chemotherapy and those with mediastinal nodal involvement (pN2-3) may benefit from adjuvant radiation therapy. Nodal staging also influences risk-stratification for clinical trials eligibility. *Defining nodal staging quality.* There are no universally accepted criteria for defining nodal staging quality, but various professional organizations, including the American College of Surgeons Oncology Group (ACOSOG), the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC), the American College of Surgeons Commission on Cancer (CoC), the European Society for Thoracic Surgery (ESTS), the International Association for the Study of Lung Cancer (IASLC) and the National Comprehensive Cancer Network (NCCN) have all proposed slightly different measures of the quality of pathologic staging, including nodal staging parameters.[1] *The nodal staging quality gap.* Despite the importance of pathologic nodal stage, the quality of application of nodal staging is highly variable. Three examples are: non-examination of lymph nodes in resection specimens (pNX) which exists in 12-18% of resections; non-examination of mediastinal lymph nodes, which is reported in up to 50% of resections; failure to achieve aggregate nodal staging quality requirements, such as the NCCN definition of quality, which is achieved in as few as 4% of surgical resections in population-based cohorts in the United States.[2] *Survival implications.* pNX resections have significantly inferior survival to pN0 resections, and are more similar to resections for pN1 NSCLC; pN0 and pN1 resections without examination of mediastinal nodes have 14% lower adjusted 5-year survival than those with at least one examined mediastinal lymph node; and achievement of all 4 elements of the NCCN definition of resection quality (anatomic resection, negative margins, examination of at least 1 hilar/intrapulmonary lymph node and at least 3 mediastinal nodal stations) is associated with 30% lower hazard of death within 5 years.[3] *Causes of the gap, corrective interventions.* The nodal staging quality gap can be localized to events during the surgical operation, the transfer of resection specimens and the pathology examination. Effective interventions must correct the problem at all its potential sites of origin. In the

'chain of responsibility' conceptual model, any breakdown in the surgical retrieval of lymph nodes, labeling of specimens, transfer of specimens, gross retrieval of lymph nodes from submitted material and pathologic examination of the retrieved material can break down the quality and accuracy of the final pathology report which is used for all subsequent oncologic care decision-making. Devices such as pre-labeled specimen collection kits are able to prevent breakdown at all links of this chain: they significantly increase the thoroughness of lymph node evaluation; rates of attainment of nodal staging quality measures; and survival. However, their impact on retrieval of intrapulmonary lymph nodes is limited. Specific interventions are also required to improve pathologic retrieval of intrapulmonary lymph nodes, given evidence that up to 90% of pulmonary resection specimens have lymph nodes discarded without examination, approximately 30% of which have metastasis, including in 12% of patients reported as having pN0. Patients with discarded intrapulmonary lymph node metastasis have worse survival than those without, irrespective of their pathologic nodal stage. Even in the mediastinal nodal dissection arm of the ACOSOG Z0030 trial, in which there was extensive evaluation of hilar and mediastinal lymph nodes, poor examination of intrapulmonary lymph nodes was common and had significant negative survival impact.[4] Novel, anatomically sound gross dissection methods designed to focus on retrieval of lymph nodes in the peri-bronchial tree with particular emphasis on sites of bronchial bifurcation, significantly improve the yield of lymph nodes and decrease the incidence of discarded lymph nodes. Therefore, combining surgery with lymph node specimen collection kits and improved gross dissection methods is necessary to comprehensively overcome the nodal staging quality gap. *What are the putative pathways for survival impact?* Correct prognostication by more accurate risk-stratification, although beneficial in itself, would only impact on stage-stratified survival, without changing survival in aggregate populations. The finding of aggregate survival differences suggests benefit beyond mere stage re-categorization. One likely mechanism is improvement in identification of candidates for adjuvant therapy, which then provides an indirect means of risk-mitigation. However, given the larger reduction in hazard for death when surgical specimen collection kits are used, than would be expected from adjuvant therapy benefits alone, another plausible hypothesis is an inherent benefit of resecting oligo-metastatic lymph node disease. This hypothesis requires further testing. Interestingly, it fits the emerging understanding of suboptimal nodal staging as a type of incomplete resection (R-uncertain) and the IASLC's proposal for creating a new category of 'R-uncertain' resections, the overwhelming majority of which are caused by poor nodal staging.[5] The emerging ability to conduct tests for minimal residual disease such as with cell-free DNA will provide a means of directly testing this hypothesis. If proven, it would open a pathway to future clinical trials of novel adjuvant treatments, such as checkpoint inhibitor therapy and other immunomodulatory treatments for these residually high-risk patients. References Smeltzer MP, et al. Association of Pathologic Nodal Staging Quality With Survival Among Patients With Non-Small Cell Lung Cancer After Resection With Curative Intent. JAMA Oncol. 2018 Jan 1;4(1):80-87. Allen JW, et al. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. Cancer. 2011 Jan 1; 117(1):134-42. Osarogiagbon RU, et al. Prognostic Value of National Comprehensive Cancer Network Lung Cancer Resection Quality Criteria. Ann Thorac Surg. 2017 May; 103(5):1557-1565. Osarogiagbon RU, et al. Survival Implications of Variation in the Thoroughness of Pathologic Lymph Node Examination in American College of Surgeons Oncology Group Z0030 (Alliance). Ann Thorac Surg. 2016 Aug;102(2):363-9. Rami-Porta, et al. Complete resection in lung cancer surgery: proposed definition. Lung Cancer. 2005 Jul;49(1):25-33.

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MONDAY, SEPTEMBER 9 11:00–12:30

MS06.05 TRANSCERVICAL LYMPHADENECTOMIES

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Introduction: The aim of his study is to analyze the issue of transcervical lympadenectomies for Non-Small-Cell Lung Cancer performed by the techniques of Video-Assisted Mediastinoscopic Lymphadenectomy (VAMLA) and Transcervical Extended Mediastinal Lymphadenectomy (TEMLA). Methods The Pubmed search was performed and there were 27 articles found on VAMLA and 33 articles on TEMLA. After further analysis there were 13 original article on VAMLA and 18 original articles on TEMLA. In the current paper all proven and possible advantages of transcervical lymphadenectomies representd by VAMLA and TEMLA are described. Results The proven advantages of VAMLA and TEMLA: 1. Superior diagnostic value in discovery of the metastatic mediastinal nodes for staging and restaging of NSCLC. 2. bilateral mediastinal lymphadenectomy, more extensive than the techniques of lymphadenectomy used during standard thoracotomy or Video-Assisted Thoracic Surgery (VATS) approaches. Possible advantages include: 1. Improved selection of patients for pulmonary resection for NSCLC 2. Combination of VAMLA/TEMLA with VATS pulmonary resection, 3. Combination of VAMLA/TEMLA with esophegeal resection, 4. Combination of TEMLA and Stereotactic Radiotherapy (SBRT) for advanced NSCLC 5. The use of TEMLA for preoperative staging of mesothelioma, 6. Combination of TEMLA and pulmonary lobectomy through a sole transcevical approach 7. Resection of various metastatic tumors, including thyroid cancer and metastatic mediastinal nodes. 8. Possible impact of VAMLA/TEMLA on improvement of survival for NSCLC patients, which is the most important issue. In case of VAMLA superior survival of patients operated on with the use pulmonary resection with VAMLA in comparison to the pulmonary resection with addition of standard mediastinoscopy. In case of TEMLA no reports on survival has been published, yet Disadvantages of VAMLA/TEMLA include 1. Possible complications, especially the left recurrent nerve palsy 2. Possible delay or elimination of some patients from pulmonary resection due to postoperative complication in case of negative result of VAMLA/TEMLA 3. Scar in the neck (cosmetic) 4. Demanding surgical technique Conclusions 1. Bilateral transcervical lymphadenectomies representd by VAMLA and TEMLA are more extensive than the techniques of lymphadenectomy used during standard thoracotomy or Video-Assisted Thoracic Surgery (VATS) approaches and superior to the other techniques of staging and restaging of NSCLC in regard to the diagnostic value. 2. There are several other possible advantages of TEMLA/VAMLA for the treatment of NSCLC, esophageal cancer, mediastinal tumors and malignant mesothelioma. 3. Possible impact of VAMLA/TEMLA on survival of NSCLC has not been proven, yet. References Hurtgen M, Friedel G, Toomes H et al: Radical video-assisted mediastinoscopic lymphadenectomy (VAMLA) – technique and first results. 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MS06 AN INTERDISCIPLINARY APPROACH TO OPTIMAL NODAL STAGING
MONDAY, SEPTEMBER 9 11:00–12:30

MS06.06 THE CONCEPT OF COMPLETE RESECTION

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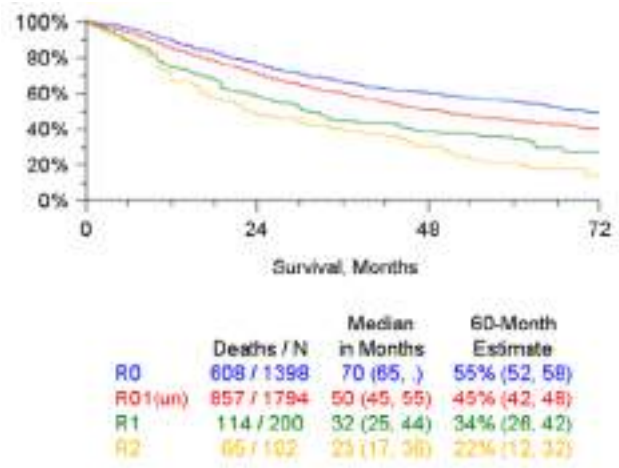
The basis of the definition of complete resection is the Union for International Cancer Control (UICC) residual tumor classification (R classification), which considers the presence or absence of tumor in the primary site, lymph nodes and distant site following treatment. It has established clinical relevance, reflects the effectiveness of treatment, may be used to determine whether further therapy is indicated and has established prognostic relevance in lung cancer [1-3]. However, there are deficiencies in that locoregional recurrence may occur after an apparent R0 resection. The Complete Resection Subcommittee was tasked by the IASLC Staging Committee in 2001 to prepare a proposal of the definition of complete resection, based on expert opinion. The proposal that was derived [4] proposed the term uncertain resection, R(un), according to the following criteria: *An uncertain resection is defined when resection margins are proved to be free of disease microscopically, but one of the following applies: (a) The intraoperative lymph node evaluation has been less rigorous than systematic nodal dissection or lobe-specific systematic nodal dissection. (b) The highest mediastinal node removed is positive. (c) The bronchial margin shows carcinoma in situ. (d) Pleural lavage cytology is positive (R1 cy+).* In addition, this proposal considered cases with positive pleural lavage cytology (PLC) as R(un), rather than R1, and cases with extracapsular extension of tumor in nodes removed separately, or those at the margin of the main lung specimen, were considered R1, rather than R0. The analysis of the proposed R Classification using the database informing the 8thEdition of the TNM was presented at the 18thWorld Conference on Lung Cancer. The predominant reason for re-classification as R(un), performed in 56% of cases, was less than systematic nodal dissection (96% of cases). Survival in the R(un) category was significantly worse than R0 in node positive cases (median survival 50 and 70 months respectively, Hazard Ratio 1.27, Figure). The status of the highest lymph node station also had prognostic significance in pN2 cases (HR 1.32). Further work, that will require the submission of high quality data to the IASLC Lung Cancer Staging Project, will investigate again the impact of the individual R factors, particularly those for which the prevalence (or data completeness) in the previous dataset was low. Participation by institutions worldwide is essential to ensure success [5]. However, there are several aspects about R Factor assessment that require clarification. These are being considered by the R Factor Subcommittee of the Staging and Prognostic Factors Committee. A survey of the current application and interpretation of the R Classification for NSCLC has been designed. The R Factor Sub-Committee will be determining and disseminating best methodological practice for intra-operative and histopathological aspects of R factor assessment



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Keywords: Resection Margins, staging, Non-Small Cell Lung Cancer

MS07 CONTROVERSIES WITH STEREOTACTIC RADIATION IN EARLY STAGE LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS07.01 PREOPERATIVE OPTIMAZITION: REDUCING SURGERY COMPLICATIONS THROUGH TOBACCO CESSATION

D. Harpole

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Optimizing Outcomes after Pulmonary Resections with Smoking Cessation Data on increased risk of complications after major thoracic surgery for current smokers has been documented for several decades, suggesting that smoking cessation for even a few weeks may significantly reduce this risk based on early return of muco-ciliary clearance of respiratory secretions and decreased risk of atelectasis and pneumonia. Moreover, the awareness of potential lung cancer mortality on patients is a potent "teachable moment" for a smoking intervention. However, the literature is anything but definitive on: 1. Method of smoking cessation / counseling (including pharmacological and non-pharmacological adjuncts) 2. Length of time required for maximal risk reduction 3. Durability of cessation after surgery This presentation will review the strongest trials in the literature, as well as recent data on a concerted risk reduction programs of Enhanced Recovery from surgery (ERAS) that include smoking cessation. References: Stokes SM, Wakeam E, Antonoff MB, Backhus LM, Meguid RA, Ordell D, Varghese TK. Optimizing health before elective thoracic surgery: systematic review of modifiable risk factors. J Thorac Dis 11: S537-554; 2109 Sardari NP, Weyler J, Colpaert C. Prognostic value of smoking status in operated NSCLC. Lung Cancer 47:351-9; 2005 Mills E, Eyawo O, Lockhart I. Smoking cessation reduces perioperative complications: A systematic review and meta-analysis. Am J Med 124:144-8; 2011 Kozower BD, Lau CL, Phillips JV. Thoracic surgeon-directed tobacco cessation intervention. Ann Thorac Surg 89:926-30, 2010 Thomasen T, Abrishami A, Yang Y. Interventions for perioperative smoking cessation. Cochrane Database Syst review 3:CD002299; 2014 Lugg ST, Tikka T, Agostini PJ, Kerr A, Kalkat MS et al. Smoking and timing of cessation on postoperative complications after curative-intent lung cancer surgery. J Cardiothorac Surg 12:52-60; 2017 Rodriguez M, Gomez-Hernandez MT, Novoa N, Jimenez MF, Aranda JL. Refraining from smoking shortly before lobectomy has no influence on the risk of pulmonary complications. Eur J Cardiothorac Surg 51:498-503; 2017 Zaman M, Bilal H, Mahmood S, Tang A. Does getting smokers to stop smoking before lung resections reduce their risk? Interact Cardiovasc Thorac Surg. 14:320-323; 2012 Gemine RE, Ghosal R, Collier G, Parry D, Campbell I, Davies G, Lewis KE. Longitudinal study to assess impact of smoking at diagnosis and quitting on 1-year survival for people with NSCLC. Lung Cancer 129:1-7; 2019

Keywords: perioperative risk, lung cancer surgery, Smoking cessation program

MS07.02 POST SBRT MANAGEMENT: SURGERY

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Background: For early stage NSCLC, lobectomy and mediastinal lymph node dissection has been a long-standing, established standard of care. For patients unable to tolerate surgical resection, several single-institution studies have demonstrated SBRT to be an efficacious and well-tolerated treatment strategy.[1-3] The RTOG-0236 trial, subsequently published in 2010, prospectively evaluated SBRT among patients at multiple North American centers, revealing high rates of local tumor control with acceptable treatment-related morbidity, which has been corroborated by other investigators with reproducibly acceptable rates of intermediate-term local control and minimal toxicities.[4-6] Given the success of using SBRT for Stage I NSCLC in medically inoperable patients, increasing interest has arisen regarding the potential application of this modality for healthier, potentially operable patients. In order to expand indications for use of this modality, important issues warranting investigation will include determination of the ideal means of following patients radiographically following SBRT as well as establishing protocols for intervention upon local failure. The outcomes for salvage lung resection following SBRT have been minimally reported. In this study, we aimed to evaluate our experience with operative lung resection in patients where SBRT has failed. Further, we review the combined outcomes in patients from our center along with those previously reported in the published literature. Methods:We utilized our Departmental surgical database to identify all patients who underwent salvage pulmonary resection after prior radiation between January 2009 and September 2015. Among 716 patients who underwent pulmonary resection after previous radiotherapy, 21 met inclusion criteria, and these patients comprised the study cohort (MDACC group). Detailed patient data were retrospectively collected from our departmentally maintained, prospectively entered database and supplemented with additional chart review. In addition, a MEDLINE search was performed to identify all previous reports of surgical resection following local failure after initial treatment with SBRT. This resulted in 56 articles, which were reviewed to specifically identify publications regarding lung resection following local recurrence after SBRT. Four studies were identified, totaling 18 patients; however, as one report[7] included resection of specimens lacking any residual disease, we used only the other 3 reports for cumulative analyses.[8-10] From these previous publications, data were extracted for each patient and were combined with those of the MDACC cohort, thus constituting the final aggregate cumulative group. Student's paired t-tests were used to compare pre-SBRT and pre-salvage surgery pulmonary function test results. Kaplan Meier analyses were performed in order to evaluate survival from the time of surgery as well as survival from completion of SBRT. Results:At our institution, 21 individuals met inclusion criteria and comprised the MDACC group, and the cumulative group included 37 patients at 4 institutions. Baseline details regarding histology, sex, age, and medical operability are included in Figure 1. Elements of the radiation treatment received are also shown in Figure 1. Salvage surgery was performed at a median of 16 months following completion of SBRT, with a range of 6.4 to 104 months. Extent of resection is shown in Figure 1. Three (8.1%) operations were performed via minimally invasive approaches (2 thoracoscopic and 1 robotic-assisted). Adhesions were noted intraoperatively for nearly all (36/37, 97.3%) patients. Final pathology resulted in upstaging for 9/15 (60%) of patients in the MDACC group. Early postoperative outcomes were available for the 21 patients in the MDACC group (Figure 2). Two (9.5%) required post-operative admission to the intensive care unit (ICU), and stayed for a median of 5.5 days. Pulmonary complications were most common, occurring in 7 (33.3%) patients. Two (9.5%) patients had a prolonged air leak and 2 (9.5%) patients were discharged home on oxygen. During follow-up of the 21 MDACC patients, 5 developed recurrence. The three-year cumulative incidence of distant recurrence was 23.8%, with all recurrences distant and median time to recurrence 36.2 months. The median disease-free survival among MDACC patients was 19.2 months. Median survival from surgery for the MDACC group was 46.9 months, with 3-year survival of 53.2%. Thirty- and 90-day mortality were both 1 (4.8%). In the cumulative group, median survival was also 46.9 months and 3-year survival was 71.8%. Conclusions: Our findings demonstrate that resection following local failure of SBRT in highly select individuals is feasible, safe, and has an overall acceptable morbidity and mortality, albeit higher than what is typically observed in non-irradiated patients. In considering salvage resection, we recommend careful consideration of the patient's performance status and the likely extent of required resection, to be discussed thoughtfully both with the patient and in a multi-disciplinary tumor board setting. Further studies are clearly warranted to establish treatment algorithms for those patients who demonstrate locally persistent or recurrent disease following SBRT and to clinically characterize the most appropriate operative candidates.

Figure 1: Baseline and Treatment Details of MDACC & Cumulative Groups

	MDACC group	Cumulative group
Total patients	21	37
NSCLC	15 (71.4%)	26 (70.3%)
Squamous cell	*10 (66.7%)*	*17 (65.4%)*
Adenocarcinoma	*4 (26.7%)*	*7 (26.9%)*
NSCLC-NOS	*1 (6.7%)*	*2 (7.7%)*
Metastatic disease	6 (28.6%)	11 (29.7%)
Colorectal	*4 (66.7%)*	*7 (63.6%)*
Esophageal	*1 (16.7%)*	*2 (18.2%)*
Thyroid	*1 (16.7%)*	*1 (9.1%)*
Pharyngeal		*1 (9.1%)*
Men	11 (52.4%)	21/31* (67.7%)
Age, years	73 (45-89)	73 (45-85)
Radiation dose	50 (48-70)	50 (48-70)
Fractions	4 (4-15)	4 (3-15)
SBRT to surgery (months)	16.2 (6.4-71.5)	16.1 (6.4-104.0)
Sublobar resection	8 (38.1%)	9 (24.3%)
Lobectomy	12 (57.1%)	27 (73.0%)
Pneumonectomy	1 (4.8%)	1 (2.7%)

Figure 2: Postoperative Outcomes from MDACC Group

	N (%)	Mean (range)	95% CI
ICU post-op	2 (9.5%)		1.17-30.3%
Initial ICU stay, days		5.5 (2-9)	3.9-8.0
Readmission to ICU	2 (9.5%)		1.17-30.3%
Prolonged post-op vent	1 (4.8%)		0.12-23.8%
Pulmonary complications	7 (33.3%)		14.6-57.0%
Pneumonia	1 (4.8%)		0.12-23.8%
Respiratory arrest	1 (4.8%)		0.12-23.8%
ARDS	1 (4.8%)		0.12-23.8%
Discharged with tube	2 (9.5%)		1.17-30.3%
Atrial arrhythmia	3 (14.3%)		3.04-36.3%
Diuretics	1 (4.8%)		0.12-23.8%
Bleeding requiring transfusion	1 (4.8%)		0.12-23.8%
Urinary tract infection	1 (4.8%)		0.12-23.8%
Thrombophlebitis	1 (4.8%)		0.12-23.8%
Retinal detachment	1 (4.8%)		0.12-23.8%
Death	1 (4.8%)		0.12-23.8%
Any complication	8 (28.6%)		11.3-52.2%
Length of stay (days)		7.1 (2-23)	4.53-9.66
Chest tube duration (days)		4.8 (0.7-14)	3.20-6.35

ICU = intensive care unit
ARDS = acute respiratory distress syndrome

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Keywords: salvage surgery, SBRT, NSCLC

MINI SYMPOSIA

MS07 CONTROVERSIES WITH STEREOTACTIC RADIATION IN EARLY STAGE LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS07.03 POST SBRT MANAGEMENT: VS RADIATION

M. Trovo

ASUIUD, Udine/Italy

Stereotactic Body Radiation Therapy (SBRT) represents the standard of care for medically inoperable patients affected by early-stage Non-small cell lung cancer. Numerous phase I/II and retrospective studies have reported very high rates of local-progression free survival, ranging from 85% to 100% at two years. Interestingly, these data are reproducible among the published series, despite their heterogeneity. Severe lung toxicity (Grade ≥3 lung toxicity) is low, excluding centrally located tumor, ranging from 0% to <10%. Because of the following factors: 1) Very high local control rate, 2) very low clinical toxicity rate, 3) fragility of the treated population, the assessment of the response after SBRT has not be considered crucial in the patient management. Recently the perspective changed. Due to the excellent results in terms of local control, the publications of several paper that documented a superior outcome of SBRT vs. limited lung resection, and comparable data vs. lobectomy, more medically operable patients and less fragile populations have been treated in recent years. Moreover prospective trials on operable patients have been conducted. It is implicit that for operable patients the evaluation of a possible failure after SBRT is mandatory to guide further local (or systemic) therapies. Most patients with recurrent disease after SBRT will succumb to progressive cancer if left untreated. Although this is a frail patient population with competing risk of death, lung cancer specific mortality remains crucial. Even though chemotherapy might improve survival, the majority of patients are unfit to receive cytotoxic chemotherapy. However this scenario is going to be completely changed by the arrival of "immune-therapy" due to the overall favorable toxicity profile. The ESTRO-ACROP consensus guideline on implementation and practice of SBRT for early-stage NSCLC were recently published (1). Patient follow-up according to published guidelines is a mandatory component of any SBRT protocol. A frequency of 3-6 months in CT of the thorax is suggested, at least for the first year, thereafter the frequency might be tailored to whether the patient is medically operable or not. Three major items are considered of crucial importance when conducting the follow-up of the patient for the correct interpretation of follow-up images: 1) knowledge of the patterns of lung injury after SBRT; 2) detailed knowledge of the SBRT dose distribution, 3) knowledge of the pattern of failure. The discrimination between malignant lesion and post-radiation pneumonitis or fibrosis is often challenging. Both the radiation oncologist and the radiologist must be aware of the radiological patterns of SBRT-induced lung injury and of their relative frequency. This will become of crucial importance as SBRT is employed for treatment of operable patients, who can eventually benefit from salvage surgery for local relapse. The pattern of changes in lung parenchyma on CT post-SBRT can generally be categorized as acute (within 6 months) or late (after 6 months). Several patterns were described both for early and late radiographic changes (2). The differential diagnosis between local recurrence and fibrosis appear to be challenging in those patients who develop pattern characterized by dense consolidation and diffuse fibrosis. Such patterns can be classified as mass-like and modified conventional pattern, as we showed. Those patterns occur in about 74–76% of the cases. Patients who relapse have lesions that enlarged during the follow-up. Thus, a PET/CT in cases of enlargement of the lung fibrosis may be reliable in the differential diagnosis between recurrence and lung injury. FDG-PET imaging is considerate mandatory in case of suspected local recurrence on CT images, but it should be considered only optional during regular follow-up. Biopsy confirmation of suspected local failure is recommended only in patients who are likely to undergo salvage therapy if recurrence is detected. We share the idea of Huang and colleagues, who proposed an algorithm for follow-up of patients who are candidates for salvage therapies (3). 1. Guckemberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017;124:11-17. 2. Trovo M, Linda A, El Naqua I, Javidan-Nejad C, Bradley J. Early and late lung radiographic injuries following stereotactic body radiation therapy (SBRT). Lung Cancer 2010;69:77-85 3. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung sterotactic ablative radiotherapy (SABR) – can we distinguish recurrence from fibrosis? A systemic review of the literature. Radiother Oncol 2012;102:335-342.

Keywords: lung sbrt, Follow-up, lung injuries

MS07 CONTROVERSIES WITH STEREOTACTIC RADIATION IN EARLY STAGE LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS07.04 STAGE I (RESECTABLE) NSCLC: SURGERY

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Lobectomy and lymph node dissection have been the standard therapeutic procedure for localized lung cancer since Cahan's "Radical lobectomy" was published in 1960 [1]. In 1995, the Lung Cancer Study Group (LCSG) published findings from a randomized controlled study of clinical stage T1N0 non-small cell lung cancer (NSCLC), [2] that showed inferior overall survival and ~3× local recurrence rate in the limited (sublobar; segmentectomy or wedge) resection arm compared with the lobectomy arm. Although the LCSG study had some flaws (30% of patients had tumors >2 cm; wedge resections without lymph node dissection were performed as limited resections; inclusion of non-peripheral NSCLC in the limited resection arm, which could cause higher local recurrence rates), its results suggested that lobectomy is the superior option. Lobectomy has since been adopted worldwide as the surgical standard of care, whereas the indication for segmentectomy to treat lung carcinomas with solid appearances on computed tomography (CT) is controversial, although several non-randomized studies have suggested that survival and recurrence may be equivalent between lobectomy and sublobar resection (SLR) in patients with smaller lesions (≤ 2 cm) [3,4]. Improvements in imaging technology, such as thin-section CT (TSCT), have led to more patients who present with localized, early-stage lung cancers; and increased detection of small, peripheral NSCLC has renewed interest in SLR as an alternative to lobectomy. In addition, tumors with ground-glass opacity (GGO) have been correlated with less-invasive pathological findings of lepidic adenocarcinoma (AD) growth. Therefore, these patients may be feasible candidates for SLR. The Japan Clinical Oncology Group (JCOG) conducted a cohort study of early peripheral lung cancer (JCOG0201) and investigated the use of TSCT criteria to diagnose non-invasive lung AD, to preoperatively predict pathological non-invasive cancers [5]. Following this observational study, three ongoing trials (JCOG0804/WJOG4507L, JCOG1211 and JCOG0802/WJOG4607L) were initiated to confirm the validity of limited resection for stage I lung cancers, stratified according to preoperative TSCT findings. A non-randomized phase III trial (JCOG0804/WJOG4507L) was conducted to evaluate the efficacy and safety of SLR for peripheral GGO-dominant small lung cancers (tumor diameter ≤ 2.0 cm) and with consolidation tumor ratio ≤ 0.25, based on TSCT [6]. Five-year relapse-free survival (RFS) was 99.7% (95% CI: 97.7–100.0%), with no local recurrences. This study showed SLR (mainly wedge resection) to provide sufficient local control and RFS for peripheral GGO-dominant lung cancer (as seen on TSCT). A randomized phase III trial (JCOG0802/WJOG4607L) was conducted to compare overall survival after segmentectomy with that of lobectomy in patients with peripheral small (≤ 2 cm) NSCLC lesions [7]. The ongoing Cancer and Leukemia Group B (CALGB) 140503 trial is another large, multicenter randomized trial to compare disease-free survival between SLR and lobectomy among patients with peripheral small (≤ 2 cm) NSCLC lesions [8]; and is similar to the JCOG0802/WJOG4607L trial. However, as CALGB 140503 allows wedge resection as a surgical intervention, the JCOG0802/WJOG4607L trial offers a more definitive comparison of segmentectomy vs lobectomy for small invasive AD. The JCOG0802/WJOG4607L trial completed enrolling 1106 patients in 2014 and will clarify whether limited resection for primary lung cancer is not only function-preserving but also curative. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend segmentectomy or wedge resection for patients with insufficient pulmonary reserve or with other major comorbidities, and for patients with tumors ≤2 cm that are either (a) pure AD *in situ* (AIS) confirmed by histopathological analysis, (b) nodules with ≥50% GGO on CT, or (c) confirmed by radiologic surveillance to have long doubling times (≥400 days) [9]. However, we need the results from all prospective randomized trials to form new treatment strategies for early-stage lung cancers. [1] Cahan WG. Radical lobectomy. J Thorac Cardiovasc Surg 1960;39:555-72. [2] Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac

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Keywords: NSCLC, surgery, Resectable

MS07 CONTROVERSIES WITH STEREOTACTIC RADIATION IN EARLY STAGE LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS07.05 STAGE I (RESECTABLE) NSCLC: RADIATION

S. Senan

Amsterdam University Medical Center, Netherlands/Netherlands

For patients with a peripheral stage I NSCLC, the non-surgical treatment of choice is stereotactic ablative radiotherapy (SABR). Patients who are fit to undergo surgery, but instead undergo SABR, have a 3-year overall survival ranging from 76-86% [Siva S, Oncologist 2016], which is superior overall survivals in medically unfit patients treated using SABR. In 2013, the ESMO Clinical Practice Guidelines recommeded that surgery 'should be offered to patients with stage I or II NSCLC who are willing to accept procedure-related risks' [Vansteenkiste J, Ann Oncol 2013]. In the absence of completed randomized clinical trials of surgery versus SABR, a number of recent propensity score matched analyses have been performed. A pooled meta-analysis of propensity score matched data showed no significant differences in cancer specific survival between the two local treatments [Chen H, IJROBP 2018]. Changes in the treatment patterns for patients with early-stage NSCLC have be reported in a number of countries, all showing an increase in the utilization of SABR in mainly elderly patients [Damhuis R, Ann Oncol 2019; Holmes JA, JNCI Ca Spectrum 2017]. These findings are in part due to the increase in the frail elderly presenting with lung cancer, and to the growing awareness of treatment-related mortality in this population. For example, data from the US National Cancer Database revealed that differences in 30- and 90-day post-treatment mortality between surgery and SABR increased as a function of age, with the largest differences in favor of SABR observed among patients older than 70 years [Stokes WA, JCO 2018[. Ongoing and future randomized studies comparing both modalities will also have to take account of the view of patient preferences. This is illustrated by recent randomized trial of surgery versus SABR (SABRTOOTH, ISRCTN13029788), in which 84 high-risk patients were approached by pulmonologists and oncology nurses for study participation, and 24 (29%) were randomized [Franks K, WCLC 2018]. The main reason for declining study participation was patient preference with 29% preferring surgery and 42% SABR. Overall 9 patients (38%) did not receive their randomized treatment. Of 7 patients who had been randomized to surgery but not undergoing surgery, 6 received SABR, 1 radical radiotherapy. Similarly, of 2 patients randomized to SABR, but who did not undergo SABR, 1 patient received radical radiotherapy, and another was lost to follow-up. Other research which may influence the ongoing debate are the effects of both local therapies on the immune system. The systemic inflammatory response induced after surgery can promote the emergence of tumors whose growth was otherwise restricted by a tumor-specific T cell response [Krall 2018]. SABR, on the other hand, is actively being investigated as an immunomodulator to enhance systemic anticancer effects [Marciscano AE, IJROBP 2019], with a randomized placebo-controlled trial of immune-checkpoint blockade underway in this population (NCT03833154). References Siva S. Curing Operable Stage I Non-Small Cell Lung Cancer With Stereotactic Ablative Body Radiotherapy: The Force Awakens. The Oncologist 2016;21:393–398 Vansteenkiste J. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013 Oct;24 Suppl 6:vi89-98. Chen H. Stereotactic Ablative Radiation Therapy Versus Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score Studies. Int J Radiat Oncol Biol Phys 101:186-194, 2018 Damhuis R. Annals of Oncology (2019) 30 (suppl_2): ii26-ii30. 10.1093/annonc/mdz064 Holmes JA, JNCI Cancer Spectrum, Volume 1, Issue 1, September 2017, https://doi.org/10.1093/jncics/pkx003 Stokes WA. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer. J Clin Oncol2018 Mar 1;36(7):642-651. Franks K. SABRTOOTH: A Feasibility Study of SABR Versus Surgery in Patients with Peripheral Stage I NSCLC Considered to be at Higher Risk for Surgery. Proceedings of WCLC 2018 P2.16-16 Marciscano AE. Immunomodulatory Effects of Stereotactic Body Radiation Therapy: Preclinical Insights and Clinical Opportunities. In press Int J Radiat Oncol Biol Phys 2019 https://doi.org/10.1016/j.ijrobp.2019.02.046 Krall JA. The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy. Sci. Transl. Med. 10, eaan3464 (2018)

Keywords: stereotactic radiotherapy, surgery, Early-stage lung cancer

MS07 CONTROVERSIES WITH STEREOTACTIC RADIATION IN EARLY STAGE LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS07.06 HOT TOPICS IN SBRT - BIOPSY, CENTRAL LESIONS, RADIOLOGIC EVALUATION

C. Le Pechoux, A. Botticella, A. Levy, O. Henry, I. Chabert, C. Caramella

Gustave Roussy Cancer Campus, Villejuif/France

Stereotactic body radiotherapy (SBRT) has taken a growing place among treatment strategies in lung cancer in the past ten years because of its reported good results and favourable risk-benefit ratio especially in high-risk patients. This treatment modality allows delivering precisely a very high dose of radiation therapy to a targetable lesion, using a small number of fractions (3 to 5 more frequently). It has become the standard of care in medically inoperable peripheral early stage non-small cell lung cancer (NSCLC) patients. It is also frequently used in metastatic patients to treat cranial as well as extra-cranial metastases. Recently small randomised studies evaluating SBRT in oligometastatic NSCLC have shown promising results. Its role is now well accepted however there are situations where SBRT is still a subject of controversy and may be regarded as a hot topic because of the lack of pre-treatment biopsy because of less favourable outcome in central lesions and higher risk of complications because of the difficulty of radiologic evaluation When a peripheral lung nodule is discovered, suspect of being lung cancer, attempt should be made to obtain a pathological diagnosis before any treatment is proposed. Percutaneous CT–guided transthoracic biopsy is the established investigation in the work-up of pulmonary nodules, but there is a risk of complications such as pneumothorax (20-40%). However in patients with poor lung function (severe COPD, emphysema.), tissue sampling can be particularly challenging especially when the nodule is beyond the reach of conventional bronchoscopy. These are typically the patients that may be considered for SBRT, possibly presenting a contra-indication to transthoracic biopsy. Criteria for definition of a nodule as lung cancer without biopsy confirmation have been proposed such as progressive growth on CT imaging or presence of a hypermetabolic lesion on PET scan, and multidisciplinary tumor board consensus on the clinical diagnosis of lung cancer; there should be at least a 85% risk of malignancy, based upon accepted criteria [Postmus; Louie, Reid]. If stereotactic radiotherapy in peripheral early NSCLC is presently a standard of care in inoperable patients due to co-morbidities and age, its role is more controversial for centrally located tumors because of less favorable outcome and higher risk of complications. In the past years, there has been a need to better classify these patients differentiating ultra-central from central lesions. The RTOG 0813 phase I/II trial, evaluated dose escalation in 120 patients with centrally-located non-small lung cancer with a five-fraction schedule that ranged from 10 to 12 Gy per

fraction [Bezjak 2019]. The maximum tolerated dose was 60 Gy (5 fractions of 12 Gy), which was associated to a 2 year local control rate of 87.9%. They reported a fatal hemoptysis rate of 4%, potentially attributable to stereotactic radiotherapy [Bejzak 2015]. Even if the authors of this prospective study reported that outcome was comparable with that of patients with peripheral early-stage tumors, the risk of severe toxicity seems to be higher than in peripheral tumors. In another prospective phase II study, the Nordic hilus trial, which included 74 patients with central tumors within 1 cm from the proximal bronchial tree (PBT), the administered dose was 8 fractions of 7 Gy [Lindberg]. The authors reported a grade 4-5 toxicity of 19% among patients with tumor close to the main bronchus (ultra-central location) versus 3% in patients with tumor close to a lobar bronchus (central location). In a retrospective study of 88 patients with ultra-central lesions defined as tumors abutting PBT or trachea, or close to esophagus, a grade 3 toxicity or higher was reported in about 20% patients [Wang]. In another smaller retrospective study, where patients received 12 fractions of 5 Gy, outcome was quite good but toxicity ≥ grade 3 was reported in 38% of patients [Tekatli]. Thereby stereotactic radiotherapy for ultra-central tumors cannot be considered a standard treatment and more studies are needed for all central tumours to find the optimal dose regimen. Radiological evaluation after SBRT is performed mostly with chest CT scan, and changes occurring early and/or late are very common but can be tricky for radiologists as well as clinicians [Ronden, Febbo]. If FDG PET-CT is well established as staging tool prior to treatment, it is generally not used for surveillance. It may be useful though to differentiate local recurrence from radiation-induced lung opacity. Ideally, a treatment failure suspicion should be confirmed with a biopsy. These hot topics regarding SBRT show the difficulty to include patients into prospective trials; efforts have been made and should be pursued. References Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv1-iv21. Louie AV, Senan S, Patel P, et al. When is a biopsy-proven diagnosis necessary before stereotactic ablative radiotherapy for lung cancer?: A decision analysis. Chest 2014; 146(4):1021-1028. Reid M, Choi HK, Han X et al. Development of a Risk Prediction Model to Estimate the Probability of Malignancy in Pulmonary Nodules Being Considered for Biopsy. Chest 2019. [Epub ahead of print] Lindberg K, P.Bergström, OT Brustugun et al. The Nordic HILUS-Trial - First Report of a Phase II Trial of SBRT of Centrally Located Lung Tumors. J Thorac Oncol 2017;12(15) Abstract S340. Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG Oncology/RTOG 0813 trial. J Clin Oncol 2019;37(15):1316-1325. C. Wang, B. Sidiqi, E. Yorke, et al. Toxicity and local control in “ultra-central” lung tumors treated with SBRT or high-dose hypofractionated RT. J Thorac Oncol 2018; 13(10). Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk Patients with “Ultracentral” Non-Small Cell Lung Cancer. J Thorac Oncol 2016;11(7):1081-1089. Ronden MI, Palma D, Slotman BJ, Senan S. Brief Report on Radiological Changes following Stereotactic Ablative Radiotherapy (SABR) for Early-Stage Lung Tumors: A Pictorial Essay. J Thorac Oncol 2018;13(6):855-862. Febbo JA, Gaddikeri RS, Shah PN. Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer: A Primer for Radiologists. Radiographics 2018;38(5):1312-1336.

Keywords: stereotactic radiotherapy, non-small-cell lung cancer

MS08 MANAGEMENT OF THYMIC CARCINOMA
MONDAY, SEPTEMBER 9 14:00–15:30

MS08.01 ADJUVANT RADIOTHERAPY FOR RESECTED THYMIC CARCINOMA

A. Brade

Trillium Health Partners, Mississauga/Canada

Thymic carcinoma is a rare malignancy with peak incidence in the 4th-6th decade. In contrast to thymoma, it is commonly associated with higher rates of both lymph node and distant metastatic spread and also with shorter disease free survival. For localized or locally advanced disease, surgical resection, with the intention of complete disease extirpation, remains the standard of care. Due to its rarity however, definitive clinical trial data regarding optimal and appropriate addition of adjuvant therapy is lacking. Thus decision making for post-operative patients is guided by data from large institutional, national or international retrospective series or databases (evidence level IV or V). Recommendations for adjuvant therapy for thymic carcinoma are influenced principally by stage and adequacy of resection (R0 vs R1 vs R2). Thymic carcinoma is classically staged us the Masaoka-Koga (MK) system but, based on recommendation to the AJCC by the IASLC Staging Prognostic Factors Committee and the International Thymic Malignancy Interest Group (ITMIG), using a database of more than 10 000 patients (Detterbeck et al 2014), a TNM-based system has now been incorporated into the 8th Edition of the AJCC/UICC TNM Classification of Malignant Tumours. However, since much of the published data regarding thymic malignancies is based on the Masaoka-Koga system, at present this remains commonly used for clinical decision-making but, as data continues to accumulate, will likely be superseded by the TNM system over time. Post-operative radiotherapy is routinely recommended for patients with MK stage III (TNM Stage I – T1bN0, Stage II, IIIA/B) thymic carcinoma following R0 resection. Similarly, adjuvant radiation is recommended following R1 resection, regardless of stage, with adjuvant chemoradiation recommended following R2 resection. Adjuvant radiotherapy is not recommended for MK I or IIA (TNM Stage 1 T1aN0 with no extension to mediastinal fat) disease. Controversy exists regarding the utility of adjuvant radiotherapy in the management of MK IIB (TNM Stage I – T1aN0 with extension to mediastinal fat) disease but can be considered for this group of patients. The optimal adjuvant radiotherapy dose remains undefined for thymic carcinoma patients but typical doses reported in the literature for patients in the above recommended groups range from 45-50 Gy in 1.8-2 Gy per fraction daily. Following R1 resection, 50-54 Gy in 1.8-2 Gy per fraction is typically recommended. Following R2 resection, 60-70 Gy (with or without concurrent chemotherapy) is considered standard. Nodal involvement is much more frequent in patients with thymic carcinoma compared with thymoma. Resected, unexpectedly N+ patients are typically recommended to receive adjuvant RT to 45-60 Gy if complete resection was obtained or 60-70 Gy (with or without concurrent chemotherapy) if residual nodal disease is suspected/documented. Under the TNM staging system, N1 nodes are defined as those in the anterior mediastinal compartment (IASLC levels 1, 3a, 6 and/or supradiaphragmatic/inferior phrenics/pericardial) and N2 nodes are defined as deep intrathoracic or cervical nodes (IASLC levels 2, 4, 5, 7, 10 and/or internal mammary nodes). Whether inclusion of N1 or N2 nodal compartments in adjuvant RT target volumes is of benefit for N0 or completely resected N1 or N2 patients remains unknown but may be prudent to consider during radiotherapy planning based on clinical factors. Radiotherapy should conform to modern standards with CT-based simulation with photon-based 3D conformal or beam-modulated treatment delivery, motion management and image guidance to reduce margins and dose to organs at risk. The utility of adjuvant proton-based RT for patients with resected thymic malignancy remains the focus of ongoing study but may offer some dosimetric advantages with respect to OAR dose (e.g. lung or heart). Selected References: N. Girard et al., Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (Supplement 5): v40–v55, 2015 Imbimbo et al., Treatment guidelines: Best practices for the management of thymic epithelial tumors: A position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME) Cancer Treatment Reviews 71 (2018) 76–87 Detterbeck et al. 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Keywords: Thymic carcinoma, radiotherapy

MS08.02 INDUCTION THERAPY FOR LOCALLY ADVANCED THYMIC CARCINOMA

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Thymic carcinoma (TC) is a rare mediastinal malignancy that occurs in approximately 10% of all patients with thymic epithelial tumors. There are several different histologic subtypes of TC with squamous cell carcinoma predominating. TC is an aggressive lesion, and frequently presents in more advanced stages and metastasizes to other organs compared to thymoma. This biologic behavior is reflected in the survival rates associated with TC, which are significantly shorter than that of thymoma. Clinical trials conducted exclusively in TC patients have been scarce with only a handful of studies reported in the literature, all focused on advanced, nonsurgical patients. Locally advanced, nonmetastatic disease is a common presentation of TC. In the largest retrospective series reported to date, locally advanced disease was the most common stage at presentation, accounting for 45% of patients in whom pathologic stage was recorded[1]. The importance of complete resection for patients with locally advanced TC cannot be overemphasized. Virtually all reported series of exclusively TC patients that undergo surgical resection have determined that the ability to perform a complete resection is an independent favorable prognostic factor. Despite this, the rate of complete resection in the large, aforementioned series for locally advanced TC was only 64%. Given that thymic epithelial tumors (thymoma and TC) are sensitive to both chemotherapy and radiotherapy, an approach that has been favored for patients with locally advanced disease is to administer one or both of these agents preoperatively (neoadjuvant therapy). This strategy is thought to increase the chances of performing a complete resection for marginally resectable or unresectable tumors. Although no clinical trials have been reported exclusively for TC patients using the neoadjuvant strategy, two retrospective reports in TC patients utilizing neoadjuvant chemotherapy or chemoradiation demonstrated complete resection rates of 86% and 69% in marginally resectable or unresectable locally advanced disease[2,3]. In a phase II clinical trial of neoadjuvant chemoradiotherapy for locally advanced thymic tumors, the complete resection rate for the seven patients that had thymic carcinoma was 71%[4]. Despite these data, the ability of neoadjuvant therapy to definitively enhance the resectability of locally advanced TC has not been demonstrated due to the absence of randomization and a control group in these studies. Some published data have also suggested that TC may respond better to neoadjuvant therapies when compared to the thymoma histotypes. In the previously described phase II trial of neoadjuvant chemoradiotherapy, the patients with TC not only had a better radiographic response to treatment, they were more likely to have a near complete pathologic response (<10% viable tumor) than the patients with thymoma (57% versus 8%)[4]. Similarly, in a retrospective pathologic analysis of 49 patients with unresectable thymic tumors that underwent neoadjuvant therapy followed by surgical resection at a single institution, the median percent viable tumor in the surgical specimen was significantly less in the TC specimens compared to thymoma (20% versus 91%)[5]. These two studies also suggest that TC may respond better to chemoradiotherapy than chemotherapy alone. Whether targeted or immune therapies can be used successfully in the neoadjuvant setting for TC remains to be determined. Active targeted agents against this disease have remained elusive and immunotherapy may be associated with autoimmune toxicities that may preclude their use in this approach[6]. In summary, the use of induction therapy for locally advanced TC is based on the premise that this approach may enhance resectability of these aggressive tumors, which is an overwhelmingly positive prognostic indicator. However, no published data has conclusively determined that this strategy is effective in enhancing resectability due to a lack of controlled studies. TC may respond better to induction therapy when compared to thymoma, and chemoradiotherapy may induce more radiographic and pathologic responses than chemotherapy alone, but these data are preliminary. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: Results of an international analysis. J Thorac Cardiovasc Surg 2015;149:95-101. Kawasaki H, Taira N, Ichi T, et al. 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Keywords: Thymic carcinoma, induction therapy

MS08.03 OPTIMAL MANAGEMENT OF METASTATIC THYMIC CARCINOMA

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Thymic carcinoma represents approximately 10-15% of all thymic epithelial tumors, it is more aggressive than thymomas and also somewhat less sensitive to chemotherapy. More often than thymomas, thymic carcinomas are not resectable and therefore the use of systemic therapies and radiation are more often required than in thymomas. In general the sensitivity of thymic carcinomas to chemotherapy is lower than with thymomas, with response rates usually less than 50% in metastatic disease, and somewhat higher in locally advanced disease. In presence of borderline operable cases, neoadjuvant chemotherapy is indicated, in order to make the tumor more easily operable. Because thymic carcinomas often infiltrate surrounding tissues, radical resection are sometimes not achievable. The use of postoperative radiation is indicated even if margins are clear. Several chemotherapy regimens have been used, and the more commonly employed remain platinum combinations, with or without an anthracycline (mainly doxorubicin). More recently data the combination carboplatin-paclitaxel has been added to the potential chemotherapy regimens and it is often preferred becasue of its milder toxicity profile. When radiation is planned, the use of doxorubicin is contraindicated, becasue of the enhanced toxicity. The role of debulking surgery, reoperation and metastasectomy is much more controversial in thymic carcinomas than in thymomas, given the more aggressive behaviour. However, the histological diagnosis sometimes is not paralleled by an aggressive phenotype and individual treatment decisions should always be considered. Unfortunately thymic carcinoma have the tendency to metastatize wildly to virtually all organs, and brain metastases are all but rare. Complete staging procedures, including brain MRI are therefore indicated in patients with thymic carcinoma. In patients with metastatic disease, chemotherapy is indicated as first line therapy, and the CAP regimen (cisplatin, doxorubicin, cyclophosphamide) or carboplatin-paclitaxel, are the preferred regimens, with response rates in the range of 30-50%. Unfortunately, chemotherapy at this stage is not curative and most patients will require further systemic therapies after failure of chemotherapy. There have been a number of studies in recent years, which have established activity of a few agents, such as sunitinib and pembrolizumab in thymic carcinomas. Both of them are now listed in the NCCN guidelines and have a response rate of about 25%. Pembrolizumab however has a much longer duration of response, albeit the frequency of severe autoimmune disorders is higher than in other diseases in which immune checkpoint inhibitors are used. Further chemotherapy also has some activity, such and the combination gemcitabine-capecitabine and other single agents, with responses in the 20-30% range. The biology of thymic carcinoma does not appear to provide clues to specific treatments, although mutations in epigenetic genes have been found in a significant number of patients. No easily targetable mutations or genetic abnormalities have so far been found. The most common mutation is in the p53 gene, in about 30% of cases, which is not targetable and is associated with a poorer survival.

Keywords: Thymic carcinoma, sunitinib, Pembrolizumab

MS08.04 NOVEL BIOMARKERS FOR THYMIC CARCINOMA

B. Casini[1], E. Gallo[1], E. Melis[1], F. Cecere[1], V. Laquintana[1], V. Cerasoli[1], F. Facciolo[1], E. Pescarmona[1], F. Fazi[2], M. Marino[1]

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Thymic carcinoma (TC), the rarer among Thymic Epithelial Tumors (TET), occur with an incidence rate of 0.2-0.5/million/yr. Difficulties in the evaluation of molecular aspects derive from the extreme rarity of these tumors. The Squamous cell carcinoma (SQCC) is the most frequently analyzed, however the other rarer histotypes could differ both in molecular pathogenesis and in clinical behaviour. The Cancer Genome Atlas Thymoma study (TCGA-THYM) in a series of ten TC cases including four SQCC, four undifferentiated carcinoma and both one large cell neuroendocrine carcinoma as well as one TC, NOS, identified a few genes rarely mutated, including KIT, HRAS, NRAS and TP53, reflecting the low mutational burden of these tumors (1). In the last years, only a limited number of TC has been investigated by other groups and only a limited number of relevant alterations has been identified. In addition to genomic events, however, epigenetic factors could contribute to TET carcinogenesis. Wang et al. in 2014 performed targeted sequencing of 197 cancer-associated genes in 78 advanced-stage TET patients, including 47 TC and 31 thymoma (THYM) cases. They reported that TC showed a higher incidence of somatic non-synonymous mutations than THYM. Moreover, they found that mutations of epigenetic regulatory genes involved in chromatin modification pathways are common in TC in comparison to THYM (2). In the last years we have been interested in the characterization of genomic and epigenetic findings related to TET development. In our earlier microRNA (miR) study, we reported, among other findings, preliminary data on mature microRNAs differentially expressed in TC vs THYM, as revealed by microarray-based unsupervised clustering analysis. Among the differentially expressed miRs, 3 were validated by RT-qPCR (miR128, miR142-5p and miR-181c-5p) (3). By a different approach, we analyzed by Next Generation Sequencing (NGS) thirteen TC cases and one Atypical Type A thymoma case. The tissues derived from Formalin-fixed, paraffin embedded (FFPE) material including biopsies/surgical specimens of tumors and a single case of matched peritumoral thymus. The percentage of neoplastic cells was not < 70-80% of total cells. The DNA was extracted using the QIAcube and QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA) from microdissected 5 μm FFPE tissue sections. The NGS platform Ion S5 (Thermofisher) and the Ion AmpliSeq™Cancer Hotspot Panel v2 were used. This panel is designed to amplify 207 amplicons covering over 2,800 COSMIC mutations from 50 oncogenes and tumor suppressor genes. Libraries from Ion AmpliSeq Cancer Hotspot Panel v2 were prepared and sequenced by Ion Chef and S5 system. Data analysis was conducted by using the dedicated Ion Reporter Software. Among other genomic variants (polymorphysms and mutations were found in four cases), in one out of these four TC cases a KIT mutation (c.1900C>T; p.R634W, exon 13), already reported in TC, was identified. Moreover, a further KIT mutation (c.1718C>T p.P573L, exon11) was found in a second case. In addition, a missense TP53 mutation (c.824G>T; p.C275F), occurring in exon 8, was observed in a single case of TC, NOS. The patient harbouring a TC with this TP53 mutation had a R0 robotic-assisted thymectomy of a pT2 Thymic carcinoma (according to the 8th TNM edition), and after adjuvant chemotherapy and radiotherapy is alive and in complete remission with a follow-up of 22 months. The recent case of Atypical Type A thymoma showed a NOTCH1 c.4732_4734delGTG p.V1578del in exon 26 of uncertain significance. Basing on the relatively few cases reported in the literature, analyzed by different techniques for their genomic alterations, it appears that the mutation status of TC is highly heterogeneous. In the cases examined so far by NGS we didn't find recurrent genetic aberrations, but a variety of alterations. Each case, with the panel available, revealed either polymorphisms or, in few cases, mutations in cancer-associated genes, both oncogenic and oncosuppressor. Among the genes involved, both the KIT reported variants could be considered relevant for targeted therapy. Moreover, the tumor suppressor gene TP53 is already known for its importance and frequency of mutations particularly in TC. Moreira et al reported recurrent TP53 mutations with unfavorable prognostic value (4). The TP53 mutation found in one of our cases (previously reported in cases of SQCC of upper respiratory tract, in lung, head & neck and esophageal carcinoma) affects, among others, the DNA damage repair, the cell cycle and the apoptosis pathways. In human thymus, the Notch pathway, activated in thymic EC, is crucial to T cell differentiation; moreover the Notch signaling is also involved in hematological and in solid tumors. The NOTCH1 c.4732_4734delGTG p.V1578del in exon 26 we reported in a Atypical case A thymoma was already described in lymphoid tissues. The clinical and prognostic value of the genomic alterations we observed needs to be definied. 1) Radovich M, et al., The integrated genomic landscape of thymic epithelial tumors - Cancer Cell, 2018 Feb 12;33(2):244-258 2) Wang Y, et al., Mutations of epigenetic regulatory genes are common in thymic carcinomas - Sci Rep. 2014 Dec 8;4:7336 3) Ganci F, et al., MicroRNAs Expression Profiling of Thymic Epithelial Tumors - Lung Cancer 2014, 85 (2) 197–204 4) Moreira AL, et al, Massively parallel sequencing identifies recurrent mutations in TP53 in thymic carcinoma associated with poor prognosis - J Thorac Oncol. 2015 Feb;10(2):373-80

Keywords: Thymic carcinoma, Next generation sequencing, genomics and epigenetics

MS08.05 BASIC PATHOLOGICAL FEATURES

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Pathologic Features The basic pathological features of thymic carcinomas are essentially those seeing in other tumors elsewhere and require the presence of conventional features such mitotic activity, cellular and nuclear atypia, and necrosis among others. However, the diagnosis of thymic carcinoma contrary to the diagnosis of carcinomas in other anatomical areas requires a more strict radiological correlation, as thymic carcinoma can show similar histological features as other tumors such lung or head and neck area. Therefore, the clinical information of an anterior mediastinal mass in the absence of tumor elsewhere becomes an important diagnostic tool in the assessment of thymic carcinoma. The histopathological features of thymic carcinomas are vast and highly heterogeneous. It is possible that such heterogeneity may be due the different cell types that may be encountered in the normal thymus. However, in general terms, thymic carcinomas can be separated into neuroendocrine and non-neuroendocrine carcinomas, and further sub-divided into: 1) low grade and 2) high grade carcinomas (see table 1). Among the neuroendocrine carcinomas, similar spectrum as in other organ systems has been recognized, including: low grade, intermediate grade, and high grade neuroendocrine carcinoma. Some of these tumors may have special association with particular syndromes. Aside from the neuroendocrine carcinomas, the vast majority of thymic carcinomas are of the squamous type, which can show diversity in their growth pattern from well-differentiated keratinizing to the high-grade lymphoepithelioma-like carcinoma and anaplastic/pleomorphic carcinoma. In addition, the tumors may show different cell types and growth patterns that may include: papillary, micropapillary, clear cell, sarcomatoid carcinomas, and micronodular among others. In addition, it is important to highlight the occurrence of salivary gland type carcinomas in the thymus, examples of that include: mucoepidermoid carcinoma, adenoid cystic carcinoma and epithelial-myoepithelial carcinoma. More interesting is the fact that a small subset of thymic carcinomas will belong to the adenocarcinoma type, with similar features as those adenocarcinomas in other organ systems – mainly a malignant glandular proliferation. These tumors may also show variability in their growth pattern and may show a solid glandular proliferation or a predominantly mucinous component. Needless to say, these thymic adenocarcinomas can mimic metastatic disease from other organ systems such as lung or colon. Therefore, a close clinical correlation is also highly suggested before determining site of origin. It is due to this heterogeneity that the diagnosis of primary thymic carcinoma requires more strict clinical-radiological-pathological criteria, as there are no pathognomonic features that can define a thymic carcinoma, mainly in cases in which there is only a small mediastinoscopic biopsy for evaluation. From the immunohistochemical point of view, thymic carcinomas commonly express keratin, keratin 5/6, p63, p40, CD5. In addition, it is also well known that some neuroendocrine markers such as synaptophysin may be seen positive in otherwise conventional thymic carcinomas. On the other hand, thymic adenocarcinomas may express different immunohistochemical phenotype that may include: keratin 7, keratin 20, CDX-2, and CEA. In cases of neuroendocrine carcinomas the use

of neuroendocrine markers including chromogranin, synaptophysin, and CD56 may prove useful. However, the grade of differentiation still can be done on morphological grounds. More recently, it has been identified a poorly differentiated carcinoma the so-called NUT carcinoma that by histology most likely represents a poorly differentiated squamous carcinoma but that shows positive staining using the immunohistochemical stain for NUT and also may show more specific cytogenetic and chromosomal abnormalities. Such diagnosis should be suspected in poorly differentiated carcinomas. Regarding the prognosis of thymic carcinoma, it has been identified that the presence of lymph node metastasis, regardless of the location of the lymph node, plays an important role in the clinical outcome of these patients. Therefore, thymic carcinomas are best suited for a TNM staging, contrary to the use of the TNM for thymomas. TABLE 1 Histological Variants of Thymic Carcinoma Low grade High grade Neuroendocrine Mucoepidermoid carcinoma lymphoepithelioma-like Low grade (carcinoid) Basaloid carcinoma P.D. squamous cell Ca Intermediate (atypical carcinoid) Epithelial-myoepithelial Ca Anaplastic Ca High-grade (Small cell Ca) Well-diff. Squamous cell Ca Sarcomatoid Ca Rhabdoid Ca Hepatoid Ca Micronodular Ca Papillary/ micropapillary Ca Clear Cell Ca NUT carcinoma Adenocarcinoma REFERENCES 1.Shimosato Y, Kameya T, Nagai K, Suemasu K. Squamous cell carcinoma of the thymus. Analysis of 8 cases. Am J Surg Pathol 1977; 1:109-121. 2.Snover DC, Levine GD, Rosai J. Thymic carcinoma. Five distinctive histological variants. Am J Surg Pathol 1982; 6:451-470. 3.Suster S, Moran CA. Thymic carcinoma. Spectrum of differentiation and histologic types. Pathology 1998; 30:111-112. 4.Moran CA, Suster S. Thymic carcinoma. Current concepts and histological features. Hematol Oncol Clin N Am 2008; 22:393-407. 5. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. Cancer 1991; 67:1025-1032. 6.Weissferdt A, Moran CA. Thymic carcinoma, part I. A clinicopathologic and immunohistochemical study of 65 cases. Am J Clin Pathol 2012; 138: 103-114. 7.Weissferdt A, Moran CA. Thymic carcinoma, part 2. A clinicopathologic correlation of 33 cases with a proposed staging system. Am J Clin Pathol 2012; 138:115-121. 8.Kalhor N, Moran CA. Primary thymic adenocarcinomas: a clinicopathological and immunohistochemical study of 16 cases with emphasis on the morphological spectrum of differentiation. Hum Pathol 2018; 74:73-82. 9.Moran CA, Suster S. Neuroendocrine carcinomas (Carcinoid Tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol 2000; 114:100-110. 10. Kalhor N, Moran CA. Mediastinal Pathology, Springer 2019, Chapter 8, pp 237-286.

MINI SYMPOSIA

MS09 IMMUNOTHERAPY IN SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS09.01 IMMUNE CHECKPOINT BLOCKADE FOR SCLC: STATE OF THE ART

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It is clear that small cell lung cancer can be an immunotherapeuticly responsive disease. Single agent anti-PD1 and anti-PD-L1 can produce tumor regressions. Anti-PD-L1 given in combination with chemotherapy produces a survival benefit when given as first-line therapy for extensive stage disease. Anti-PD1 is also an option in third line. Although responses are produced in the second line setting neither anti-PD1 nor anti-PD-L1 has proven to produce a survival benefit in unselected patients. The proper application of relevant biomarkers such as TMB has the potential to identify patients who are likely to benefit. Given the fact that small cell lung cancer tumors have a paucity of tumor infiltrating lymphocytes, it is not surprising that immunotherapeutics solely directed at the immune suppressed tumor microenvironment have limited clinical activity. It is likely that combination immunotherapy, with a component of the combination influencing the lymphoid compartment to increase the number of tumor reactive T cells will be necessary to significantly increase the clinical activity of immune-based therapies. There are several potential ways that this could be accomplished. Anti-CTLA.4 can have an impact on regulatory T cells in the tumor microenvironment, however at least in melanoma it has been shown to be operational within the lymphoid compartment as well to increase circulating tumor reactive T cells. Anti-CTLA.4 has been combined with both anti-PD1 and anti-PD-L1. Response rates of the combination have been higher than what can be produced with anti-PD 1 monotherapy. The combination has not yet been shown to produce a survival advantage. Another approach to increasing tumor reactive T cells is to utilize radiation which can release tumor antigens and immunogenic fashion. Trials are ongoing combining radiation with anti-PD1 and anti-CTLA.4. Vaccines offer another potential means to accomplish expansion of tumor reactive T cells. An autologous dendritic cell based vaccine with p53 as the tumor antigen has been shown to produce clinical responses in small cell lung cancer as monotherapy, and is now being combined with anti-PD1 and anti-CTLA.4. An alternative approach is to redirect peripheral T cells through ex vivo transduction with tumor protein-specific antigen binding molecules. An example of this is a chimeric antigen receptor specific for DLL 3. These sorts of combinations have the potential to advance the efficacy of immunotherapy for small cell lung cancer.

Keywords: immunotherapy; small cell lung cancer;

MS09 IMMUNOTHERAPY IN SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS09.02 CLINCAL AND MOLECULAR BIOMARKERS FOR SELECTION OF SCLC PATIENTS CANDIDATE TO IMMUNECHECKPOINT BLOCKADE

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Immunotherapy has dramatically altered the treatment options available to patients with lung cancer. In the past year, small cell lung cancer (SCLC) fully joined the immunotherapy era with approvals by the US Federal Drug Administration (FDA) for three separate immune checkpoint inhibitors – atezolizumab for frontline therapy in patients with extensive stage SCLC (ES-SCLC) (in combination with platinum-etoposide chemotherapy) and nivolumab and pembrolizumab (each as monotherapy) for relapsed SCLC. The combination of nivolumab plus ipilimumab also demonstrated durable activity in a subset of patients treated on the Phase 1/2 CheckMate032 trial, with an overall response rate of 22% and a 2 year overall survival rate of 26%.1 The addition of atezolizumab to carboplatin and etoposide as a new standard of care was based on results from the Phase 3 IMpower133 trial.2 In that randomized trial, the addition of atezolizumab to carboplatin-etoposide, followed by atezolizumab maintenance, led to improvements in both progression free survival (PFS) (4.3 months in the placebo control arm versus 5.2 months in patients receiving atezolizumab) and overall survival (OS) (10.3 months with placebo versus 12.3 months with atezolizumab). Additional randomized trials testing other immune checkpoint inhibitors in combination with standard platinum-etoposide chemotherapy are ongoing, with clinical findings expected in the next several months. This includes the phase 3 trial of durvalumab plus platinum-etoposide (CASPIAN), which has now been reported to show improved overall survival (OS) with the addition of durvalumab at a planned interim analysis (press release). Despite these landmark approvals for immune checkpoint inhibitors in ES-SCLC, a large number of patients with SCLC do not appear to receive clinic benefit with the currently available inhibitors of PD-1/ PD-L1 and/or CTLA-4. Furthermore, there are not yet established biomarkers for identifying those patients with SCLC who are likely to respond. As with non-small cell lung cancer, immunohistochemistry (IHC) for PD-L1 levels and tumor mutation burden (TMB) are both candidate biomarkers.3,4 However, neither of these have been prospectively validated to date in SCLC and there may be important differences in their performance depending on how testing is done (e.g., variation between antibodies, scoring methods/cutoffs, or technical differences between molecular platforms). Recently, new combinations of targeted therapies together with immune checkpoint inhibitors (such as inhibitors of DNA damage response (DDR) such as PARP1 or Chk1 to enhance STING pathway activation) have demonstrated promise in preclinical studies of SCLC and are being translated into the clinic for further investigation.5 In addition, other new immunotherapeutic approaches are being tested in ongoing trials. Examples of these include studies of chimeric antigen receptor T-cells (CAR-T) and bi-specific T-cell engagers (BiTE molecules) targeting the notch inhibitor ligand DLL3 for patients with relapsed SCLC. In this context, additional biomarkers related to specific combinations of targeted and immune-therapies and/or new classes of immunotherapy (e.g., SLFN11 levels for PARP inhibitors; cMyc status for Chk1 inhibitors; markers of STING pathway activation; or DLL3 expression levels) may emerge as additional biomarkers relevant to immune responses. Finally, a better understanding of tumor and immune environment heterogeneity between patients – as well as intra-tumoral heterogeneity – will lead to more effective

strategies for matching patients to specific immunotherapies and overcoming immunotherapy resistance. REFERENCES 1. Della Corte CM, Gay CM, Byers LA. Beyond chemotherapy: Emerging biomarkers and therapies as small cell lung cancer enters the immune checkpoint era. Cancer 2019;125:496-8. 2. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9. 3. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-95. 4. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell 2018;33:853-61 e4. 5. Sen T, Rodriguez BL, Chen L, et al. Targeting DNA Damage Response Promotes Antitumor Immunity through STING-Mediated T-cell Activation in Small Cell Lung Cancer. Cancer Discov 2019;9:646-61.

Keywords: small cell lung cancer (SCLC), Immunotherapy, biomarkers

MS09 IMMUNOTHERAPY IN SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

MS09.03 SMALL CELL LUNG CANCER: THE IMMUNE MICROENVIRONMENT

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Based in part on the relatively high tumor mutational burden (TMB) and the strong link to tobacco use, there was a relative optimism regarding the prospects of success with immunotherapy in small cell lung cancer (SCLC). Over the past few years, while we have seen promising activity with checkpoint inhibitors in SCLC, the gains have been somewhat modest. As in other immune-responsive tumors, durable responses and long-term survival are possible. Nivolumab and pembrolizumab monotherapy have both demonstrated impressive durations of response, circling 18 months in the third line setting (Ready, JTO 2018; Chung, AACR 2019). Landmark survival rates far exceed historic controls in this setting. Meaningful benefit, though, is limited to a subset of patients, with response rates of only 12-19%. Both agents received accelerated approval by the FDA as third-line therapy for SCLC, but given the high attrition rate in SCLC, the impact of these approvals will be limited. Second-line and maintenance trials have failed to improve upon historic standards (Reck, ESMO 2018; Owonikoko, ELCC 2019). Fortunately, the addition of the PD-L1 inhibitor atezolizumab to first line carboplatin and etoposide improved both progression-free survival and overall survival (Horn, NEJM 2018). While the long-overdue improvement in survival was important and led to the FDA approval of atezolizumab in March 2019, there is significant room for improvement. The current use of checkpoint inhibitors in SCLC is empiric, though it is glaringly obvious that the true, durable benefit is limited to a subset of patients. Biomarkers are needed to identify those patients – to ensure they receive the appropriate therapy but also to help direct other patients to novel strategies. Predictive biomarkers can also provide valuable insight into the underlying biology of immune responses. Biomarker studies are challenging in SCLC; tissue samples are often scant, and the aggressive nature of the disease often precludes in depth study. Early data, though, speak to particular importance of the immune microenvironment in SCLC. Expression of PD-L1 by immunohistochemistry holds predictive value in non-small cell lung cancer (NSCLC). Its role in SCLC is evolving. In the CheckMate-032 study, nivolumab alone or in combination with the anti-CTLA-4 antibody ipilimumab, was explored in patients with previously treated SCLC (Hellmann, ASCO 2017). Using the 28-8 PD-L1 clone and a cutoff of 1%, only 18% of evaluable samples expressed PD-L1. Surprisingly, responses were more frequent in the PD-L1 negative tumors. With nivolumab alone, the response rate was 9% in PD-L1 positive tumors compared to 14% in PD-L1 negative tumors. With the combination of nivolumab and ipilimumab, the difference was even greater with a 10% response rate in PD-L1 positive tumors compared to 32% in PD-L1 negative. Some parallels are seen with pembrolizumab, but our understanding of PD-L1 as a biomarker is evolving. In a single arm study of maintenance pembrolizumab for SCLC (Gadgeel, JTO 2018), only 3 out of 30 patients had tumors with PD-L1 expression using the 22C3 clone (tumor proportion score, TPS). While the median PFS for the entire population was only 1.4 months, the 3 patients with TPS PD-L1 positive tumors all had a PFS over 10 months. Expression of PD-L1 at the stromal interface was also explored (combined proportion score, CPS). More patients had PD-L1 positive tumors using the CPS approach (8/20, 40%) and outcomes were superior in the CPS PD-L1 positive population: response rate was 37.5% vs. 8.3%, median PFS was 6.5 months vs. 1.3 months, and median overall survival was 12.8 months compared to 7.6 months. Similar results were seen in the salvage setting. In KEYNOTE-158, patients with previously treated SCLC received pembrolizumab monotherapy (Chung, ASCO 2018). Using the CPS approach, 39% of patients were PD-L1 positive, 47% were negative and 14% were non-evaluable. Again, outcomes favored the CPS PD-L1 positive subset including response rate (35.7% vs. 6%) and overall survival (14.9 months vs. 5.9 months). A separate retrospective analysis of a 95-sample cohort noted tumor expression of PD-L1 in 18% of samples but PD-L1 expression on tumor infiltrating lymphocytes (TILs) was seen in 67% of samples (Rivalland, ASCO 2017). There was no difference in survival based on tumoral expression of PD-L1, but median survival was longer in patients with PD-L1 positive TILs compared to PD-L1 negative TILs (17.2 months vs. 7.9 months, HR 0.36; 95% CI 0.22-0.60). The importance of the immune microenvironment in facilitating an immune response is becoming increasingly clear but it extends beyond expression of PD-L1. The presence and the specific location of tumor-infiltrating T-cells also holds value. Specific immunophenotypes are present and have been described as immune-desert (with few or no CD8+ T cells), immune-excluded (with CD8+ T cells present but limited to the adjacent stroma), and immune-inflamed (with CD8+ T cells in contact with tumor cells). A study of olaparib and durvalumab examined these phenotypes in patients with advanced SCLC (Thomas, JTO 2019) and found 14% with an immune-desert phenotype, 64% of samples with an immune-excluded phenotype and 21% with an immune-inflamed phenotype. PD-L1 expression was noted in all patients who achieved a response but was also noted in non-responders. In contrast, all of the patients with an immune-inflamed phenotype achieved a response. Much more work is needed to fully understand how the immune microenvironment facilitates (or precludes) immune responses. It is not yet clear whether these characteristics can be used as a predictive marker for use of checkpoint inhibitors. It is also not clear whether strategies to alter the microenvironment (with radiation therapy or other immune modulators) will induce effective immune responses. What is clear is that empiric therapy can only take us so far in the management of this exceptionally lethal disease. The path forward will require insight into the complexities orchestrating immune responses and a personalization of therapy for specific subsets of SCLC, subsets that certainly exist but, to date, evade proper detection. We have made tremendous strides in recent years to improve outcomes in SCLC but there remains much work to do.

Keywords: small cell lung cancer, immune microenvironment, tumor microenvironment

MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.01 COPD/EMPHYSEMA

J. Zulueta

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Lung cancer and COPD are now the second and third most frequent causes of death in the US. Mortality from COPD has increased by 86% in the last 25 years (1), but remains a greatly underdiagnosed disease. Furthermore, COPD, and in particular emphysema, has been shown to signficantly increase the risk of having, and dying from, lung cancer (2-4). In spite of these facts, the USPSTF continues to recommend against screening for COPD mainly because there is no evidence showing that any treatment or intervention can have an impact on the outcome of COPD. In this presentation we will review the latest data showing that lung cancer screeing may be an opportunity to uncover a large proportion of patients with underdiagnosed COPD, and that screening for lung cancer may have an impact on long term outcome of COPD. In addtition, the presence of COPD and/or specific subtypes of emphysema may be key in improving the selection of optimal candidates for lung cancer screening. Questions regarding the potential harms involved in screening for lung cancer in individuals with COPD/emphysema will be addressed. 1. Mulshine. AJPH 2018; 108:1294-5 2. de Torres et al.

Chest 2007;132:1932-8 3. Zulueta et al. Chest. 2012;141(5):1216-23 4. Wilson et al. Am J Respir Crit Care Med. 2008;178:738 5. Gonzalez et al. PLoS One 2019; in press.

Keywords: Emphysema, lung cancer screening, COPD

MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.02 CORONARY ARTERY DISEASES

J. Shemesh

Sheba Medical Center Affiliated to Tel Aviv University, Ramat-Gan/Israel

CT-based Coronary artery calcification (CAC) Agatston score on Lung cancer screening has an unequivocal prognostic contribution to future cardiovascular (CV) events and mortality. : To provide the radiologists with helpful information regarding on how to diagnose, quantify and routinely report on CAC while reading low dose chest CT (LDCT) performed for lung cancer screening. : CAC can be easily detected and its extent can be quantify or semi-quantify while reading the chest CT without extra radiation, efforts or cost. Most of the target subjects for lung screening are at the same time at high risk to develop cardiovascular (CV) events and mortality (1). Reporting on CAC enhances the lung screening benefit by providing the clinicians with an additive powerful risk stratification tool that can improve the management of primary prevention of CV events particularly the need for statin. Recently the Society of Cardiovascular Computed Tomography (SCCT) and the Society of Thoracic Radiology (STR) have jointly published guidelines for coronary artery calcium scoring derived from non contrast noncardiac chest CT scans (2). The experts of this guideline, recommend reporting on CAC as indication. It has been shown that the absence, presence and severity of CAC identify those who are most likely to benefit from statin therapy for primary prevention (3) Comparing those with and without statin exposure, statin therapy was associated with reduced risk of MACE in patients with CAC but not in patients without CAC. They further found that the effect of statin use on MACE was significantly related to the severity of CAC, with the number needed to treat to prevent 1 initial MACE outcome over 10 years ranging from 100 (CAC 1 to 100) to 12 (CAC >100). The most recent guidelines recognize the CAC score as disease score that can individualize the CVD risk and recommended its use to refine the risk estimation in order to better allocate asymptomatic subjects to statin treatment,intensification or avoidance, for primary prevention of CVD (4). The Multi-Ethnic Study of Atherosclerosis (MESA) score is a new score that incorporates the Agatston CAC score in addition to traditional risk factors to estimate the 10 years cardiac risk (5) CAC is the most prevalent incidental finding on LDCT. It can be easily detected measured and reported on lung screening CT without extra radiation, efforts or cost. CAC score helps to avoid or recommend life time statin or aspirin treatment. 10 Take home messages Most of the target subjects for lung screening are at the same time at high risk to develop cardiovascular (CV) events and mortality. CAC is the most prevalent incidental finding on LDCT CAC is the best biologic prognostic marker for the prediction of CV events and mortality. The measure of CAC is now accepted as common practice for primary prevention of CV events. CAC can and should be measured and reported on chest CT done for lung cancer screening. CAC is associated strongly and in a graded fashion with 10-year risk of incident ASCVD as it is for CHD, independent of standard risk factors, and similarly by age, gender, and ethnicity. While those with zero CAC are almost exclusively below 5% 10 years risk (statin is not indicated), those with CAC≥100 were consistently above 7.5% (statin is indicated). In a large-scale cohort without baseline ASCVD, the presence and severity of CAC identified patients most likely to benefit from statins for the primary prevention of CVDs: There was no benefit of statins in those with no CAC and low or intermediate baseline risk. Patients with a CAC >100 had a 64-71% reduction in MACE even with low (<5%) or intermediate risk (5-20%). Reporting on CAC enhances the lung screening benefit by providing the clinicians with an additive powerful risk stratification tool that can improve the management of primary prevention of CV events particularly for the initiation / withhold / intensification / avoidance of statin treatment. CAC can be estimated as none, mild, moderate or severe but it is recommended to perform the Agatston CAC score. CAC score can recategorize up to half of those who underwent chest CT into a higher or lower CV risk category. REFERENCES Hecht HS, Henschke CI, Yankelevitz D et al. Combined detection of coronary artery disease and lung cancer. Eur Heart J. 2014;35:2792–6 Harvey S. Hecht, Paul Cronin Michael J. 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MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.03 AORTIC VALVE CALCIFICATIONS

Y. Zhu[1], Y. Wang[2], W. Gioia[1], R. Yip[1], A. Jirapatnakul[1], M. Chung[1], D. Yankelevitz[1], C. Henschke[1]

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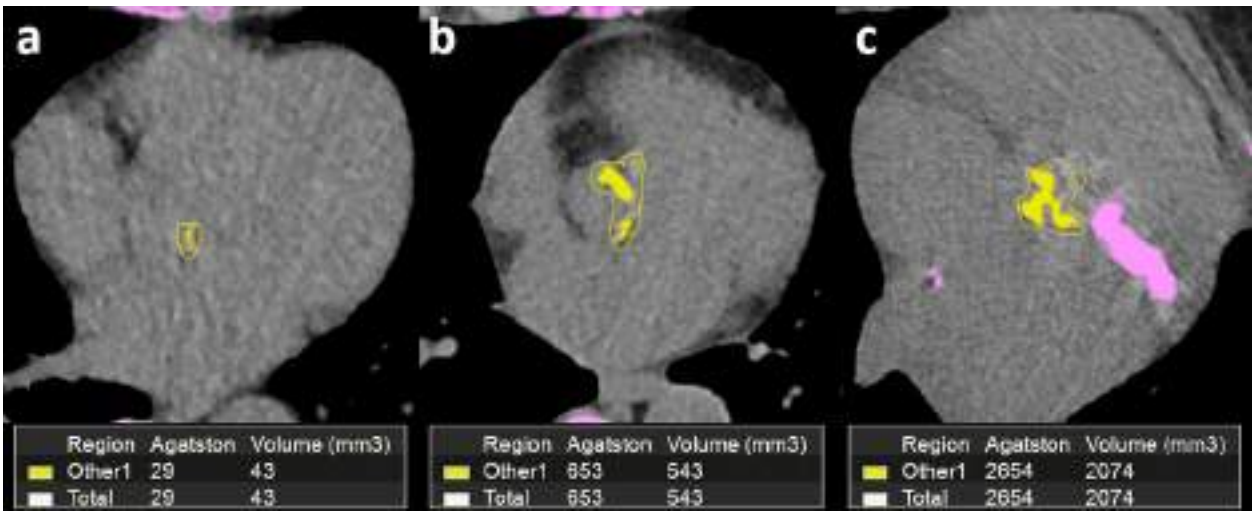
Smoking is a major risk factor for both cardiovascular disease and lung cancer. Low-dose computed tomography (LDCT) screening for lung cancer provides an opportunity to identify both diseases in asymptomatic smokers (1). The extent of aortic valve calcification (AVC) is the predominant driver of degenerative aortic valve stenosis (AS) (2), which is an underdiagnosed and undertreated disease. Cardiovascular morbidity and mortality is higher for people with moderate/severe AVC as compared to those with none or mild AVC as demonstrated on echocardiography (3). Our study aimed to assess sensitivity and reliability of visual AVC scoring on LDCT for predicting AS in older smokers. In addition, we aimed to determine the frequency of any AVC and its significant predictors in a program of LDCT screening for lung cancer, separately on baseline and annual repeat screenings. We reviewed 1225 consecutive participants in annual LDCT screening for lung cancer at the Mount Sinai Hospital before July 2018, who had at least two LDCTs without aortic valve replacement (AVR) before enrolled. The baseline LDCT was the first scan obtained at the time of enrollment and the most recent LDCT was the last LDCT obtained before July 2018, unless the participant had either AVR or had died before July 2018; for these cases, the last LDCT scan before surgery or death was used. Sensitivity and specificity of moderate/severe visual AVC score on LDCT to identify AS on echocardiogram was calculated for 126 participants who had both tests within 12 months. Using regression analyses, risk factors for AVC at baseline, for progression, and for new AVC on annual rounds of screening were identified. Reliability of AVC assessment on LDCT was assessed by comparing AVC visual scores with 1) standard-dose, electrocardiography (ECG)-gated CT for 31 participants who had both tests within 12 months, 2) with Agatston scores of 1225 participants on the most recent follow-up LDCT, and 3) by determining the intra-reader agreement on baseline LDCTs and separately for the most recent LDCTs of all participants. Results:Among these 126 participants who had LDCT and echocardiography within 12 months, 7 (5.6%) were diagnosed with moderate/severe AS, 3 (2.4%) were diagnosed with mild AS, 37 (29.4%) with aortic sclerosis, and 79 (62.7%) with no sclerosis or AS (Table 1). Of the 3 diagnosed as severe AS on echocardiography, all 3 had severe (grade 3) AVC on LDCT and of the 4 diagnosed as moderate AS on echocardiography, all 4 had moderate (grade 2) AVC on LDCT. Visual AVC scores on LDCT had substantial agreement with the severity of AS on echocardiography (weighted kappa=0.68, 95% CI: 0.56, 0.80). In addition, correlation was significant between the AVC visual scores on LDCT and both the echocardiographically determined mean pressure gradient (p = 0.02) and aortic valve area (p = 0.02) in these 10 participants with AS. Sensitivity and specificity of moderate/severe visual AVC scores for moderate/severe AS on echocardiogram was 100% and 94%, respectively. There is substantial inter- (total weighted kappa of 0.73) and excellent intra-observer agreement (Baseline LDCT: weighted Kappa=0.91, 95%

CI: 0.88-0.95; The most recent LDCT: weighted Kappa=0.90, 95% CI: 0.88-0.92). Of the 1225 participants, no AVC was identified on the baseline LDCT in 1081 (88.2%), while 116 had mild AVC (grade 1), 26 moderate AVC (grade 2), and 2 severe AVC (grade 3). On the most recent LDCT, median follow-up time from baseline LDCT was 10.9 years (IQR: 4.2 to 15.1 yrs.), 865 (70.6%) had no AVC, 262 (21.4%) mild AVC, 80 (6.5%) moderate AVC, and 18 (1.5%) severe AVC. Multivariable logistic regression analysis showed significant predictors for baseline AVC were male sex (OR=3.39), age (OR=1.11) and CAC score (OR=1.28), for AVC progression after baseline, was pack-years of smoking (HR=1.01), and for new AVC on annual LDCT, were male sex (HR=1.65), age (HR=1.06), and BMI (HR=1.06). Conclusions: Our results suggest that moderate to severe AVC scores could be reliably obtained on LDCT, should also be reported on screening LDCTs and further workup by echocardiography should be recommended as finding moderate or severe AVC on LDCT was associated with a high probability of AS in asymptomatic smokers. 1. Lu MT, Onuma OK, Massaro JM, D'Agostino RB, Sr., O'Donnell CJ, Hoffmann U. Lung Cancer Screening Eligibility in the Community: Cardiovascular Risk Factors, Coronary Artery Calcification, and Cardiovascular Events. Circulation. 2016;134(12):897-9. 2. Nguyen V, Cimadevilla C, Estellat C, et al. Haemodynamic and anatomic progression of aortic stenosis. Heart. 2015;101(12):943-7. 3. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. The New England journal of medicine. 1999;341(3):142-7.

		Aortic stenosis categories based on Echocardiography*					
		No Aortic Stenosis		Aortic Stenosis			Total
		None	Aortic sclerosis	Mild	Moderate	Severe	
Visual AVC scores †	None (0)	72	14	0	0	0	86
	Mild (1)	7	18	1	0	0	26
	Moderate (2)	0	5	2	4	0	11
	Severe (3)	0	0	0	0	3	3
	Total	79	37	3	4	3	126

Weighted Kappa=0.68 (95% CI: 0.56, 0.80).



Keywords: Visual scoring of aortic valve calcifications, lung cancer screening, Aortic valve stenosis

MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.04 LIVER - PULMONARY DISEASE

A. Branch

Icahn School of Medicine at Mount Sinai, New York City/United States of America

Evidence of an Association between Pulmonary Dysfunction and Fatty Liver Disease Background:There is an epidemiological association between pulmonary dysfunction and fatty liver disease. To investigate the association between pulmonary dysfunction and liver steatosis in members of the World Trade Center General Responder Cohort and other populations. : FIB-4 scores were calculated from the most recent data in electronic health records; fibrosis was defined as a FIB-4 score ≥ 2.67, which is associated with a 43-fold increased risk of liver-related mortality. Fatty liver was determined by automated analysis of non-contrast chest CT scans; attenuation < 40 Hounsfeld Units (HU) indicated moderate-to-severe steatosis, which means that ≥ 30% of hepatocytes contain excessive lipid. Primary liver cancer was identified by filtering on international classification of diseases (ICD9/10) codes 155/C22, and verifying the diagnosis by chart review. Multivariable logistic (MVL) regression was used to identify factors independently associated with liver fibrosis and steatosis. All reported findings are significant at $p < 0.05$. : Among 18,231 responders, 414 (2.3%) had liver fibrosis, which was associated with lower body mass index (BMI), obstructive pulmonary disease, male sex, smoking history, alcohol history, and less education. Among 7227 responders who denied smoking and/or heavy alcohol consumption, 112 (1.5%) had liver fibrosis, which was again associated with lower BMI, reduced pulmonary function, male sex, and less education. Among 1248 responders with CT scans available for analysis of liver status, 184 (15%) had moderate-to-severe steatosis. Fatty liver was associated with arrival at the WTC site on 9/11 and higher values of ALT, AST, bilirubin, neutrophils, and BMI. Among the responders with fatty liver, 38 (21%) were not obese (BMI < 30 kg/m^2). The non-obese responders had higher values of ALT, AST, and bilirubin, and lower values of platelets, indicating that they had more advanced liver disease. Thirty-three responders had primary liver cancer. : Among WTC responders, liver fibrosis was associated with pulmonary dysfunction and lower BMI; excessive weight and metabolic disease were not the primary drivers. Among responders with liver fat, those with lower BMI had more extensive liver damage, as often occurs in toxicant-associated steatohepatitis (FAMRI, NIOSHU01OH011489).

Keywords: fatty liver, toxicant-associated steatohepatitis, liver fibrosis, pulmonary dysfunction

MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.06 INTERSTITIAL LUNG DISEASES

M. Salvatore

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Patients with a history of smoking are enriched population for studying pulmonary fibrosis and as patients are living longer with fibrosis, they are becoming an enriched population for studying lung cancer (1). Usual interstitial Pneumonitis is the most frequent pattern of pulmonary fibrosis in the United States. There are 48,000 new patients with IPF each year in the US and 40,000 die (2). Ozawa found that the cumulative incidence of lung cancer is 3.3%, 15.4%, and 54.7% at 1, 5, and 10 years of IPF (3). Adenocarcinoma is most common lung cancer in the general population. Kawasaki found that of 53 patients with IPF and lung cancer, there was no predominant histology. There are similarities between lung cancer and fibrosis, which include invasion of normal tissue, lack of monoclonality, mutation of tumor suppressor genes and epithelial mesenchymal transformation (4). The tumor microenvironment often causes cancers in fibrosis to have shorter doubling times. The survival of patients with lung fibrosis and cancer is poor with up to 93% 5-year mortality (5). Screening for lung cancer in patients with fibrosis is different from screening in non-fibrotic patients because of the potential rapid growth of some cancers. Lung cancer occurring in a patient with fibrosis are different from lung cancer occurring in a patient with emphysema. The patients are often not candidates for surgery. If they have surgery, it should be as limited as possible to decrease the risk of exacerbation (6). Chemotherapy increase risk of an exacerbation as does immunotherapy (7). Radiation has an increased risk of exacerbation as well; perhaps proton therapy may have better outcomes (8). In summary as patients are living longer with fibrosis the incidence of lung cancer is increasing however the treatments for early cancer in patients with lung cancer increase the risk of fibrosis exacerbation and further study is necessary in this area to make recommendations for best practices. References: 1. Salvatore M, Henschke CI, Yip R, Jacobi A, Eber C, Padilla M, Knoll A, Yankelevitz D. JOURNAL CLUB: Evidence of Interstitial Lung Disease on Low-Dose Chest CT Images: Prevalence, Patterns, and Progression. AJR Am J Roentgenol 2016 Mar; 206(3):487-94. 2. G. Raghu, S.Y. Chen, Q. Hou, W.S. Yeh, H.R. Collard, Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old, Eur. Respir. J.48 (1) (2016). 3. Ozawa Y, Suda T, Naito T, Enomoto N, Hashimoto D, Fujisawa T, Nakamura Y, Inui N, Nakamura H, Chida K.: Cumulative incidence of and predictive factors for lung cancer in IPF. Respirol. Carlt. Vic., 14 (5) (2009), pp. 723-728. 4. H. Kawasaki, K. Nagai, T. Yokose, J. Yoshida, M. Nishimura, K. Takahashi Clinicopathological characteristics of surgically resected lung cancer associated with idiopathic pulmonary fibrosis. J. Surg. Oncol., 76 (1) (2001), pp. 53-57. 5. Teixeira MR, Heim S. Cytogenetic analysis of tumor clonality. Adv Cancer Res. 2011; 112: 127–149. 6. Joo S, Kim DK, Sim HJ, Lee GD, Hwang SK, Choi S, Kim HR, Kim YH, Park SI. Clinical results of sublobar resection versus lobectomy or more extensive resection for lung cancer patients with idiopathic pulmonary fibrosis. J Thorac Dis. 2016; 8(5): 977–984. 7. E Watanabe N, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishiyama O, Kondo M, Hasegawa Y. Efficacy of chemotherapy for advanced non-small cell lung cancer with idiopathic pulmonary fibrosis. Respiration 2013; 85(4): 326–331. 8. Hakyoung Kim, Hongryull Pyo, Jae Myoung Noh, Woojin Lee, Byoungsuk Park, Hye Yun Park and Hongseok Yoo. Preliminary result of definitive radiotherapy in patients with non-small cell lung cancer who have underlying idiopathic pulmonary fibrosis: comparison between X-ray and proton therapy. Radiat Oncol. 2019 Jan 28; 14(1):19.

Keywords: pulmonary fibrosis

MS10 LUNG CANCER SCREENING, OPPORTUNISTIC EVALUATION OF FINDINGS
MONDAY, SEPTEMBER 9 15:45–17:15

MS10.07 BREAST EVALUATION

L. Margolies

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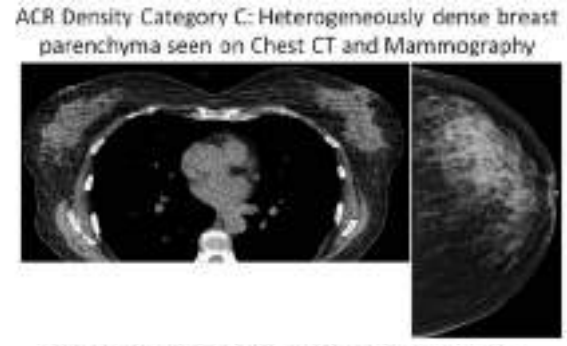
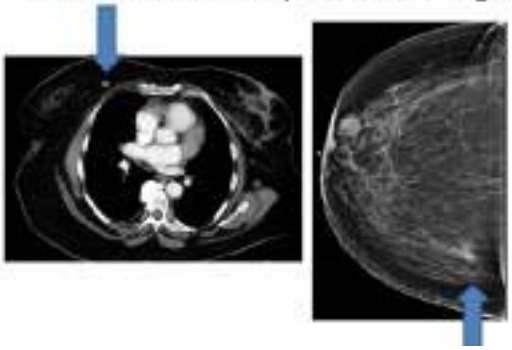


Figure 2: Medial Right Breast Mass is much easier to see on CT compared to mammogram



Opportunistic Evaluation of the Breast on Cross Sectional Imaging Breast tissue is visualized on Chest CT, Chest MRI and to a limited extent on cross sectional imaging of the abdomen; much information about the breasts can be obtained. While cross sectional imaging does not substitute for mammography, for those women who have not had recent mammograms it may be the only opportunity for the breasts to be evaluated. Additionally, there are portions of the medial and posterior breast which can sometimes be seen to better advantage on cross sectional imaging. Breast Density is a known risk factor for breast cancer development and can mask tumors on mammography. Traditionally, it has been taught that breast density can only be determined by mammography, but it can be reliably determined by evaluating the breasts on CT.[i] (figure shows a Chest CT of a woman with heterogenously dense breasts and corresponding cranio-caudal mammogram image) Reporting of breast density on Chest CT can better inform the patient of her risk and possible imaging strategies. Masses and some calcifications can be seen on CT. Some are known and require no further evaluation, others are classically benign and also require no further evaluation, but some appear new or changed and do require dedicated breast imaging. By using a breast assessment and recommendatin score (BARCS) system to evaluate and report breast CT findings one can communicate to referring physicians what the next steps if any might be. This is similar to the BI-RADS system used for reporting mammography A BARCS score of 1 or 2 is analogous to the commonly used BI-RADS 1 or 2 and indicates that the findings are negative or benign and no special evaluation is needed. A CT-BI-RADS 2 might be used, for example, in the setting of a classic fibroadenoma. A mass that does not exhibit classic benign features, however, might be given a BARCS 0 and the patient referred for dedicated breast imaging (or review and correlation with prior breast imaging) as the imaging evaluation is incomplete. [ii] Some of these findings will be breast cancer (figure 2 shows a mass in the medial right breast that is easier to see on Chest CT than on mammogram where there is only a developing asymmetry - arrows). The opportunity to fully include and evaluate the breasts on cross sectional imaging should not be missed.[iii] Breast masses can also be an incidental MRI finding.[iv] Dedicated breast imaging also has the opportunity to detect lung and other disease. Breast MRI, for example, typically includes portions of the lung and abdomen where osseous, lung, liver and renal lesions can be seen.[v] Mammography can detect lymphoma, metastatic melanoma and other systemic diseases such as congestive heart failure [vi] or even be the first indication of re-activation of Tuberculosis.[vii]Cardiovascular disease can manifest itself with breast arterial calcification evident on mammography; this often correlates with coronary artery calcification despite the differences in the pathogenesis of the calcifications. [viii] Patients[ix] and providers[x] want interpreting radiologists to report on all the imaging findings; chest imagers have the opportunity to detect breast disease and promote appropriate evaluation of findings as well as to assist in personalizing breast cancer screening algorithms. [i] Salvatore M, Margolies L, Kale M, et al. Breast Density: Comparison of Chest CT with Mammography. Radiology 2014 270:1, 67-73. [ii] Margolies, LR, Salvatore M, Yip R, et al. The chest radiologist's role in invasive breast cancer detection. Clinical Imaging 2018, Volume 50, 13 - 19. [iii] Salvatore M, Margolies, L, Bertolini, A, et al. The need to be all inclusive: Chest CT scans should include imaged breast parenchyma. Clinical Imaging 2018 Volume 50, 243-245. [iv] Bignotti B, Succio G, Nosenzo F, et al. Breast findings incidentally detected on body MRI. Springerplus. 2016;5(1):781. [v] Gao Y, Ibidapo O, Toth HK and Moy L. Delineating Extramammary Findings at Breast MR Imaging. Radiographics. 2017; 37:10–31. [vi] Cao MM, Hoyt AC, Bassett LW. Mammographic Signs of Systemic Disease. RadioGraphics 2011 31:4, 1085-1100 [vii] Hwang E, Szabo J, Federman A and Margolies LR. Reactivation tuberculosis presenting with unilateral axillary lymphadenopathy. Radiology Case Reports. 2018: 13(6): 1188-1191. [viii] Margolies L, Salvatore M, Hecht HS, et al. Digital Mammography and Screening for Coronary Artery Disease. JACC Cardiovasc Imaging. 2016 Apr;9(4):350-60. [ix] Margolies LR, Yip R. Hwang E, et al. Breast Arterial Calcification in the Mammogram Report: The Patient Perspective. AJR Am J Roentgenol. 2019 Jan;212(1):209-214. [x] Nasir K and McEvoy JW. Recognizing Breast Arterial Calcification as Atherosclerotic CVD Risk Equivalent. JACC: Cardiovascular Imaging Apr 2016, 9 (4) 361-363.

Keywords: Breast cancer, mammography, Screening

MS11 ADDRESSING CHALLENGES WITH SURGICAL RESECTION OF LUNG CANCER
MONDAY, SEPTEMBER 9 15:45–17:15

MS11.01 NEOADJUVANT CHEMOTHERAPY OR NEOADJUVANT CHEMORADIATION FOR POTENTIALLY RESECTABLE NSCLC - A SURGEON'S PERSPECTIVE

R. Terra

Sao Paulo State Cancer Institute (ICESP) University of São Paulo, Sao Paulo/ Brazil

Early studies of neoadjuvant therapy compared chemotherapy alone to surgery alone. Later, the Intergroup 0139 study utilized concurrent chemotherapy and radiation as its induction strategy, and this was the basis for adding radiation in the neoadjuvant strategy. Both strategies, neoadjuvant chemotherapy and neoadjuvant chemoradiation are considered alternatives for patients with stage IIIA non-small cell lung cancer deemed operable. However, the toxicity of combined chemotherapy and radiation is significant. Radiotherapy has an inflammatory effect that leads to a more difficult surgical procedure and increases the number of postoperative complications. Moreover, studies comparing both strategies failed to demonstrate superiority of any of the two strategies in terms of overall survival. On top of that, due to the limited number of radiotherapy clinics in emerging countries, radiotherapy schedules might delay the beginning of the patient's treatment. This is also an issue to be considered when offering neoadjuvant chemoradiation.

Keywords: neadjuvant chemotherapy, Thoracic surgery, Lung cancer

MS11 ADDRESSING CHALLENGES WITH SURGICAL RESECTION OF LUNG CANCER
MONDAY, SEPTEMBER 9 15:45–17:15

MS11.02 ROLE OF SURGERY IN OLIGOMETASTATIC NSCLC

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The management of oligometastatic non-small cell lung cancer (NSCLC) is controversial. Sixty percent of patients with NSCLC present with metastatic disease; 45% of those with initially localized disease eventually develop metastatic disease. With 15% of these being oligometastatic disease, this is a significant problem. Over the last two decades, several advances have occurred which frame this question better. First, advances in imaging techniques including improved PET-CT and MRI have helped identify what is likely to be truly oligometastatic disease. Second, there have been advances in local therapy including minimally invasive and robotic approaches and perioperative management, as well as advanced radiation techniques including stereotactic ablative radiotherapy (SABR) which have made it safer. Finally, systemic therapy has undergone major changes with targeted therapy and immunotherapy making considerable progress. Most patients with metastatic NSCLC would be treated with systemic therapy with local treatment being offered only for symptomatic palliation. However, recognition of a "oligometastatic" state (where metastases are limited in number and location) has led to series of patients being treated with potentially curative intent using local treatment options, predominantly surgical. Randomized trials to evaluate the role of surgery in oligometastatic NSCLC have not been performed, compelling a reliance on several published case series and meta analysis of these studies. These series have included highly selected patients with oligometastases, typically 1-3 metastases, most commonly located in the brain, and long term outcomes have been highly variable. Overall median five year survival of a meta analysis of studies was 23.3 percent. Five year survivals in patients treated with surgery both for the primary and the metastases range from as low as <10% to as high as 80% - this wide range is more likely a reflection of selection criteria for patients undergoing surgery rather than true variations in care. Moreover, with the lack of a true comparator arm, these results should be interpreted with caution. Important favourable prognostic factors include definitive treatment of the primary tumour, negative mediastinal nodal status and a longer disease-free interval. Lack of well conducted prospective studies make conclusive recommendations on surgery for treatment of oligometastatic disease difficult. This is especially true now when better radiation techniques like SABR and improved outcomes with systemic treatment in selected patients

with targeted and immunotherapy are available. Given the available evidence, it appears reasonable to consider surgical treatment in patients with oligometastatic disease fulfilling the following criteria: good performance status, accurately staged, with PET-CT and MRI brain showing no other sites of metastases, metachronous disease with relatively long disease free interval, negative mediastinal nodes on invasive staging, and controlled primary disease. With randomized trials being unlikely in this setting, further studies are required which prospectively collect real-world data systematically, enabling better selection criteria for patients for surgery in oligometastatic NSCLC.

Keywords: NSCLC, Oligometastases, surgery

MS11 ADDRESSING CHALLENGES WITH SURGICAL RESECTION OF LUNG CANCER
MONDAY, SEPTEMBER 9 15:45–17:15

MS11.03 MINIMIZING PERI-OPERATIVE MORBIDITY WITH PNEUMONECTOMY

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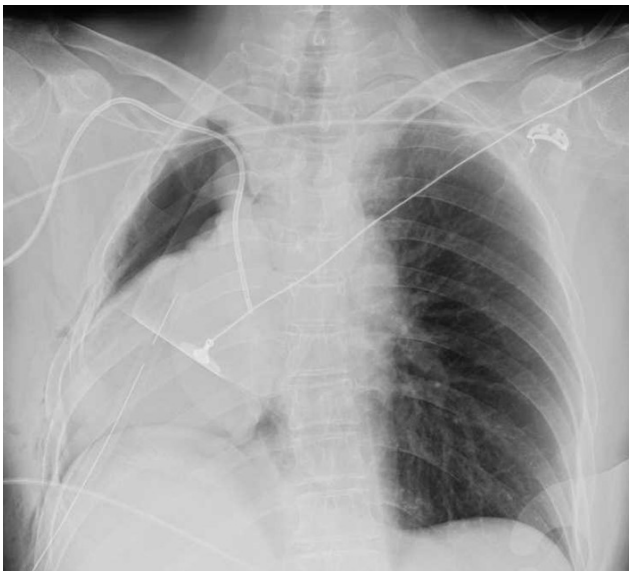
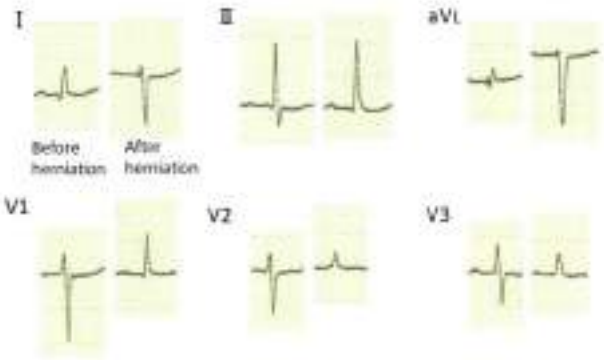
National Cancer Center Hospital, Tokyo/Japan

1. Introduction The incidence of surgical morbidity after standard pneumonectomy is reportedly 30 to 60%. Many previous studies have addressed several risk factors for surgical morbidity after pneumonectomy, including age, cardiovascular disease, recent body weight loss, high smoking index, low FEV1.0 value, chronic obstructive pulmonary disease (COPD), right pneumonectomy, massive blood loss during surgery, long operation time, neoadjuvant therapy and so on. Although surgical morbidity after pneumonectomy easily lead to patients' mortality. When pneumonectomy seems to be inevitable to remove the tumor, surgeons sometimes intraoperatively weigh the oncological benefit of pneumonectomy against the postoperative poor QOL and high morbidity rate. In this paper, the cause and proper management of postpneumonectomy complications are discussed to minimize peri-operative morbidity with pneumonectomy as for especially following two life-threatening categories, cardiovascular and respiratory complications. 2. Type of Complications 2.1 Cardiovascular Complications 2.1.1 Supraventricular Arrhythmias Most of supraventricular arrhythmias present 1 to 4 days after standard pneumonectomy, but it sometimes present even a week after surgery. The incidence of supraventricular arrhythmia after pneumonectomy is reportedly 4 to 25%. Risk factors for supraventricular arrhythmias include old age, right pneumonectomy, intrapericardial pneumonectomy, major co-morbidities, and so on. For patients who are considered to be high risk for postoperative atrial fibrillation, following prevention strategies are indicated. According to the 2014 AATS guidelines, continuing β blockers in patients taking β-blockers before surgery, using intravenous magnesium supplementation if serum magnesium levels are low, using diltiazem in those patients with preserved cardiac function who were not taking β-blockers preoperatively, or using amiodarone in patients at an intermediate to high risk of developing postoperative atrial fibrillation. For hemodynamically stable patients with new onset atrial fibrillation, intravenous β-blockers or calcium channel blockers are used to reduce a heart rate down to 100 beats per minute. When patients are hemodynamically unstable, direct current cardioversion should be used. And for patients with refractory atrial fibrillation, systemic anticoagulation therapy should be used carefully weighing benefits against the risk of bleeding, especially after EPP. 2.1.2 Ischemic Heart Disease Ischemic heart disease is known to be an independent risk factor for severe complications after pneumonectomy. The risk of a myocardial infarction after pneumonectomy is reportedly approximately 0.2 to 2.1%. Patients who are candidates for pneumonectomy should undergo careful preoperative assessment to screen for untreated coronary ischemic disease. 2.1.3 Cardiac Herniation Cardiac herniation is a rare complication after intrapericardial pneumonectomy. Patients develop cardiac herniation when the intrathoracic pressure changes rapidly by severe cough or vomit with decubitus position. Rapid and severe hemodynamic collapse following a change in patient positioning should heighten the clinical suspicion. Chest X-ray and electric cardiogram clearly show the abnormal position of the heart (Figure 1 and 2). Correction of the cardiac herniation should be conducted immediately by re-thoracotomy after successful resuscitation. Sewing the patch to the weak tissues around the pericardium rather than the pericardium itself after intrapericardial pneumonectomy could increase the risk of cardiac herniation. 2.2 Respiratory Complications 2.2.1 Pneumonia The incidence of pneumonia after pneumonectomy is reportedly 2 to 10%. Since pneumonia after pneumonectomy could be a life-threatening complication, care must be taken to lessen the risk of pneumonectomy. Preoperative smoking cessation, chest physiotherapy by nurses or respiratory therapists, use of enough amount of post-thoracotomy painkillers, and bronchial toilet by bronchoscope are important practical factors for minimizing the risk of pneumonia. 2.2.2 Acute Respiratory Distress Syndrome (ARDS) According to the previous literatures, ARDS occurs in 2.7 to 3.1% of patients after standard pneumonectomy with very high mortality of 50 to 70%. Treatment of ARDS is supportive. Mechanical ventilation with small tidal volumes of less than 6 mg/kg body weight should be used to minimize the barotrauma, and the FiO2 level should be decreased to the lowest level to minimize the oxidative trauma. There has been no evidence that steroids improve the prognosis of patients developing ARDS. 2.2.3 Bronchopleural Fistula (BPF) The incidence of BPF, which is a life-threatening complication, is reportedly 2 to 11%. The mortality of BPF after pneumonectomy is very high rate of around 40%. Risk factors for BPF includes diabetes mellitus, malnutrition, long stump (especially for left side), right pneumonectomy, preoperative chemoradiation therapy, and so on. When a patient develop the BPF, open window technique should be applied to control thoracic cavity infection which can lead the patient to death. 3. Conclusion The mortality and morbidity rates after pneumonectomy are very high compared with those after lobectomy, simply because the patients have less cardio-pulmonary reservations. Therefore, when complications occur, surgeons must aggressively treat them not to lose the patient with taking abovementioned knowledge into consideration. Figure 1





Keywords: pneumonectomy, morbidity, mortality

MINI SYMPOSIA

MS11 ADDRESSING CHALLENGES WITH SURGICAL RESECTION OF LUNG CANCER
MONDAY, SEPTEMBER 9 15:45–17:15

MS11.04 SURGICAL RESECTION OF SCLC - NOT SO OBSOLETE ANY LONGER

G. Lyons

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More than 2 million new lung cancer cases were detected worldwide in 2018, and small cell lung cancer (SCLC) represents about 13-15 % of all lung cancers. Although surgery was initially regarded as the treatment of choice for all types of lung cancer, it was abandoned for SCLC almost 30 years ago after the results of the Medical Research Council (MRC) randomized trial conducted by Fox et al. in 1973, which showed poor mean survival for the surgical group when compared to the RT group (6.5 months vs. 10 months, P = 0.04). (1) These results led to the abandonment of surgery as a standard treatment in favor of chemotherapy. Two subsequent meta-analyses revealed that the addition of thoracic radiation to systemic chemotherapy improved survival, and that has become the standard of care. (2) After the introduction of TNM classification, investigators proposed that surgery was postulated to be indicated in limited-SCLC, particularly stage T1, N0, with 5-year survival rates of as high as 52.6% for stage 1 disease. (3) Further, surgical resection after induction chemoradiotherapy demonstrated a control of local relapse in almost 100% of the patients and 5- and 10-year survival rates for patients with stage IIB to IIA were 39% and 35%, respectively, for all patients (resected or not) and 44% and 41% for patients treated with a trimodality approach including adjuvant surgery. (4) Another argument for surgical resection is that the final histology of SCLC might reveal a component of NSCLC in 11-25% cases. (5) In a recent series of Wakeam et al. including 2,089 patients with SCLC undergoing surgery who were matched 1:1 to those undergoing NST, surgery was associated with longer survival for stage I (median overall survival [OS] 38.6 months vs. 22.9 months), for stage II (median OS 23.4 months vs. 20.7 months), and stage IIIA (median OS 21.7 vs. 16.0 months. In analyses by T and N stage, longer OS was observed in resected patients with stage T3/T4 N0 (median OS 33.0 vs. 16.8 months, p=0.008) and node positivity (N1+ 24.4 vs. 18.3 months p=0.03; N2+ 20.1 vs. 14.6 months p=0.007). (6) A recent meta-analysis that included a total of 41,483 patients concluded that surgical resection was associated with superior OS in stage I (HR = 0.56, 95% CI: 0.49–0.64, p< 0.001), stage II (HR = 0.75, 95% CI: 0.57–0.99, P = 0.04), and stage III diseases (HR = 0.70, 95% CI: 0.56–0.88, P = 0.002). (11) Unlike stage I disease, there is no consensus for surgery in stage II and stage IIIA SCLC. Surgical resection is concordant with NCCN and ASCO guidelines; however, evidence shows that in the vast majority of T1 and T2 N0M0 patients, surgery is not offered in the absence of any documented contraindication. Rostadt et al., in a series of 2,442 patients with SCLC, found out that 26% were stages IA and IB and thus candidates for surgical resection, while only 38 patients (1.5%) underwent surgical therapy. (8) CT screening identifies SCLC at an earlier stage – with better survival – than usual care and offers the hope that more SCLC patients may become long-term survivors. Austin et al. carried out a multinational study of baseline and annual repeat CT screenings of 48,037 volunteers at risk for lung cancer. (9) They found 48 SCLC cases, 92% of which were asymptomatic at diagnosis. Clinical stage was IA in 16 patients (33%), II in 5 (11%), III in 20 (42%), and IV in 7 (15%). Estimated cure rates were 36% overall and 54% for the clinical stage I cases. Surgical resection is indicated in SCLC in stages I and IIA after precise staging including mediastinoscopy. Patients should receive systemic therapy after resection and mediastinal radiation therapy in cases with nodal metastases. Surgical resection in stages I and IIA SCLC is concordant with NCCN and ASCO guidelines; however, surgery is offered only in one-third of the patients in the absence of any documented contraindication. CT screening identifies SCLC at an earlier stage and offers the hope that more SCLC patients may be candidates for surgical resection and become long-term survivors. Selected cases in stages IIB and IIIA may be candidates for surgery as part of the multidisciplinary treatment. 1) Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet. 1973; 2: 63–5.) 2) Pignon JP, Arriagada R, Ihde DC, et al. 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Keywords: small cell lung cancer, surgery

MS11 ADDRESSING CHALLENGES WITH SURGICAL RESECTION OF LUNG CANCER
MONDAY, SEPTEMBER 9 15:45–17:15

MS11.05 PATHOLOGICAL REPORTING OF RESECTED LUNG CANCER - THE IMPORTANCE OF USING ADDITIONAL TNM DESCRIPTORS

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Context. The anatomopathological examination aims to establish a specific diagnosis of the tumor and to provide essential information related to cancer staging, patient management and prognosis. Such information, as histologic type, lymphovascular invasion, spread through air spaces, margins, treatment effect, and TNM descriptors should be disclosed concisely, following previously defined protocols, and correlate satisfactorily with radiological exams and clinical aspects in order to allow the best management for the patient. Histopathological (macroscopic and microscopic evaluation) combined with complementary immunohistochemical and molecular studies, provides prognostic and predictive information on tumor biology and clinical behavior. The TNM staging classifies the tumors according to the anatomic extent with an important prognostic impact. In addition, it allows the establishment of criteria for inclusion and exclusion of patients in protocol studies and subgroups of treatment, cancer registry, epidemiology and multidisciplinary management. The T component analysis is complex because it has many elements: presence or absence of invasion, tumor size, endobronchial location, atelectasis / pneumonitis and invasion of the various anatomical structures around the lung. The determination of the largest tumor diameter requires accurate measurements since in the eighth edition TNM stage classification for lung cancer each centimeter separates tumors with different prognoses from 1 to 5 centimeters (cm). Appropriate size measurement is especially important when it comes to subsolid tumors since the correlation with the computed tomographic imaging in this context is of great value. Tumors measuring larger than 5 cm up to 7 cm (T3 in the eighth edition) had a worse prognosis than found in the seventh edition of the TNM classification. Tumors larger than 7 cm (T4 in the eighth edition) have similar prognosis to other descriptors in the T4 category. Atelectasis or pneumonitis involving the whole lung (T3 in the seventh edition) has the same prognosis for partial atelectasis / pneumonitis (T2 descriptor in the seventh edition). Endobronchial tumor location less than 2 cm from carina (a T3 descriptor in the seventh edition), but without carina involvement, had the same prognosis as the endobronchial location further than 2 cm from carina (a T2 descriptor in the seventh edition). In the eighth edition, tumors involving the main bronchus and associated with atelectasis / pneumonitis are classified as T2. On the other hand, diaphragm invasion (a T3 descriptor in the seventh edition was upstaged to T4 in the eighth edition) since it has similar prognosis of T4 tumors. No changes to the N descriptors were proposed in the 8th TNM as the four N categories (N0, N1, N2, N3). The reassessment of the M

component validated the proposed M1a category descriptors in the seventh edition and separated the distant metastases into two categories with different prognoses, M1b (single metastatic tumor in one organ), and M1c (multiple metastases in either single organ or multiple organs). Objective. To review and discuss the 8th edition of the TNM classification of lung cancer with an emphasis on prognostic relevance and implications for the pathologist's report. Data Sources. The review is based on the available literature. Conclusion. The TNM (tumor-node-metastasis) classification system for lung cancer is the strongest prognostic indicator and fundamental for decisions on therapy. The eighth edition of the TNM classification of lung cancer enhances the prognostic discrimination of the different T categories and differentiates unique extrathoracic metastasis (better prognosis) from multiple metastases in one or several organs providing better definition of oligometastatic disease. Thus, the eighth edition of TNM improves the understanding of tumor anatomic extent and stratification of tumors for clinical trials. References: 1) Rami-Porta R, Call S, Dooms C, Obiols C, Sanchez M, Travis WD et al. Lung cancer staging: a concise update. Eur Respir J. 2018;51(5). 2) Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G et al. The IALSC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2015;10(7):990-1003. 3) Detterbeck FC. The eighth edition TNM stage classification for lung cancer: what does it mean on main street? J Thorac Cardiovasc Surg. 2018;155(1):356-359. 4) Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A 3rd et al. The IALSC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2015;10(11):1515-1522. 5) Kay FU, Kandathil A, Batra K, Saboo SS, Abbara S, Rajiah P. Revisions to the tumor, node, metastasis staging of lung cancer (8th edition): rationale, radiologic findings and clinical implications. World J Radiol. 2017;9(6):269-279. 6) Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer – major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155. 7) Nicholson AG, Tsao MS, Travis WD, Patil DT, Galateau-Salle F, Marino M et al. Eight edition staging of thoracic malignancies: implications of the reporting pathologist. Arch Pathol Lab Med. 2018;142(5):645-661. 8) Aokage K, Miyoshi T, Ishii G, Kusumoto M, Nomura S, Katsumata S et al. Clinical and pathological staging validation in the eighth edition of the TNM classification for lung cancer: correlation between solid size on thin-section computed tomography and invasive size in pathological findings in the new T classification. J Thorac Oncol. 2017;12(9):1403-1412. 9) Butnor KJ, Beasley MB, Dacic S, Berman M, Flieder D, Jones K et al. Protocol for the examination of specimens from patients with primary non-small cell carcinoma, small cell carcinoma or carcinoid tumor of the lung. Version: Lung 4.0.0.3. 2017. https://documents.cap.org/protocols/cp-thorax-lung-2017-protocol-4003.pdf

Keywords: TNM classification, pathology report, staging

MS12 GENOME SCREENINGS
TUESDAY, SEPTEMBER 10 11:30–13:00

MS12.01 CIRCULATING BIOMARKERS

C. Dive

Cancer Research UK Manchester Institute, Manchester/United Kingdom

I will describe ongoing studies that seek to develop circulating biomarkers for the early detection of lung cancer. We are taking a multi-assay approach to develop a blood test with sufficient sensitivity and specificity. Our efforts are supported with targeted sample collection from a cohort that are typically described as the high risk, hard to reach. Individuals are asked to attend free lung health checks in supermarket car parks in socially deprived areas of North Manchester where many are offered a low dose CT scan. This approach has allowed a paradigm shift from detection of lung cancer at stage 4 to stage 1-2 where surgery can often be offered with curative intent. Individuals are also asked to provide a blood sample for exploratory research. This approach is generating an optimal blood sample set comprising samples from individuals with a CT positive scan (a proportional of which are false positives) or a negative CT scan with full clinical follow up. I will discuss the challenges of early detection with liquid biopsies (ctDNA, CTCs and plasma proteomes) and our strategies to mitigate them.

Keywords: early detection, liquid biopsies

MS12 GENOME SCREENINGS
TUESDAY, SEPTEMBER 10 11:30–13:00

MS12.02 GENOMIC AND FUNCTIONAL APPROACHES TO UNDERSTANDING CANCER ANEUPLOIDY

A. Taylor[1], J. Shih[2], G. Ha[1], G. Gao[2], X. Zhang[1], A. Berger[2], A. Cherniack[1], R. Beroukhim[1], M. Meyerson[1]

[1]*Dana-Farber Cancer Institute and Broad Institute, Boston/United States of America,* [2]*Broad Institute, Cambridge/United States of America*

Aneuploidy, whole chromosome or chromosome arm copy number imbalance, is a near-universal characteristic of human cancers. We applied methods that define chromosome arm-level aneuploidy and a global cancer aneuploidy score to 10,522 tumors of 33 types in the Cancer Genome Atlas (TCGA). Aneuploidy level was correlated with *TP53* mutation, somatic mutation rate, and expression of proliferation genes. Aneuploidy was anti-correlated with expression of immune signaling genes, due to decreased leukocyte infiltrates in high-aneuploidy samples. Although yeast and mammalian models of whole chromosome aneuploidies have been extensively investigated, chromosome arm-level aneuploidies have rarely been modeled. Cancer subtypes are often characterized by tumor specific patterns of these arm-level copy number alterations; for example, squamous cell carcinomas (SCCs) from different tissues of origin (including lung, esophagus, and bladder) have a pattern of chromosome 3p loss and chromosome 3q gain. Our analysis of 495 lung SCCs found chromosome 3p deletion to be the most frequent genomic alteration, occurring in almost 80% of the tumors and covering the entire length of the chromosome arm. Over two-thirds of chromosome 3p genes showed significantly decreased expression in these samples. Without models of chromosome arm-level alterations, the phenotypic effects of specific aneuploidies in cancer, such as 3p deletion, remain unknown. However, recent advances in genome engineering and targeting of endonucleases allow new approaches to generate chromosomal alterations. Here, we used the CRISPR-Cas9 system to delete one copy of chromosome 3p *in vitro*. We successfully isolated almost 90 clones of immortalized lung epithelial cells with deletion of the 3p arm, with 8 validated by whole genome sequencing. Consistent with patient data, expression of 3p genes was also decreased upon deletion, as well as increased expression of interferon response genes. Phenotypic characterization revealed that cells with chromosome 3p deletion initially proliferated more slowly than their siblings. These chromosome 3p deleted cells had increased G1 arrest, but did not undergo increased apoptosis or cell death. Interestingly, after several passages in culture, the proliferation defect was rescued in chromosome 3p deleted cells; genome sequencing and karyotype analyses suggested that this was the result of chromosome 3 duplication. With our cellular model of chromosome arm-level aneuploidy, we uncovered a possible selection mechanism that allows aneuploidy tolerance *in vitro*. We used genome engineering to model chromosome arm-level deletions, providing a robust model that will address a gap in our understanding of aneuploidy in cancer.

Keywords: aneuploidy, squamous cancers, genome engineering

MS12 GENOME SCREENINGS
TUESDAY, SEPTEMBER 10 11:30–13:00

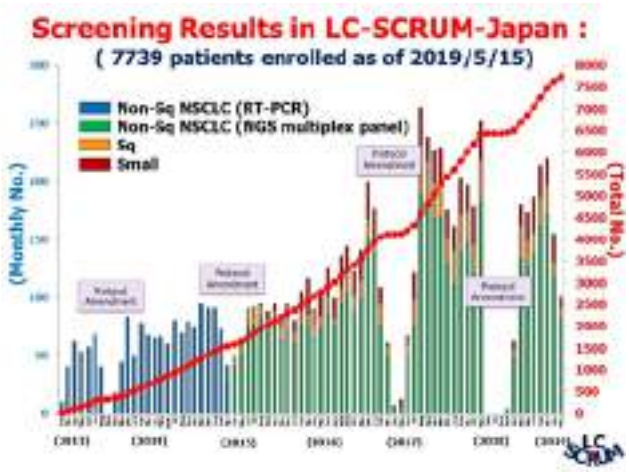
MS12.03 LC-SCRM-JAPAN, A PAN-JAPAN GENETIC SECREENING OF LUNG CANCER

K. Goto

National Cancer Center Hospital East, Kashiwa/Japan

Background: Recently many actionable driver oncogenes such as EGFR, ALK, RET, ROS1, BRAF and MET have been identified in non-small cell lung cancer (NSCLC). However, most of these driver oncogenes are rare and found in only about 1-2% of lung adenocarcinomas. To develop new molecular targeted agents for rare alterations, efficient genomic screening is needed to identify patients. A nationwide genomic screening platform (LC-SCRUM-Japan) was established to primarily screen for ALK, RET and ROS1 fusions using RT-PCR and FISH in advanced non-squamous NSCLC without EGFR mutations in February 2013. From March 2015, this project was expanded to an academic-industrial collaboration initiative with broader eligibility criteria and tumor samples were analyzed by next-generation sequencing (NGS multiplex analysis

with Oncomine™ Cancer Research Panel). In addition, non-squamous NSCLC regardless of EGFR mutation status and other histological type of lung cancer including squamous NSCLC and small cell lung cancer (SCLC) were enrolled. Clinical information of all patients have also been collected to generate a clinical-genomic database that enables detailed outcome analysis of the cohort. Since its inception, more than 200 Japanese hospitals participated in this project and 7739 patients were enrolled into LC-SCRUM-Japan. 776 squamous NSCLCs and 823 SCLCs were enrolled. Through this platform, many patients with rare driver oncogenes were identified for approved targeted therapies or successfully enrolled into various clinical trials that have helped develop new targeted agents. Based on our project, crizotinib and dabrafenib/trametinib were approved for ROS1 fusions and BRAF mutation positive lung cancers in Japan, respectively. From December 2017, liquid screening with Guardant 360 (LC-SCRUM-Liquid) was initiated and a large concordance study between tissue and liquid NGS analysis was performed in 2000 patients. Additionally, to identify novel biomarkers for immune checkpoint inhibitors, an immuno-oncology biomarker study (LC-SCRUM-IBIS) was conducted with 1017 patients enrolled from February 2017 to May 2018. PD-L1 assessment by IHC and whole exon sequencing was performed. The LC-SCRUM platform was recently expanded to hospitals in Taiwan and we will expand the collaboration to China and other Southeast Asia to establish an integrated Asia cancer clinical genomic database.



Genomic screening in LC-SCRUM has provided clinical value by identifying patients with actionable mutations and has helped accelerate clinical development of novel agents. To continue to elevate the standard of cancer care and treatment options for patients in Asia, we are establishing a high quality platform of genomic screening technologies and a mechanism of collecting clinical data that will help elevate precision medicine and drug development in Asia.

Keywords: Precision medicine, genomic screening, driver oncogene

MS12 GENOME SCREENINGS
TUESDAY, SEPTEMBER 10 11:30–13:00

MS12.04 THE INTERNATIONAL LUNG CANCER CONSORTIUM (ILCCO), AN INTERNATIONAL STUDY TO IDENTIFY RISK FACTORS FOR LUNG CANCER DEVELOPMENT

R.J. Hung on Behalf of The International Lung Cancer Consortium

Lunenfeld-Tanenbaum Research Institute, Sinai Health System and University of Toronto, Toronto/Canada

Background: The International Lung Cancer Consortium (ILCCO) was established in 2004 to maximize research efficiency for lung cancer and to share comparable epidemiological and clinical data, and biological samples across studies. Since its establishment, over 70 studies have participated in the ILCCO and shared comparable clinico-epidemiological data and a subset with biological samples and genomic data. The data harmonization was conducted at the Sinai Health System in Toronto, and genomic data is managed at the Dartmouth College of Medicine/Baylor College of Medicine. In total, the ILCCO Data Repository now has epidemiological data for over 1.2 million study participants, including 100,000 lung cancer patients, and genomic data on approximately 50,000 study participants. The large-scale epidemiological and genomic data allow us to extensively study and characterize the etiological factors, including lifestyle risk factors, medical history and genomic architectures for lung cancer development. Data submitted from all studies are systematically checked for missing values, outliers, inadmissible values, aberrant distributions and internal inconsistencies before harmonization. Common variable definitions were developed. For lifestyle risk factors and medical history, we conducted meta-analysis based on study-specific estimates, when applicable. If heterogeneities were present, random effects models were employed to account for the heterogeneity across studies. For subgroup of interests or when sample size is limited, pooled-analyses based on individual-level data were applied. When applicable, the non-linearity relationship was assessed. For genetic susceptibility of lung cancer, we investigated the genetic loci associated with lung cancer risk using log-additive model adjusted for population ancestry and account for multiple comparisons. To assess the causality of specific exposures and lung cancer risk, we applied Mendelian Randomization and mediation analytical approaches. To estimate 5-year lung cancer absolute risk, we incorporated risk factors, medical history and genetic factors based on age-specific lung cancer incidence and the competing risk. Based on 17 ILCCO studies (24,000 cases and 81,000 controls), we observed a robust association between lung cancer risk and emphysema and pneumonia, even among never smokers, and after long latency period. Based on 24 ILCCO studies, we quantified the association between family history of lung cancer and its risk by their smoking status and affected relative types. Based on 6 studies in UK, Canada, UK and New Zealand, we assessed the association between cannabis smoking and lung cancer risk by intensity, duration and cumulative exposures and by histological subtypes. We have recently completed a largest lung cancer genetic analysis based over 29,000 lung cancer cases and 56,000 controls. We identified 10 novel lung cancer susceptibility loci, in addition to the known regions, such as *TERT/CLPTM1L, CHRNA5*, MHC region, *RAD52, CHEK2* and found specific associations mediated through mRNA expression. We helped to quantify the effect of specific genetic variant in nicotinic receptor gene on smoking cessation and age of onset. Using genetic instruments and Mendelian Randomization approach, we confirmed the association between lung cancer risk and long telomere length. Most recently, we investigated the association between impaired lung function and lung cancer risk based on UK Biobank and ILCCO OncoArray data, and we found that impaired lung function was associated with lung cancer risk in never smokers and particularly for adenocarcinoma, most likely through immune-mediated pathways. When combining all factors into an integrative risk model, we found that individuals with highly polygenic risk scores reached lung cancer screening threshold at younger age than those with average genetic risk background. ILCCO provides a powerful research platform for research on lung cancer. The collaborative projects based on ILCCO have contributed to the understanding of lung cancer etiology beyond tobacco smoking. As future perspectives, ILCCO has obtained clinical prognosis data for over 50,000 lung cancer patients and will also be able to investigate factors associated with lung cancer prognosis in depth. Finally, ILCCO has built close collaborations with several lung cancer low-dose computed tomography screening programs to jointly investigate the optimal strategy for risk stratification and early detection for lung cancer.

Keywords: Genomics, Risk Factors, Risk prediction

MS13 IMMUNOTHERAPY FOR MESOTHELIOMA
TUESDAY, SEPTEMBER 10 11:30–13:00

MS13.02 CON - RAPHAEL BUENO IS RIGHT (IT DOES NOT WORK)

R. Bueno

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Mesothelioma is a heterogeneous cancer and it is not always correctly staged in the absence of surgical extirpation. While some clinical trials utilizing a remarkably small number of patients showed some response to immunotherapy in mesothelioma, the response rate is relatively low (in the 10% rate) and it is unclear how durable. The heterogeneity of the tumor makes interpretation of such small number difficults leading to the conclusion that at this time immunotherapy remains experimental in mesothelioma

MS13 IMMUNOTHERAPY FOR MESOTHELIOMA
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MS13.03 IMMUNOTHERAPY AND MESOTHELIOMA: UPDATE; REVIEW OF ALL PUBLISHED LITERATURE AND EPI/STATISTICAL EVIDENCE

J. Van Meerbeeck

Antwerp University Hospital, EDEGEM/Belgium

Unresectable malignant pleural mesothelioma (MPM) is a uniformly fatal rare cancer with increasing incidence worldwide. Combination chemotherapy with platinum/antifolate –either pemetrexed or raltitrexed- is the only standard of care 1st line treatment with proven improvement of survival, which varies according to series and patient selection between 12-16 months median overall survival (mOS), with corresponding 1 year survival rate of 50-60%. After a median progression-free survival of ~ 3 months, patients relapse and few if any drugs have any proven efficacy at this stage. Survival after progression varies from 3-18 months according to tumors' biological behavior and patient's prognostic factors. Therefore, innovative drugs are urgently needed. Although called 'immunologically cold tumours' and presenting with a low mutational burden, MPM express distinct targetable antigens (WT1, mesothelin), contain tumour-infiltrating lymphocytes (TILs) and PDL-1 expression is variably present, mostly on the sarcomatoid subtype. Experimental models have demonstrated chronic inflammation and local tumor suppression as crucial to MPM pathogenesis. This led to the investigation of immunotherapy in MPM. Monoclonal antibodies against immune check point inhibition (ICI-) molecules have been evaluated as salvage therapy after first-line chemotherapy in several phase 2 trials, either as single agent or in combination. The randomized DETERMINE trial evaluated in 564 patients the anti–CTLA-4 antibody tremelimumab versus placebo in second or third line and found no benefit in outcome (hazard ratio 0.92; p = 0.408). Results from the anti–PD-1 or anti–PD-L1 trials with nivolumab, pembrolizumab and durvalumab are fairly consistent with a response rate of 19-30%, a median PFS of 3.5 – 6.0 months and mOS of 12-18 m, all uncontrolled in selected patients with good prognostic features. Addition of CTLA-4 inhibitors to PD(L)-1 seem to increase efficacy and prolong the time-to-event endpoints. Preliminary results suggest that PD-L1 tumour proportional score (TPS) is both a predictive and prognostic biomarker. Several trials are underway investigating ICI alone or in combination with SOC-chemotherapy as frontline treatment. The DREAM trial, a single-arm, open-label phase II trial of durvalumab with cisplatin/pemetrexed, followed by durvalumab maintenance therapy for 1 year. The primary endpoint was PFS at 6months. Interim results in the first 54 patients show a mPFS of 6.2 months, with 48% achieved a partial response based on immune-modified RECIST. The -immature- 1-year OS estimate is 65% at a median follow-up of 14.4 months. Other randomized studies of triplet combinations are ongoing, including SOC-chemotherapy w/ wo pembrolizumab (NCT02784171) or durvalumab (NCT02899195). The phase III CheckMate743 (NCT02899299) trial randomly selected 600 patients with treatment-naïve MPM to nivolumab plus ipilimumab -until progression or unacceptable toxicity- versus up to six cycles of SOC-chemotherapy. Surgical management in resectable MPM represents an excellent opportunity for window-of-opportunity trials when treating patients with neo-adjuvant immunotherapies to improve resectability, fight residual disease and improve patient outcome. Several studies are ongoing with anti–PD(L)-1 with or without CTLA-4 inhibitors or chemotherapy in the neo-adjuvant setting, but results have not yet been published. Immunotherapy beyond ICI have been also tested in MPM but with discordant results. Several randomized phase II trials have targeted mesothelin, including amatuximab, an antimesothelin chimeric monoclonal antibody, anetumab-ravtansine, an antibody drug conjugate, and CRS-207, a vaccine targeting mesothelin: these have not yet shown any efficacy in MPM (unpublished data). Cell therapies in phase I trials are being investigated in MPM, including chimeric antigen receptor (CAR) T cells targeting surface antigens such as mesothelin, given both intravenously (NCT02159716) and intrapleuraly (NCT02414269). Vaccines targeting the Wilms tumor-1 (WT-1) antigen have also been tested in MPM with variable results. Dendritic cell vaccination was found to be efficacious in small trials of MPM, providing the rationale for ongoing trials, such as the large randomized phase II trial (DENIM) with dendritic cell therapy as maintenance after P/P frontline chemotherapy or a phase I/II trial testing autologous dendritic cells loaded with WT-1 tumor antigen following standard first-line chemotherapy. Autologous tumor infiltrating lymphocytes and interleukin-2 (IL-2) infusion after lympho-depletion are also currently under investigation in a phase I/II trial in MPM. Immune-gene therapy using intrapleural delivery of adenovirus-expressing interferon-α combined with celecoxib and chemotherapy was well tolerated and provided a remarkable mOS of 21.5 months as second-line treatment. Finally, oncoviral therapy is being assessed in a phase I trial with intrapleural injection of measles virus (NCT01503177), or with an oncolytic adenovirus coding for GM-CSF combined with chemotherapy and cyclophosphamide versus chemotherapy alone in a randomized phase II trial (NCT02879669). In conclusion, immunotherapies are being investigated in different settings of MPM. Regulatory approval is anticipated soon for ICI (anti–PD-1 with or without anti–CTLA-4) as salvage treatment in MPM. However, state of the art phase III trials comparing ICI with SOC-chemotherapy are needed to firmly establish immunotherapy, either alone or in combination with standard treatment, and to validate biomarkers for patient selection.

Keywords: mesothelioma, immunotherapy, checkpoint inhibition

MS13 IMMUNOTHERAPY FOR MESOTHELIOMA
TUESDAY, SEPTEMBER 10 11:30–13:00

MS13.04 BIOMARKERS OF ANTI-PD1 THERAPY IN MESOTHELIOMA

P. Baas

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Biomarkers of Anti-PD1 Therapy in Mesothelioma. Biomarkers have attracted attention for their usefulness in selecting the right treatment for the right patient. There are different types of biomakers; blood based, clinical markers and histological markers. Most of the biomarker studies have focused on the prognosis of patients while only a limited number examined the predictive value of a marker; to correctly predict the outcome of a certain treatment. After the reported successes of check-point inhibitors in melanoma and NSCLC (1-4), the use of these agents have found its way to mesothelioma(5-8). Since 2015 many studies have been initiated whit a comparable efficacy compared to NSCLC outcomes. Around 20-25% of cases do respond favorably to this approach. This is considered to be of great importance since there is a limited 2 years survival rate (8) and no standard second line therapy has yet been defined. There are a number of factors that have to be considered before embarking on Immuno-Oncology (IO) therapies as single agent or in combination. The choice of the drug or combination; the expected outcome in short time; the toxicity profile and the costs. Because of the lack of registration, there is a limited availability and patients can only join in studies or be part of a compassionate use program. When registration is a fact we merely have to deal with the questions; who will benefit, who will experience toxicity and is the treatment cost effective? In a series of studies we performed in patients with pleural mesothelioma we have collected samples to be used as biomarkers (6,7). Currently we are analyzing the predictive value of these biomarkers. 1. Histological biopsies: It is well known that the expression PD-L1 can be predictive in NSCLC of a success while in melanoma there is a better correlation with tumor mutational burden. For mesothelioma the expression of PD-L1 varies between the different subtypes of mesothelioma (with sarcomatoid type expressing higher PD-L1 levels) (9). In general the high expression correlates with a worse survival. In addition, the

expression of PD-L1 on tumor stroma also influences the outcome of IO treatment. In our study of 34 patients (7), we observed a clinical benefit of 18% in PD-L1 tumor negative patients compared with 15% in the (TIL+) stroma and 32% versus 35% in stroma for any PD-L1 expression. When analyzed for PD-L1 > 50% the stromal T+ cells showed a factor of 2 higher clinical benefit. This implies that a single analysis of the PD-L1 of the tumor cells might underestimate the effect of IO therapy. 2. eNose analyses. The use of exhaled air has attracted clinical interest since early data indicate that the Volatile Organic Compounds (VOCs) can predict an outcome of IO therapy (11). These VOCs probably represent a complex combination of tumor and immune cell interactions. Ongoing studies focus on the use of these electronic noses to select only patients for whom a treatment has a high chance of success. 3. Blood based biomarkers have been tested in many studies in mesothelioma. For well-known markers such as mesothelin, cyfra 21-1, osteopontin and fibulin-3 no positive outcomes have been reported in prediction studies. 4. MicroRNAs. These short, non-coding RNA sequences have attracted attention because of their prognostic capability in mesothelioma and other cancers. The huge number of miR's identified and the lack of comparative studies to date indicate that these markers can only be used for diagnostic and perhaps treatment purposes. (12) 5. BAP1 is a nuclear deubiquitinase which regulates the ubiquitination of selected histones and other translational factors. This mutation is occurring both in germline or, more frequently, as a somatic mutation in mesothelioma. It has different functions and can influence the inflammation status of the microenvironment. Although not tested in a proper study setting this marker may well have a predictive potential(13). 6. Other biomarkers. Finally there are a number of interesting biomarkers including chemokines like IL-6 which acts as a pro-inflammatory cytokine and is closely related to T cell function. Ongoing studies will try to elucidate the predictive effect of this and other markers. To date there is a lot of activity ongoing in mesothelioma and the introduction of the IO drugs have been welcomed full-heartedly. Although we have identified an abundant number of prognostic factors in cancer, the high costs of IO therapies presses us to find solid predictive markers. The combination therapies of IO drugs now proposed do increase the toxicity profile and we must not lose precious time of patients and doctors spend on ineffective and costly therapies. References are available at the author at request

Keywords: Mesothelioma, Immunotherapy, biomarkers

MS13 IMMUNOTHERAPY FOR MESOTHELIOMA
TUESDAY, SEPTEMBER 10 11:30–13:00

MS13.05 CAR T CELL IN MESOTHELIOMA

P. Adusumilli

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Chimeric antigen receptor (CAR) T-cell therapy has shown great promise in hematological malignancies and was approved by FDA for the treatment of leukemia and lymphoma patients. Adotpive cell therapy by use of CARs involves transducing patient's own T lymphocytes with antigen-specific CAR by retro or lenti virus, and infusing back to the patient following Cyclophosphamide preconditioning. This presentation will dicuss the challenges in developing CAR T-cell therapy, progress to date in translation of CAR T-cell therapy for thoracic cancers. Advances in understanding thoracic cancers tumor immune microenvironment and successes with checkpoint blockade agents has opened doors to devlop combiantion immunotherapy for thoracic cancer patients. Our laboratory has shown that in the presence of high tumor burden as in patients with metastases, a low-dose of CAR T cells adminsitered in phase I clinical trials can be exhausted. Addition of anti-PD-1 agents can rescue functionally exhausted CAR T cells and prolong their anti-tumor efficacy. Based on this strong rationale, our laboratory has translated mesothelin-targeted CAR T-cell therapy for patients with malignant pleural mesothelioma and demonstrated anti-tumor efficacy in addition to safety in combination with anti-PD-1 agents. The results of the ongoing trials will be discussed. While extrinsic anti-PD-1 agent administration requires multiple doses and potential off-tumor side effects, we have developed T-cell intrinsic anti-PD-1 strategies which are in translation. The preclinical and clinical data supporting this upcoming clinical trial will be presented.

Keywords: CAR T-cell therapy, Immunotherapy, Checkpoint Blockade

MS13 IMMUNOTHERAPY FOR MESOTHELIOMA
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MS13.06 ROLE OF SECOND LINE CHEMOTHERAPY AND NEW TARGET TREATMENT IN RECURRENT MESOTHELIOMA

S. Novello, P. Bironzo

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Malignant pleural mesothelioma (MPM) is a highly lethal disease, with a median overall survival (OS) between 12 and 18 months. Following first-line treatment, neither chemotherapy nor target treatments have clearly shown to increase overall survival (OS), to date. Historically, second-line cytoxic drugs, such as gemcitabine and vinorelbine have been the backbone in pre-treated patients, with response rates ranging from 7% to 16% [*Zucali PA, Perrino M, Lorenzi E, et al. Vinorelbine in pemetrexed-pretreated patients with malignant pleural mesothelioma. Lung Cancer 2014; 84:265-270; Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009; 63:94-97; van Meerbeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organisation for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85(12):2577-2582*]. Pemetrexed rechallenge was assessed in small retrospective studies, suggesting its role, especially when combined with platinum compounds, in selected patients with a pemetrexed-free interval of at least 3 to 6 months [*Zucali PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung cancer 2012; 75: 360-367*]. "*Omics*" studies have enlarged our knowledge of MPM, describing high prevalence of TP53, *NF2*, *BAP1* and cyclin dependent kinase inhibitor 2A (*CDKN2A*) mutations, along with the lack of tyrosine receptor kinase (TRK) activating mutations [*Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced malignant pleural mesothelioma: a retrospective study.J Thorac Oncol 2015;10(3):492-9*]. For this reason, the development of target treatment approaches in MPM has been more difficult and slower as compared to non-small-cell lung cancer (NSCLC), for example. However, many drugs have been tested, while others are currently under evaluation. Among the first studied agents, mTOR inhibitors failed to show activity in pre-treated MPM patients [*Ou SH, Moon J, Garland LL, et al.SWOG S0722: phase II study of mTOR inhibitor everolimus (RAD001) in advanced malignant pleural mesothelioma (MPM). J Thorac Oncol 2015;10(2):387-91*]. Enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) is upregulated in MPM with *BAP1* inactivation and its inhibition showed to be synthethic lethal in *BAP1*-negative tumors. The EZH2 inhibitor tazemetostat demonstrated a 51% disease control rate (DCR) in 74 MPM patients (95% with *BAP1* inactivation) enrolled in a phase 2 study [*Zauderer MG, Szlosarek P, Le Moulec S, et al. Phase 2, multicenter study of the EZH2 inhibitor tazemetostat as monotherapy in adults with relapsed or refrectory (R/R) malignant mesothelioma (MM) with BAP1 inactivation. J Clin Oncol 36, 2018 (suppl.abstr 8515)*]. As *BAP1* loss leads to homologous repair deficiency, PARP inhibitors are currently being tested in this subgroup [NCT03531840; NCT03207347; NCT03654833]. Neurofibromin 2 (NF2) inactivation, which encodes for merlin, has been proposed to be synthetic lethal to focal adhesion kinase (FAK) inhibition. However, the COMMAND trial, exploring the use of the FAK inhibitor defactinib as a maintenance treatment after first-line chemotherapy in MPM patients stratified for merlin expression, failed to show any improvement as compared to placebo [*Fennell DA, Baas P, Taylor P, et al. Maintenance defactinib versus placebo after first-line chemotherapy in patients with merlin-stratified pleural mesothelioma: COMMAND-a double-blind, randomized, phase II study. J Clin Oncol 2019;37(10):790-798*]. Defactinib is currently under investigation in combination with anti programmed-death 1 (PD-1) monoclonal antibody pembrolizumab in a phase I/IIA clinical trial enrolling pretreated MPM patients along with pancreatic cancer and NSCLC ones [NCT02758587]. The identification of argininosuccinate synthetase 1 (ASS1) loss in MPM, leading to arginine auxotrophy, paved the way to the use of the arginine depletor pegylated adenosine deiminase ADI-PEG20 in a phase 2 randomized trial in 70 ASS1-deficient patients [*Szlosarek PW, Steele JP, Nolan L, et al. Arginine deprivation with pegylated arginine deiminase in patients with argininosuccinate synthetase 1-deficient malignant pleural mesothelioma: a randomized clinical trial. JAMA Oncol 2017;3(1):58-66*]. Among the 68 treated patients,

the drug improved progression free survival (PFS) as compared to best supportive care (BSC) (HR 0.56, 95% CI, 0-33-0.96), although by only 1.2 months (median PFS 3.2 vs 2.0 months for ADI-PEG20 and BSC, respectively; p=0.03). Currently, ADA-PEG20 is being explored in combination with first-line chemotherapy in biphasic and sarcomatous MPM only [NCT02709512]. Recent studies described novel prognostic MPM subsets with specific genomic characteristics that could further shape personalized treatment approaches, especially when looking at immunotherapic approaches [*Hmljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov 2018;8(12):1548-1565*]. Indeed, the high expression of V-domain immunoglobulin suppressor of T-cell activation (VISTA) negative immune-checkpoint in epithelioid MPM reported in this study, suggests a possible of role of specific inhibitors alone or in combination with other agents in advanced MPM.

Keywords: pretreated, second line, malignant pleural mesothelioma

MS14 MOLECULAR SUBSETS AND NOVEL TARGETED APPROACHES TO SMALL CELL AND NEUROENDOCRINE CANCERS
TUESDAY, SEPTEMBER 10 11:30–13:00

MS14.01 MOLECULAR SUBSETS OF NEUROENDOCRINE TUMORS

C. Hann

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Small cell lung cancer (SCLC) is an aggressive tumor with one of the highest case-fatality rates among cancer. Clinically SCLC is hallmarked by early metastatic behavior and rapid development of therapeutic resistance. Over the past decades multiple research teams have used genomic, epigenomic, transcriptomic and proteomic approaches to further characterize SCLC. Long considered a relatively homogeneous tumor, these data have led to a deeper understanding of SCLC biology and support the concept that there are distinct biologic subsets of SCLC. Complementary work using patient-derived xenografts and genetically engineered mouse models have validated some of this data and these models serve as platforms for novel therapeutic development. These studies support translational efforts in SCLC focused on distinct vulnerabilities in subsets of this disease and the development of predictive biomarkers.

MS14 MOLECULAR SUBSETS AND NOVEL TARGETED APPROACHES TO SMALL CELL AND NEUROENDOCRINE CANCERS
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MS14.02 SUBCLONAL ARCHITECTURE AND GENOMIC EVOLUTION OF SCLC

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Small cell lung cancer (SCLC) accounts for 15-20% of all of lung cancer worldwide and it is a highly aggressive and rapidly progressive tumor with rapid growth speed and strongly associated with smoking. SCLC is divided to limited disease and extensive disease. The staging systems for SCLC are Veterans Administration scheme (VA), the AJCC TNM staging systemand NCCN staging, among of these VA is most commonly used. In recent several decades, chemotherapy combined radiotherapy is the main treatment for SCLC. The overall survival (OS) in patients with limited disease-SCLC and extensive disease were 15-18 months and 10-12 months, respectively. Immunotherapy is becoming a promising treatment for SCLC nowadays. Targeted therapy based on genotyping in non-small cell lung cancer is a main treatment. However, targeted therapy in SCLC is not successful and studies on the genomic evolution of SCLC are rare. ctDNA (circulating cell-free tumor DNA) is a good tool for monitoring the genomic changing in patients with malignant tumors, especially for monitoring acquired resistance of targeted therapy. ctDNA and CTCs are useful for genomic evolution of cancer. However, isolation and identification of CTCs are not satisfied in lung cancer, though there are more CTCs in small call lung cancer because of tumor cells are more easily to shed to blood stream in SCLC. ctDNA can provide more accurate genomic landscape of SCLC through overcome heterogeneity. We conducted a study that aimed to explore the genomic structure and gene evolution pattern of SCLC using next-generation sequencing and who had been followed by dynamic samples after chemotherapy or/and radiotherapy. We found that TP53 and RB1 are the most common mutations in SCLC, and NOTCH1-4, CREBBP, EG300, MYC, MYCL1, and MYCN are also frequently mutated genes and copy number alterations. We also compared the tissue and blood ctNDA genome and we found that a majority of mutations detected in tumor DNA were also detected in paired ctDNA samples suggesting ctDNA sequencing is sensitive and reliable for detecting mutations in SCLC patients. We used the average VAF (Variant allelic frequencies) of mutations from the major clones as a surrogate for overall ctDNA level. We found higher median ctDNA level was associated with shorter progression-free survival (PFS) and overall survival (OS). Dynamic ctDNA levels are correlated with tumor measurements on imaging suggesting that ctDNA sequencing has the potential for monitoring the clinical course of SCLC. The genomic profiles derived from pre-treatment ctDNA to the genomic profiles from ctDNA at different time points during treatment from post-treatment plasma samples available. Some new mutations that were not exist in pre-treatment blood samples. Immunotherapy is an important method for lung cancer. PD-L1 expression and tumor mutation burden (TMB) are two common predictors for immunotherapy. In our cohort, tumor mutation burden is not higher based on the large gene panel. PD-L1 expression is about more than 10% in SCLC. The treatment for SCLC is still highly challenging. TMB based on ctDNA is worth further investigation on predicting SCLC immunotherapy. A previous study showed that SCLC with high TMB had a better response to checkpoint inhibitors. Shedding of ctDNA is a complicated process affected by many factors. With the technique development and increasing understanding of tumor biology, the genome of SCLC will be a useful tool for guiding the treatment and predicting the prognosis of SCLC in the future.

MS14 MOLECULAR SUBSETS AND NOVEL TARGETED APPROACHES TO SMALL CELL AND NEUROENDOCRINE CANCERS
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MS14.04 TARGETING DNA DAMAGE AND REPAIR

T. Sen

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Genomic profiling of small cell lung cancer has revealed nearly universal inactivation of the key tumor suppressor genes TP53 and RB1. Loss of these critical regulators of cell cycle entry and DNA damage response together results in selective sensitivity to DNA damaging agents, inhibitors of DNA damage repair, and inhibitors of the remaining late phase cell cycle checkpoints. Multiple preclinical studies and recent clinical data nominate these pathways as potential synthetic lethal vulnerabilities in small cell lung cancer. Recent study has also demonstrated that targeting DNA damage response can activate the anti-tumor immunity and potentiate the response of immune checkpoint blockade antibodies. This talk will review these recent studies, focusing on opportunities and future directions in investigational therapy for patients with small cell lung cancer.

Keywords: small cell lung cancer, DNA damage repair, Immune checkpoint blockade

MS14 MOLECULAR SUBSETS AND NOVEL TARGETED APPROACHES TO SMALL CELL AND NEUROENDOCRINE CANCERS
TUESDAY, SEPTEMBER 10 11:30–13:00

MS14.05 DLL3 TARGETING AGENTS

J. Poirier

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Delta-like ligand 3 (DLL3) is a single-pass transmembrane Notch ligand that interacts with full-length, unprocessed NOTCH1 in the Golgi apparatus, inhibiting the pathway *in cis*. DLL3 is selectively overexpressed in the subtype of small cell lung cancer (SCLC) driven by the transcription factor ASCL1 (SCLC-A) that accounts for ~70% percent of SCLC diagnoses (95% CI [60 – 79])[1]. In one study immunoreactivity was observed in 1,040/1,363 (70.4%) of SCLC specimens, consistent with this incidence[2]. Overexpression of DLL3 leads to low-level cell surface expression of the protein on the order of 10,000 proteins per cell while expression in normal tissues is restricted to intracellular compartments: the same study demonstrated only low to moderate cytoplasmic or nuclear immunoreactivity in normal adult tissues[3]. High expression of DLL3 has also been reported in low-grade glioma[4,5], neuroendocrine prostate[6], and occasionally in other cancer types when neuroendocrine features are present[7,8]. The exquisitely selective expression of surface DLL3 on cancer cells presents an attractive target for a variety of therapeutic strategies. Rovalpituzumab teserine (Rova-T; SC16LD6.5) is an antibody drug conjugate consisting of a monoclonal antibody targeting DLL3, a cathepsin-cleavable linker, and a pyrrolobenzodiazepine (PBD) warhead[4]. The first-in-human clinical trial of Rova-T in recurrent SCLC demonstrated encouraging activity despite often severe side-effects attributable to the PBD warhead[9]; however, the phase 2 TRINITY study showed a disappointing 16% objective response rate while reporting a similar toxicity profile (NCT02674568). Subsequently, the phase 3 TAHOE study was halted due to shorter overall survival in the treatment arm. An active phase 3 trial of Rova-T in the maintenance setting (MERU) is ongoing (NCT03033511). Other DLL3-targeting therapies under active investigation include the bispecific T cell engager (BiTE) AMG 757 (NCT03319940), and a chimeric antigen receptor CAR-T AMG119 (NCT03392064). These agents have shown significant anti-tumor activity in preclinical models of SCLC; however, AMG 119 required direct delivery of the engineered T cells for activity. AMG 757 was therefore the more potent of the two strategies in preclinical models and may therefore be better suited to overcome known barriers to CAR-T activity in solid tumors. Alternative strategies remain under exploration including the use of ^{89}Zr-SC16, a PET radiotracer, for *in vivo* imaging and as a companion diagnostic to optimize the selection of patients for treatment with DLL3-directed therapeutic agents. ^{89}Zr-labeled-SC16 antibody successfully delineated normal tissue from subcutaneous and orthotopic SCLC tumor xenografts. Radiotracer accumulation in tumors was directly correlated with the degree of DLL3 expression and, also correlated with response to SC16LD6.5 therapy in SCLC patient–derived xenograft models. 1 Rudin, C. M. et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer 19, 289-297, doi:10.1038/s41568-019-0133-9 (2019). 2 Huang, R. S. P. et al. Delta-like Protein 3 Prevalence in Small Cell Lung Cancer and DLL3 (SP347) Assay Characteristics. Arch Pathol Lab Med, doi:10.5858/arpa.2018-0497-OA (2019). 3 Sharma, S. K. et al. Non-invasive Interrogation of DLL3 Expression in Metastatic Small Cell Lung Cancer. Cancer Res, doi:10.1158/0008-5472.CAN-17-0299 (2017). 4 Saunders, L. R. et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med 7, 302ra136, doi:10.1126/scitranslmed.aac9459 (2015). 5 Spino, M. et al. Cell Surface Notch Ligand DLL3 is a Therapeutic Target in Isocitrate Dehydrogenase-mutant Glioma. Clin Cancer Res 25, 1261-1271, doi:10.1158/1078-0432.CCR-18-2312 (2019). 6 Puca, L. et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med 11, doi:10.1126/scitranslmed.aav0891 (2019). 7 Koshkin, V. S. et al. Transcriptomic and Protein Analysis of Small-cell Bladder Cancer (SCBC) Identifies Prognostic Biomarkers and DLL3 as a Relevant Therapeutic Target. Clin Cancer Res 25, 210-221, doi:10.1158/1078-0432.CCR-18-1278 (2019). 8 Ding, X., Li, F. & Zhang, L. Knockdown of Delta-like 3 restricts lipopolysaccharide-induced inflammation, migration and invasion of A2058 melanoma cells via blocking Twist1-mediated epithelial-mesenchymal transition. Life Sci 226, 149-155, doi:10.1016/j.lfs.2019.04.024 (2019). 9 Rudin, C. M. et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 18, 42-51, doi:10.1016/S1470-2045(16)30565-4 (2017).

Keywords: DLL3, SCLC

MS15 HOW TO GET PATIENTS TO QUIT SMOKING; PRACTICAL IMPLEMENTATION OF EVIDENCE-BASED CESSATION PRACTICES
TUESDAY, SEPTEMBER 10 11:30–13:00

MS15.01 THE IMPORTANCE OF CESSATION AND "5AS" AS A FRAMEWORK FOR CESSATION

B. Faseru

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Almost two-thirds of newly diagnosed cancer patients have used or currently use tobacco. Evidence shows that continuous use of tobacco after cancer diagnosis adversely affects treatment outcomes among cancer patients compared to their counterparts who stop using tobacco. These outcomes include recovery, quality of life and survivorship. According to the United States Department of Health and Human Services clinical practice guideline for treating tobacco use and dependence, 5As include 1) Ask about tobacco use at every visit to identify and document tobacco use status of every patient 2) Advise every tobacco user to stop using tobacco – the message must be clear, strong and personal 3) Assess readiness to quit - implement strategies to motivate those who are not ready with 5Rs [Relevance, Risks, Rewards, Roadblocks and Repetition] 4) Assist those who are ready quit - develop (a) a quit plan using the STAR method [Set a quit date, Tell friends, family and co-workers and ask for their support, Anticipate challenges to the quit attempt, Remove all tobacco products] (b) recommend smoking cessation medication as indicated, provide counseling support and supplemental materials including information about the quitline where available 5) Arrange follow-up for additional support to avoid relapse. The efficacy of the 5As brief intervention recommendations have been described in the clinical practice guidelines. For example, clinicians who work in a setting where tobacco use status are easily captured are three times more likely to provide tobacco treatment to their patients OR 3.1 95% CI (2.2-4.2); physician advice to patients who smoke increases the odds of quitting compared to no physician advice OR 1.3 95% CI (1.1-1.6); and a combination of counseling and medication outperforms counseling alone OR 1.7 95% CI (1.3 - 2.1). This brief smoking cessation intervention approach using the 5As framework is feasible and cost effective. However, gaps in smoking cessation knowledge and practices in cancer care persist and tobacco use treatment remain suboptimal. During this mini symposium, we will discuss the effectiveness of 5As at various settings, examine other adaptations such as 3As, ABC, ABCD, AAR and identify ways to overcome the multi-level challenges of implementing evidence-based tobacco dependence treatment during cancer care. References Karam-Hage M, Cinciripini PM, Gritz ER. Tobacco use and cessation for cancer survivors: an overview for clinicians. CA Cancer J Clin. 2014;64(4):272-290. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer. 2013;132(2):401–10. Gritz ER, Toll BA, Warren GW. Tobacco use in the oncology setting: advancing clinical practice and research. Cancer Epidemiol Biomarkers Prev 2014;23:3-9 Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569 Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update, Clinical Practice Guideline. Rockville, MD: U. S. Department of Health and Human Services. Public Health Service; 2008. Warren GW, Dibaj S, Hutson A, Cummings KM, Dresler C, Marshall JR. Identifying targeted strategies to improve smoking cessation support for cancer patients. J Thorac Oncol 2015;10:1532-1537. Price SN, Studts JL, Hamann HA. Tobacco Use Assessment and Treatment in Cancer Patients: A Scoping Review of Oncology Care Clinician Adherence to Clinical Practice Guidelines in the U.S. The oncologist. 2019;24(2):229-238 Warren GW, Marshall JR, Cummings KM, Toll B, Gritz ER, Hutson A, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. J Thorac Oncol. 2013;8:543–548 McRobbie H Bullen C Glover M et al. New Zealand smoking cessation guidelines. N Z Med J. 2008;121(1276):57–70 Gould GS Bittoun R Clarke MJ. A pragmatic guide for smoking cessation counselling and the initiation of nicotine replacement therapy for pregnant Aboriginal and Torres Strait Islander smokers. J Smoking Cessation. 2015;10(2):96–105 Vidrine

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Keywords: Tobacco, Cessation, 5As

MS15 HOW TO GET PATIENTS TO QUIT SMOKING; PRACTICAL IMPLEMENTATION OF EVIDENCE-BASED CESSATION PRACTICES
TUESDAY, SEPTEMBER 10 11:30–13:00

MS15.02 PHARMACOTHERAPY SUPPORTS CESSATION

C. Dresler

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It should be acknowledged that smoking cessation is one of the hardest things the patient has ever tried to do. There are two key aspects to tobacco cessation: appropriate pharmacotherapy and behavioral modification. This abstract will address only the pharmacotherapy, but the practitioner must also try to provide or refer to behavioral modication interventions to amplify the effect of the pharmacotherapy. : The most common type of medication for quitting smoking is called 'nicotine replacement therapy' or 'NRT". NRT that has had regulatory approval comes as a gum, a lozenge, or a transdermal patch, or in a device that you 'smoke' like a cigarette' or a nasal spray. In the United States, the nicotine gum, nicotine lozenge and nicotine patch can be purchased without a doctor's prescription. The device that is 'smoked' (I call an inhaler or inhalator - as it is mostly absorbed by buccal mucosa) and the nasal spray must have a doctor's prescription. is a pill that is taken once in the morning and once in the evening. This medication requires a doctor's prescription. This drug does not yet (as of 2019) come in a generic form. To use varenicline – take 0.5 mg by mouth once in the morning for 3 days. On the fourth day – take 0.5 mg by mouth once in the morning and once in the evening. On the 7th day the person should QUIT SMOKING and use 1 mg by mouth once in the morning and once in the evening. Use varenicline for at least 3 months. A discussion between doctor and patient should occur if a longer term treatment period is needed to maintain cessation. is also taken as a pill once in the morning and once in the evening. This medication should not be taken if there is any risk of a seizure, alcoholism, or anorexia. This drug does come as a generic and requires a doctor's prescription. To use bupropion: Take 150 mg by mouth once a AM for 3 days. On the fourth day, take 150 mg by mouth once q AM and a PM. On the 7th day – quit smoking. Use bupropion for at least 3 months. A discussion between doctor and patient should occur if a longer term treatment period is needed to maintain cessation. Nicotine gum: the labeling on the box states that if more than 25 cigarettes per day are smoked, use the 4 mg dose and if less than 25 cigarettes are smoked per day, use the 2 mg dose. However, one can try either and see which dose works better in relieving or preventing cravings for a cigarette. It is very important to take the nicotine gum frequently! Most people do not take enough of the gum during the day to be effective. Instruct the quitter to use at least 9 pieces in the first days of quitting. One should SLOWLY taper down. Plan on having the quitter using the gum for at least 3 months! The worst day is the first day, and then the first week. After about 7-10 days, all of the nicotine and its breakdown products are cleared from the system and the body is starting to become normal again. It is probable that the quitter is still having cravings – and the nicotine gum will help prevent them and make the cravings more manageable. : The nicotine lozenge has a little bit different dosing instruction: if the first cigarette of the day is within 30 minutes after waking up in the morning – use the 4 mg nicotine lozenge. If the first cigarette of the day is had after 30 minutes after getting up – use the 2 mg nicotine lozenge. Again – one can try one and see how it works in relieving cravings without any side effects. If it doesn't seem to relieve cravings – try the other, higher dose. Follow the same instructions above for the gum. AGAIN – it is important to be sure and use enough lozenges per day – the most common problem is people NOT using enough lozenges per day. : The nicotine patch comes in a variety of doses and dosing instructions. Most commonly, people use the 15 mg dose (Nicotrol or generic patch) or the 21 mg patch (Nicoderm, Habitrol or generic). These patches should be put on an area of clean and dry skin. It can be put anywhere on the body, but it is best to put it somewhere on the upper body. Try to put it on a place that is not hairy – so it doesn't hurt when taken it off! Don't put it on the hips where one might sit on it, don't put it under the breast – these places are just common sense places NOT to put the patch. The best place is somewhere on the chest, upper back or arms. It is important to put the new patch on each morning in a DIFFERENT place than the patch before. Some skin redness is common, and it should resolve in the next day or so – but it is important to NOT keep using the same place to put the patch. After about 8 weeks on the highest dose patch, the quitter should start to 'step-down' the dose and use the 14 mg or the 7 mg patch. These decreasing doses are intended to help wean the quitter off of nicotine. Of course, the smaller amount of nicotine will also help with the decreasing cravings and withdrawal symptoms as they get further from the quit date. Even if there is a slip - the quitter has had even one puff – it doesn't mean failure. If there is a slip, work with the quitter, resolve to 'get back on the wagon' and not to have another cigarette. They should learn from the experience about what made that 'slip' occur and try and stay away from that temptation again.

Keywords: pharmacotherapy, smoking cessation

MS15 HOW TO GET PATIENTS TO QUIT SMOKING; PRACTICAL IMPLEMENTATION OF EVIDENCE-BASED CESSATION PRACTICES
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MS15.03 SPEAKING WITH PATIENTS, MOTIVATIONAL INTERVIEWING DEMONSTRATION

D. Arenberg

University of Michigan Medical School, Ann Arbor/United States of America

Ongoing tobacco use accounts for significant treatment and disease related morbidity, mortality, and decreased quality of life among patients undergoing cancer treatment. A common misconception is that it is too late to pursue tobacco cessation for individuals with advanced lung cancer. Data from existing studies do not support this, yet support for tobacco cessation services among cancer centers is often lukewarm or frankly lacking. For individuals undergoing active cancer therapy, even brief interventions from their oncologist can have an enormous impact on their willingness, and motivation to make a quit attempt. The purpose of this presentation is to arm lung cancer clinicians with tools to help patient's find internal motivation to make quit attempts, and to support them with counseling, as well as cessation pharmacotherapy. Common misconceptions among both providers and their patients who use tobacco will be presented, along with strategies to undserstand and overcome ambivalence towards tobacco cessation.

MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
TUESDAY, SEPTEMBER 10 14:30–16:00

MS16.01 GETTING TO THE TARGET: TRANSPARENCHIMAL APPROACHES

D. Gompelmann

Thoraxklinik at University of Heidelberg, Heidelberg/Germany

The Bronchoscopic Transparenchymal Nodule Access (BTPNA) is a guidance technique that provides to establish tissue diagnosis for peripheral pulmonary nodules. This method differs completely from other guidance techniques as it allows to access nodules via the healthy lung parenchyma and thus is independent on the need to have an airway leading into the lesion [1]. Prior to bronchoscopy, a virtual bronchoscopy navigation system is used that calculates the point of entry (POE) with a straight line, vessel-free access to the lesion and displays the tunnel path from the POE on the airway wall to the target nodule on the basis of the patient´s computed tomography scan. During the endoscopy, the POE is identified under virtual guidance. Then a coring needle is used to penetrate the airway wall and this hole is enlarged by a balloon dilator. Afterwards, a sheath is advanced through the lung parenchyma in order to create a tunnel to the target lesion under fluoroscopic guidance. Once the nodule is achieved, the stylet can be removed and a biopsy forceps is advanced through the sheath in order to sample the lesion. So far, the BTPNA is still investigational and different trials are ongoing to evaluate the diagnostic yield of the BTPNA. Up to date, two prospective trials confirmed the safety and feasibility of the BTPNA in 18 patients with peripheral lesions from suspected lung cancer or metastatic disease [2; 3]. The tunnel path was successfully created in 89% and adequate histological sampling was attained. The only adverse events were pneumothorax in two patients with

the need for chest tube insertion in one of them and a transient rise in troponin levels in another patient. In a further prospective trial of BTPNA that was presented on this year´s ATS congress a diagnostic yield of 83.3% was found. References: [1] Gompelmann D. Upcoming techniques. In: Interventional Pulmonology. Herth, Shah, Gompelmann (eds). ERS monograph 2017. [2] Herth FJ, Eberhardt R, Sterman D, Silvestri GA, Hoffmann H, Shah PL. Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules. Thorax 2015. 70:326-323. [3] Harzheim D, Sterman D, Shah PL, Eberhardt R, Herth FJ. Bronchoscopic Transparenchymal Nodule Access: Feasibility and Safety in an Endoscopic Unit. Respiration 2016. 91:302-306. [4] Criner G. Bronchoscopic Transparenchymal Access of a Peripheral Pulmonary Nodule. Session D83. ATS 2019.

Keywords: interventional pulmonology, solitary pulmonary nodule, Bronchoscopic Transparenchymal Nodule Access

MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
TUESDAY, SEPTEMBER 10 14:30–16:00

MS16.02 ROBOTIC BRONCHOSCOPY: DRIVELESS IP?

D. Fielding

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Introduction: Robotic bronchoscopy has been developed in response to challenges which face bronchoscopists in the diagnosis of peripheral pulmonary nodules. Further, such nodules are increasingly presented to bronchoscopists because of CT screening programs, and a general increase in the performance of chest CT in the community with resultant incidental detection of small nodules. Two platforms have undergone preliminary lab evaluations followed by in-human feasibility and safety studies. These are the Auris system and the Intuitive surgical system and the results of these studies are now published (1,2). Both have since had FDA approval and are undergoing post- marketing multicentre studies, the first as the Monarch system, the second as the Ion system. The challenges facing bronchoscopists are 1. The small size of nodules, 2. The peripheral nature of the nodules requiring small calibre scopes to reach them, 3. The complex anatomic pathways to reach them, and 4. The position of the nodules in relation to the airway, with many being "extrinsic" to the bronchus, making biopsy sampling difficult. Robotic bronchoscopy seeks to answer these challenges by integrating an array of components incorporating small size of the distal scope, excellent manoeuvrability of the distal end of the scope, real time display of CT-derived navigational assistance, and biopsy channel size in the distal end of the scope to allow good quality samples. Methods: The robotic aspect of the systems means robotic arms (2 with Auris and 1 with Intuitive) drive the scope into the airway under the direction of a physician operated console, as opposed to the hands of a physician holding the scope and advancing and directing the scope. Important in this regard is the system is not "automatic", meaning the physician is in control of the device at all times, directing the scope into pre-planned airways under direct vision provided by the system. The robotic aspect of the devices means that the driving and directing of the scope are much more precise and not prone to slipping out of airways between biopsy attempts, reducing the need to re-navigate back to a nodule. The main difference in the systems relates to the design of the catheter (Figs 1 and 2). The Auris system has a telescoping end, with a scope extending out of an outer sheath, while the Intuitive scope has a single catheter, within which a removable optic can be removed to allow deployment of biopsy instruments. Figure 1: Distal end of the Auris system incorporating a sheath (light blue) and an inner bronchoscope (dark blue). The outer sheath(6mm) is wedged in a segmental bronchus, then the inner bronchoscope (4.2mm) is advanced to the distal airways. Figure 2. The distal catheter tip of the Intuitive system (outer diameter 3.4mm), showing accompanying shape sensing image which is displayed real time, providing continuous position feedback. Results: The Auris study reported 15 patients, and the Intuitive study 29 patients, mean lesion size 26mm (1.0-6.3) and 12.2 ± 4.2 mm respectively. Bronchus was sign was absent in all cases with Auris (predefined) whereas 44% were bronchus sign absent in the Intuitive study. All patients were intubated and the procedure performed under general anaesthesia. Most patients were discharged the same day. Both systems reported no adverse events from the device itself. One SAE was reported in the Intuitive study which was an anaesthetic complication related to use of muscle relaxants from which there were no long term sequelae. Successful navigation to the nodule was made in 14 of 15 and 28 of 29 patients respectively. EBUS Guide sheath confirmation was allowed just before biopsy in the Intuitive study but not the Auris study. The devices allowed multiple samples to be taken quickly; the use of needle sampling was common in the Intuitive study because of the nature of the extrabronchial lesions. Malignancy was confirmed in 7 of 9 cases with the Auris device and 13 of 15 cases with the Intuitive device. Conclusions: Robotic bronchoscopy offers unique capability for a proceduralists in combing excellent navigation with thin scopes and stability at the biopsy tip. These early results of sampling difficult nodules need to be followed up in multicentre studies, but suggest a significant potential in dealing with small peripheral nodule biopsy. Further the large size of the biopsy channels and the stability of the tip of the instruments due to the robotics could allow further evaluation of these devices to permit endolumenal therapies for small peripheral lung cancers. Rferences: 1. Rojas-Solano, JR., Ugalde-Gamboa, L, Machuzak M. Robotic Bronchoscopy for Diagnosis of Suspected Lung Cancer: A Feasibility Study. 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MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
TUESDAY, SEPTEMBER 10 14:30–16:00

MS16.03 BRONCHOSCOPY AND OPTICAL BIOPSY

L. Wijmans

GZO Wetzikon, Zurich/Switzerland

Diagnosing lung cancer in the absence of endobronchial abnormalities is challenging. Needle-based confocal laser endomicroscopy (nCLE) enables real-time microscopic imaging of cells. We assessed the feasibility and safety of using nCLE for real-time identification of lung cancer. In patients with suspected or proven lung cancer scheduled for endoscopic ultrasound (EUS), lung tumours and mediastinal lymph nodes were imaged with nCLE before fine-needle aspiration (FNA) was performed. nCLE lung cancer characteristics were identified by comparison with pathology. Multiple blinded raters validated CLE videos of lung tumours and mediastinal nodes twice. EUS-nCLE-FNA was performed in 22 patients with suspected or proven lung cancer in whom 27 lesions (six tumours, 21 mediastinal nodes) were evaluated without complications. Three nCLE lung cancer criteria (dark enlarged pleomorphic cells, dark clumps and directional streaming) were identified. The accuracy of nCLE imaging for detecting malignancy was 90% in tumours and 89% in metastatic lymph nodes. Both inter-observer agreement (mean κ=0.68, 95% CI 0.66–0.70) and intra-observer agreement (mean±sd κ=0.70±0.15) were substantial. Real-time lung cancer detection by endosonography-guided nCLE was feasible and safe. Lung cancer characteristics were accurately recognised

Keywords: needle based confocal laser endomicroscopy

MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
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MS16.04 BRONCHOSCOPIC LUNG CANCER ABLATION

K. Yasufuku

Toronto General Hospital, University of Toronto, Canada/Canada

Lung cancer is the leading cause of cancer mortality in the western world. Around 80% of cases are classified as non-small cell lung cancer (NSCLC). Surgical resection by lobectomy is the standard of care for patients with localized and early stage NSCLC (1). However, patients with comorbidities may not tolerate standard surgery. With the aging population and the wide-spread use of CT scan for lung cancer screening, we are faced with increasing number of patients with early stage lung cancer who are medically inoperable. Currently, stereotactic body radiation therapy (SBRT) is the standard-of-care for treatment of early stage peripheral NSCLC in medically inoperable

patients (1). Although SBRT has become a standard option for treatment of peripheral NSCLC, it is still not clear whether the survival rates and recurrence rates are similar to those after standard curative surgical resection. SBRT also has risks such as radiation lung toxicity and therefore it not applicable to all patients as well as limited with location of the tumor (2). Percutaneous thermal ablation typically performed by interventional radiologist is an alternative approach for treatment of medically inoperable patients. Hot therapy such as radiofrequency ablation (RFA) and microwave ablation (MWA) are used for treatment of lung tumors. Cold therapy is also available using the cryotherapy (3). Although thermal therapy has shown good local control rates, complications related to percutaneous ablative approach including pneumothorax, BP fistula, bleeding, needle tract seeding cannot be ignored, since the majority of patients requiring such therapy in general do not have good lung function. A safer approach and therapeutic option for medically inoperable patients with NSCLC is desired. Recently we have seen advances in technology that allow bronchoscopists to navigate and approach peripheral lung cancer via transbronchial approach. Development of smaller bronchoscopes allow better manipulation of the scope to reach out to the peripheral lung (4). Navigational bronchoscopy aids bronchoscopist by providing actual pathway to the peripheral nodule (5). The radial probe endobronchial ultrasound (RP-EBUS) allow confirmation of the tumor location during peripheral transbronchial biopsies (6). Combining these bronchoscopic technologies with an ablation catheter that will fit through the channel of the flexible bronchoscope may allow minimally invasive transbronchial ablation of peripheral lung cancer. Fore real-time confirmation of probe positioning during transbronchial ablation, cone-beam CT scan is suitable even during bronchoscopy. The development of such technology is still in its infancy. Based on current publications including animal studies and human case studies, possible transbronchial ablative technologies include transbronchial RFA, MWA, cryotherapy, photodynamic therapy (PDT), photothermal therapy (PTT) and thermal vapor ablation (7). Although the evidence is not available yet, multiple clinical trials under way and hopefully these technologies will become available in the future. Details of each modality will be discussed in the presentation. Reference Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28: 1-21. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e278S-313S. Palussière J, Catena V, Buy X. Percutaneous thermal ablation of lung tumors - Radiofrequency, microwave and cryotherapy: Where are we going? Diagn Interv Imaging. 2017; 98: 619-25. Oki M, Saka H, Ando M, et al. Ultrathin Bronchoscopy with Multimodal Devices for Peripheral Pulmonary Lesions. A Randomized Trial. Am J Respir Crit Care Med. 2015; 192(4): 468-76. Khandhar SJ, Bowling MR, Flandes J, et al; NAVIGATE Study Investigators. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. BMC Pulm Med. 2017 11; 17(1): 59. Sabath BF, Casal RF. Bronchoscopic ablation of peripheral lung tumors. J Thorac Dis 2019. doi: 10.21037/jtd.2019.01.65

Keywords: Bronchoscopy, lung nodule, ablation

MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
TUESDAY, SEPTEMBER 10 14:30–16:00

MS16.05 OPTIMAL TREATMENT SELECTION FOR SCREEN-DETECTED LUNG CANCERS

N. Ikeda

Tokyo Medical University, Tokyo/Japan

In recent years, the number of early stage lung cancers, especially cases showing ground-glass opacity (GGO) has enormously increased mainly due to frequent use of chest CT in routine practice or screening purpose. The surgical approach has enormously changed to pursue both curability and minimal inavasiveness for such early disease. Increased number of VATS lobectomy and sublobar resection for selected patients is the international trend.Conventional bronchoscopic examination for screening detected tiny cancers shows low diagnostic rate therefore the combination of virtual bronchoscopic navigation (VBN) and EBUS guide-sheath has been employed. A total of 40000 lung cancers were resected in Japan in 2015 and 70% of surgeries were performed by video-assisted1). Although there are a few randomized controlled trial, the evidence of VATS lobectomy is supported many propensity-matched studies, several high quality meta-analyses as well as outcome studies2). Segmentectomy has been performed intentionally mainly for lung cancer 2cm or less in diameter. Several comparative studies between lobectomy and segmentectomy for tumors < 2cm showed no significant difference in survival3). Recently, segmentectomy is selected based on the size, location as well as the consolidation size in the primary lesion in preoperative high resolution CT (HRCT). The proportion of consolidation diameter to tumor diameter (C/T ratio) correlates with biological malignancy and the establishment of robust image criteria predicting non-invasive cancer is desirable to find candidates for segmentectomy. The Japan Clinical Oncology Group (JCOG) conducted a prospective cohort study to recognize the relationship between HRCT finding and pathological non-invasiveness (no lymph node metastasis or vessel invasion) in clicical stage IA cancer (JCOG0201)4). This study revealed that adenocarcinoma <2.0 cm with <0.25 consolidation to the maximum tumor diameter showed pathological non-invasiveness in 98.7% and this criterion could be used to as radiological non-invasive adenocarcinoma5). Based on the result of JCOG0201, two prospective studies were performed and finished recruitment, phase II trial of wide wedge resection for radiological non-invasive adenocarcinoma (tumor diameter 2cm or less and consolidation ratio<0.25) (JCOG0804) and randomised phase III trial for radiological invasive adenocarcinoma (tumor diameter 2cm or less and consolidation ratio>0.25) to evaluate non-inferiority in OS of segmentectomy compared to lobectomy (JCOG0802)6). The indication of segmentectomy will be demonstrated by the results of these studies. Although C/T ratio in the maximum plane of the tumor has been applied clinically as an index of malignancy, objective measurement is sometimes difficult due to the irregular shape of objectives. It should be more accurate to analyze the ratio of the consolidation part volume to whole tumor volume quantitatively by creating 3D-CT image. In our analysis of 252 cases of stage I lung cancer, the solid part volume of the tumor had a statistically significant correlation with prognosis7). In addition, PET-CT has been routinely used for the management of lung cancer and another approach to evaluate the biological aggressiveness. The standardized uptake value (SUV) of the main tumor is recognized to be as a predictor of the clinicopathological characteristics. Our data showed that more accurate prognosis of stage IA adenocarcinoma could be predicted by the combination of SUVmax and solid part volume of the primary tumor8). Since CT reflects the histologic grade of the tumor and SUVmax reflects the intratumoral metabolism, the combined use of these may be expected to evaluate nature of lung cancer more precisely than each alone.The information on the grade of malignancy obtained from preoperative images is useful for selecting appropriate treatment. In the near future, radiomics can analyze the radiologic images and extract important pathological and genomic information non-invasively before treatment. Advances in imaging and quantitative analysis will be powerful support to select interventions of screening detected lung cancer. References 1) Committee for Scientific Affairs The Japanese Association for Thoracic Surgery, Thoracic and cardiovascular surgery in Japan during 2015:Annual report by the Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg.2018;66:581-615. 2) Ikeda N Updates on minimally inavasive surgery in non-small cell lung cancer. Curr. Treat. 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Keywords: VATS, segmentectomy, PET-CT

MS16 THE INTERVENTIONAL PULMONOLOGIST'S CONTRIBUTION TO SCREEN-DETECTED NODULES: FROM DIAGNOSIS TO TREATMENT
TUESDAY, SEPTEMBER 10 14:30–16:00

MS16.06 SMOKING CESSATION IN A PULMONARY CLINIC

P. Lee
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Lung cancer is the leading cause of cancer related death worldwide. NLST showed 20% reduction in mortality from lung cancer among long-term heavy smokers screened with low dose CT. However, screening for early stage lung cancers can be controversial as the number of lives saved through early diagnosis should be assessed against potential harms of invasive testing, over diagnosis of indolent tumors and surgery for benign conditions. Of the positive CT scans in NLST, 96.4% were false positives, and the risks of death and major complications pertaining to diagnostic tests for benign nodules are 4.1 and 4.5 per 10,000 respectively. The decision to pursue surveillance imaging or invasive evaluation requires careful assessment of the risk for cancer, access for biopsy, fitness for surgery and patient's preferences. When biopsy is required, the approach includes bronchoscopy, transthoracic needle biopsy or surgical lung biopsy. Selection of the appropriate intervention depends on lesion size and location, presence of lymphadenopathy, and local expertise. Bronchoscopy is safe but limited by its sensitivity which in turn depends on location and size of the pulmonary nodule. There has been substantial evolution in bronchoscopic approaches towards achieving access of these small peripheral pulmonary nodules, improved tools to acquire specimens necessary for early diagnosis so as to facilitate curative therapy not confined to surgical resection but heralds an era of innovative techniques performed in minimally invasive manner.

Keywords: early detection of lung cancer, CT screening, bronchoscopy

MS17 PATHOLOGY OF THE FUTURE
TUESDAY, SEPTEMBER 10 14:30–16:00

MS17.01 ROLE OF LIQUID BIOPSY IN THE PATHOLOGY DIAGNOSIS WORKFLOW (INCLUDING DNA, RNA AD EXOSOMES)

F. Lopez-Rios

HM Hospitales (Madrid, Galicia & Barcelona), Madrid/Spain

Although liquid biopsy approaches have considerable potential to improve patient care, integrating them into the pathology diagnosis workflow could be a challenge. In the presentation I will address the most frequent barriers for inmediate implementation of the recommendations released by the IASLC and other academic groups. Briefly, plasma is preferred over serum for ctDNA and ctRNA extraction. The choice of analytical methodology should balance availability, cost, turnaround time, sensitivity and specificity. Recent cross-platform comparisons will be presented because technical factors could explain both discordance between assays and with tissue-based genotyping. The results of liquid biopsies should follow the standards of molecular pathology reporting. Taking into consideration that the number of pathology and biomarker reports per patient will be growing over the next few years, it is important to integrate all of them before discussion of treatment options take place at the molecular tumour board. The recent tier classifications of molecular alterations released by professional organisations could help implement this strategy. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC - challenges to implementing ctDNA-based screening and MRD detection. Nat Rev Clin Oncol 2018; 15: 577-586. Aggarwal C, Thompson JC, Black TA, et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. JAMA Oncol 2018. doi: 10.1001/jamaoncol.2018.4305. Laufer-Geva S, Rozenblum AB, Twito T, et al. The Clinical Impact of Comprehensive Genomic Testing of Circulating Cell-Free DNA in Advanced Lung Cancer. J Thorac Oncol 2018; 13: 1705-1716. Leighl NB, Page RD, Raymond VM, et al. Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clin Cancer Res 2019. doi: 10.1158/1078-0432. Li BT, Janku F, Jung B, et al. Ultra-deep next-generation sequencing of plasma cell-free DNA in patients with advanced lung cancers: results from the Actionable Genome Consortium. Ann Oncol 2019; 30: 597-603. Rolfo C, Mack PC, Scagliotti GV, et al. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC. J Thorac Oncol 2018; 13: 1248-1268. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. Nat Rev Clin Oncol 2017; 14: 531-548. Torga G, Pienta KJ. Patient-Paired Sample Congruence Between 2 Commercial Liquid Biopsy Tests. JAMA Oncol 2018; 4: 868-870. Sabari JK, Offin M, Stephens D, et al. A Prospective Study of Circulating Tumor DNA to Guide Matched Targeted Therapy in Lung Cancers. J Natl Cancer Inst 2018. doi: 10.1093/jnci/djy156.

Keywords: liquid biopsy, plasma, NGS

MS17 PATHOLOGY OF THE FUTURE
TUESDAY, SEPTEMBER 10 14:30–16:00

MS17.02 MAJOR PATHOLOGICAL EVALUATION IN NEOADJUVANT IMMUNOTHERAPY

J. Ramirez

Hospital Clinic, Barcelona/Spain

The pathologists play different roles in the care of cancer patients. The main part of this activity is to make the diagnosis of the tumor type, followed by the support to the clinicians in the staging of the patient. In the group of patients that receive Chemotherapy (CT) and / or Radiotherapy (RT) before surgery, the pathologist has to evaluate the results of these treatments by evaluating the tumor bed and the response of the lung. There is a lot of experience in the literature referred to the different types of pathological response to lung cancer treatment after the use of either CT or RT. There are guidelines for the pathologists in order to give an objective evaluation of the treatment results (1). All of them ask the pathologists to evaluate the percentage of viable tumor cells, necrosis and stromal reaction. We can also find different attempts to find molecular markers useful for predicting survival after these traditional treatments (2). In order to have an objective evaluation of the lung cancer patients after CT in 2014 emerged the concept of Major Pathological Response (MPR) as a possible predictor of overall survival (3). This term was applied to describe those patients with a viability of 10% of the tumor cells after neoadjuvant CT. In this report, they propose the MPR as a surrogate endpoint. Since that, the concept of MPR has been used in different reports and assays, becoming a usual parameter for patients with lung resections after receiving chemotherapy. The percentage of viable cells became an important data that has to be evaluated with accuracy in order to avoid subjective results. One of the best ways is to use any of the commercial systems to make measurements on the slides. In our department, we use digital slides to get objective and reproducible data for this type of evaluation. The recent implementation of immunotherapy (IT) for NSCLC that is being applied to an increasing number of patients all over the world makes it necessary to study deeply its morphological effects over de tumor in lung specimens. As most of the patients will never go to the operating room, it becomes important to be aware of the limited knowledge that we have so far. There are some reports comparing the effects of the traditional chemotherapy with immunotherapy. One of these studies shows that the pathologist should look for the same features that are routinely evaluated in the cases after CT (4). The pathologist might evaluate the classic features (viable cells, necrosis and stromal reaction) and other characteristics such as macrophages, cholesterol clefts, lymphoid aggregates, giant cells and neovascularization. In this review, they did not find important differences between the type of morphological changes in both types of treatment, so they propose to use the same parameters in CT and in IT A recent report proposes the concept of Immuno related Pathological Response Criteria (irPRC) (5). They pay attention to the Immune activation with dense lymphoid infiltrate, macrophages and tertiary lymphoid structures as the main characteristics. They also evaluate the massive tumor cell death with destructive features such as cholesterol clefts and those indicative of tissue repair with neovascularization and fibrosis. Last year a review collected different assays done with neoadjuvant IT in patients with resectable lung cancer (6). There is no enough experience in these special groups of patients, as today the IT is given only to advanced lung carcinoma patients. Conclusions: At the present time there are no guidelines for the evaluation of lung tissues after IT. The pathologists have to be aware of the effects of these new biological treatments for lung cancer patients, in order to give as much information as possible in the short number of cases that are

seen in the real clinical situation. The previous experience in resected lungs after neoadjuvant therapy is not enough to evaluate the cases after IT. The data obtained from these lung specimens have to give more information in order to improve the knowledge of the effects of these new therapies. References: 1. Pataer A, Kalhor N, Correa AM et al. Histopathologic Response Criteria Predict survival of Patients with Resected Lung Cancer After Neoadjuvant Chemotherapy. J Thorac Oncol. 2012;7: 825–832. 2. Pataer A, Shao R, Correa AM et al. Major pathologic response and RAD51 predict survival in lung cancer patients receiving neoadjuvant chemotherapy. Cancer Medicine 2018; 7(6):2405–2414. 3. Hellman MD, Chaft JE, William NW et al. Pathologic response after neoadjuvant chemotherapy in resectable non-small cell lung cancers: proposal for the use of "major pathologic response" as a surrogate endpoint. Lancet Oncol. 2014 January; 15(1): e42–e50. 4. Weissferdt A, Sepesi B, Pataer A et al. Pathologic assessment following neoadjuvant immunotherapy or chemotherapy demonstrates similar patterns in non-small cell lung cancer (NSCLC). Ann Oncol 2018: 29(S8). 5. Cottrell TR, Thompson ED, Forde PM et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Annals of Oncology 2018; 29: 1853–1860. 6. Owen D, Chaft JE. Immunotherapy in surgically resectable non-small cell lung cancer. J Thorac Dis 2018; 10(S3): 404-411.

Keywords: pathological response, Immunotherapy

MINI SYMPOSIA

MS17 PATHOLOGY OF THE FUTURE
TUESDAY, SEPTEMBER 10 14:30–16:00

MS17.03 QUANTITATIVE IMAGE ANALYSIS, IMAGE-BASED PROFILING INCLUDING 3D DIGITAL PRINTING AND AI

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Digital pathology and AI Digital pathology refers to the use of computer stations to analyze images of whole slides scanned at high resolution for teaching or research purposes; these images are analyzed by algorithms that allow standardization and reproducibility of the analyses. Recently, artificial intelligence has been used to build even more powerful algorithms. The idea is not to reproduce the visual analysis of pathologists but to improve it and to identify new predictive or prognostic morphological characteristics or to couple them with genomic analysis to better stratify tumours (1,2). Technical considerations The digital workflow requires specific equipement (slide scanner, image storage and digital pathology workstation). Image analysis needs well-standardized pre-analytical conditions, especially if IHC stainings are analyzed, where colour variations and absence of background noise must be controlled during different validation steps. Some methods exist to correct artifacts such as section fold, fuzzy area. SOPs (standardised operating procedures) and regulations must also be respected concerning the scanning platforms, which must be CE IVD or FDA approved, the construction of databases, anonymisation, sending and image analysis. Algorithms used for analyses perform different operations on digital images: quality improvement, filtering, recording and segmentation and they must also be validated by correlation measuring the reproducibility between pathologists and algorithms. In addition, The large amount of data requires significant computer processing with accelerated calculations by CNNs (Convolutional Neural Networks) and large image storage capacity. Applications:Quantitative analyses and Image-Based Profiling: most image analyses proposed by commercial softwares (VisionPharm, Definiens Tissue Studio, Indica Labs HALO), or open source softwares such as QuPath Open Source Software for Quantitative pathology or ImageJ, are area or cells-based measurements. Area- based measurements include quantification of stained zones (using IHC stain for example); cell_ based measurements require segmentation steps to delineate tissue compartments, to distinguish for example tumor from begnin regions or to identify subcellular structures (such as nuclei). Some modules or algorithms are CE-IVD or FDA approved such as those used to quantify the expression of ER, PR, Her2 and KI67 in breast cancers. Other algorithms enable the estimation of the percentage of tumour cells before molecular analysis for the detection of genes mutations (Tissue Mark, Philipps pathology). They can also enable to localise and quantify the immune infiltrate (CD3 and CD8+ T Cells) within the tumor stroma (Immunoscore, Laboratory of Integrative cancer Immunology INSERM Paris). Some machine Learning methods can also automatically differentiate tumor cells from stroma cells and inflammatory cells or identify lymph node metastases. In thoracic pathology, automated whole slide scoring of PDL1 has been proposed in NSCLC with an excellent agreement for tumor cells scoring and a good concordance for immune cells (3). Image based analysis has been used for quantification of immune checkpoints molecules co expression in NSCLC (4). Several studies have showed the interest of automatic image-based analysis for the optimization of histological or cytological classification of lung cancer and prediction of prognosis (5,6). Deep learning technology has been used to classify lung tumour subtypes from the virtual slides available in the TCGA (7), or to classifiy adenocarcinoma according to the predominant pattern with a kappa score of 0.525 and an agreement of 66.6% with three pathologists (8). Deep learning was also proposed for genomic profiling of tumours, with a prediction of STK11, EGFR, FAT1, SETBP1, KRAS and TP53 mutations from pathology images showing an AUCs ranging from 0.733 to 0.856 (9,10). Applications: 3D dimensions modeling and digital Printing Three-dimensional (3D) photogrammetry is a method of image-based modeling in which data points in digital images, taken from offset viewpoints, are analyzed to generate a 3D model. This technique can be used to generate 3D representation sof surgical specimens, for routine gross examination, in multidisciplinary meetings to improve clinicopathologic correlation between surgeon and pathologists, and for education purposes via 3D printing specimen models (11). References 1. Niazi MKK, Parwani AV, Gurcan MN. Digital pathology and artificial intelligence. Lancet Oncol. mai 2019;20(5):e25361. 2. Aeffner F, Zarella M, Buchbinder N, Bui M, Goodman M, Hartman D, et al. Introduction to digital image analysis in whole-slide imaging: A white paper from the digital pathology association. J Pathol Inform. 2019;10(1):9. 3. Taylor CR, Jadhav AP, Gholap A, Kamble G, Huang J, Gown A, et al. A Multi-Institutional Study to Evaluate Automated Whole Slide Scoring of Immunohistochemistry for Assessment of Programmed Death-Ligand 1 (PD-L1) Expression in Non–Small Cell Lung Cancer: Appl Immunohistochem Mol Morphol. avr 2019;27(4):2639. 4. 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Keywords: digital pathology, image analysis, deep learning

MS17 PATHOLOGY OF THE FUTURE
TUESDAY, SEPTEMBER 10 14:30–16:00

MS17.04 MULTIPLEX IMMUNOHISTOCHEMISTRY

I. Wistuba, E. Parra, A. Francisco Cruz

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Multiplexed imaging platforms to simultaneously detect multiple epitopes in the same tissue section emerged in the last years as very powerful tools to study tumor immune contexture. These revolutionary technologies are providing a deep methodology for tumor evaluation in formalin-fixed and paraffin-embedded (FFPE) to improve the understanding of tumor microenvironment, new targets for treatment, prognostic and predictive biomarkers, and translational studies. Multiplexed imaging platforms allow the identification of several antigens simultaneously from a single tissue section, core needle biopsies, and tissue microarrays. In recent years, multiplexed immunohistochemistry, immunofluorescence, mass spectometry and other imaging modalities have improved the abilities to characterize the different types of cell populations in malignant and non-malignant tissues, and their spatial distribution in relationship to clinical outcomes. Multiplexed technologies associated with digital image analysis software offer a high-quality throughput assay to study cancer specimens, inc;luding lung cancer, at multiple timepoints before, during and after treatment. The aim of this resentation is to provide a review of multiplexed tissue imaging applied to lung cancer focusing in the use of multiplex immunofluorescence with tyramine signal amplification staining for lung cancer immune profiling and translational research.

Keywords: Multiplex immunofluorescence, immune-profiling, microenvironment

MS17 PATHOLOGY OF THE FUTURE
TUESDAY, SEPTEMBER 10 14:30–16:00

MS17.05 CONTROVERSIES IN PATHOLOGIC STAGING

M. Yotsukura

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The 8th edition of the TNM classification system was implemented in January 2017, except in the United States, where it was delayed until January 2018. The 8th edition was proposed by the Staging and Prognostic Factors Committee (SPFC) of the International Association for the Study of Lung Cancer (IASLC), and accepted by the Union for International Cancer Control and American Joint Committee on Cancer. The SPFC's proposed changes from the 7th to 8th edition were essentially based on prognostic data from the IASLC database, which included 70,697 evaluable patients with non-small cell lung cancer and 6,189 patients with small cell lung cancer. Although the TNM system is the result of a scientific analysis of the anatomical extent of the tumor, some of the classification points are still controversial. 1. Ground glass opacity Regarding the T descriptor, the main issue revolves around ground glass opacity (GGO)-related matters. The invasive area can pathologically be well-defined under microscopic evaluation, sometimes in combination with Elastica van Gieson stain. However, the difference between pathological and clinical staging has been a problem. Clinical staging depends on how to measure the GGO component by computed tomography (CT), which has not been defined very well. Another point to be addressed related to GGO is the separation of GGO-containing tumors from solid tumors. For example, if a tumor has a solid component of 1.5 cm without any surrounding GGO component, it will be defined as clinical T1b, whereas if a tumor has a solid component of 1.5 cm along with 1.0 cm of surrounding GGO component (total tumor diameter of 1.5 + 1.0 = 2.5 cm), it would also be defined as clinical T1b. However, the malignant capacity of a purely solid tumor is reported to be worse than that of GGO-containing tumors. Thus, from a prognostic viewpoint, it might be better to consider these two types of tumors separately. 2. Visceral pleural invasion Another controversy regarding the T descriptor in pathologic staging involves visceral pleural invasion (VPI). First, data should be collected using a standardized definition. A standardized definition of VPI was incorporated into the 7th edition of TNM and maintained in the 8th edition. PL1, 2, and 3 are pathologically evaluated based on tumor invasion to the elastic layer, pleural surface, and parietal pleura. In case of doubt regarding VPI, the use of elastic stains is recommended. The collection of data using this definition and the use of elastic stains are important for accurate evaluation in future revisions. Second, the difficulty of clinical evaluation of VPI might be a problem. In the current staging system, clinicians have to speculate on the presence of VPI, based solely on the findings of CT imaging. A clear imaging-based definition of VPI might be beneficial. Third, in the current staging system, interlobar PL3 is classified as T2a. Since little is known about the prognosis of this interlobar PL3, data should be collected for use in a future revision of the TNM classification. 3. Nodal evaluation Regarding the N descriptor, as previously reported in the literature, tumors with nodal metastases to multiple lymph node stations have a worse prognosis than those with single-station metastasis. Counting the number of positive nodes instead of the number of stations might be considered as well, especially from the viewpoint of emphasizing prognostic impact. However, a standardized method for pathological nodal evaluation has been lacking. How should pathologic slides be made for an accurate evaluation of nodal status? The number of nodes that are incorporated on the same slide, and the number and depth of sections to be evaluated per slide, are not well defined. It is also not clear how to handle an intraoperatively separated node, when counting the number of metastatic nodes. It would be desirable to have some consensus about the evaluation methodology to achieve a more accurate prognostic analysis. 4. Molecular information There are some disagreements about how to use molecular information, in relation to TNM classification. Over the past decades, dramatic advances have been made in the fields of molecular diagnosis and precision medicine. The therapeutic strategy has been developed in detail depending on the molecular status, especially in advanced tumors. Accordingly, the prognosis has been influenced by the molecular status of the tumor, and thus molecular biomarkers have become some of the most important prognostic factors. In principle, the TNM classification describes the anatomic extent of tumors, arranged according to prognostic differences. From the perspective of the prognostic impact, molecular biomarkers might be as important as TNM staging. The combination of molecular status and TNM classification could be considered. However, based on the principal concept of the anatomic classification of the TNM system, it might be better to consider molecular factors as a different methodology of the classification system. Further discussions will be needed regarding the relationship between molecular markers and the anatomic TNM classification system. These issues reflect only some of the controversies surrounding the TNM staging system. Along with other issues, they are expected to be discussed in detail in the SPFC meetings for the forthcoming update of the TNM classification system.

Keywords: staging, TNM classification

MS18 ROLE OF BIOMARKERS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10 14:30–16:00

MS18.01 EXHALED BREATH BIOMARKERS

N. Peled

Soroka University Medical Center, Beer-Sheva/Israel

The evoloving field of early detection of lung cancer is being implemented around the globe. Low Dose CT scans are standard of care in all guidelines, however real world implementation is stil lacking. Biomarker to support early detection is the current UNMET need, as well as non-invasive biomarkers to follow early disease recurrence and monitoring response to therapy. The exhaled breath approach is a growing field of interest, where several groups have contributed significant abount of data. There are numerous technologies available while clinical validation is varies between groups. This talk will score the current knoledge associated with the exhaled breath analysis associated with lung cancer. Surprizingly, the volatille signature is associated with disesae existance, disesae burden, response to therapy, disease profile and even the related mutatoins.

Keywords: Exhaled breath, Non invasive biomarkers, early detection

MS18 ROLE OF BIOMARKERS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10 14:30–16:00

MS18.02 CIRCULATING NUCLEIC ACID BIOMARKERS

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Encouraging results in lung cancer (LC) mortality reduction were obtained by the introduction of low dose computed tomography (LDCT) for lung cancer screening. The results of Nelson screening trial showed a 26% reduction in lung cancer mortality in the LDCT arm thus confirming the benefit of LC screening with LDCT already published by the NLST group (1). In MILD trial we showed that at 10 years follow up the mortality reduction was even higher (-39%) proving that extended LDCT screening is effective in reducing lung cancer mortality (2). Nonetheless, the development of non-invasive complementary biomarkers could be helpful to improve the efficacy of LDCT screening by improving LC risk prediction and defining personalised LDCT screening intervals as well as to decrease false positives identified by LDCT and monitor disease evolution in patients after curative resection. The value of circulating tumor DNA (ctDNA) as a biomarker in advanced tumor stages is well established. However, its role in early lung cancer detection is still uncertain. The biggest technical challenge is sensitivity. Current efforts to develop next-generation sequencing (NGS) technologies to study ctDNA in the context of early detection might improve sensitivity in this context. The scientific community is awaiting the results of the Circulating Cell-free Genome Atlas (CCGA) Study for early cancer detection, enrolling 15,000 participants in the United States and Canada. Plasma samples collected at baseline and during 5 years of follow-up will be analyzed by whole genome sequencing(WGS) for copy number variation(CNV), targeted DNA sequencing (a 507-gene panel), and whole genome methylome profiling. Preliminary results in an observational case-control setting include 95% specificity, high sensitivity for advanced lung cancer in 54 patients (85% for targeted sequencing, 91% for CNV WGS, and 93% for methylome profiling), and modest sensitivity for 63 patients with stage I to III lung cancer (48% for targeted NGS, 54% for CNV WGS, and 56% for methylome profiling)(3). Therefore, the generalizability of these findings to the screening setting is uncertain. In order to implement lung cancer screening programs, we focused on circulating microRNAs which may reflect the contribution not only of the tumor but also of its microenvironment and the host. We developed a plasma miRNA Classifier (MSC) composed of 24 miRNAs which showed high performance in terms of sensitivity (87%) and specificity (81%) in 940 subjects enrolled in the MILD screening trial. The classifier was able to identify, in longitudinal plasma samples of the patients, a risk profile to develop LC up to two years before a significant tumor burden was visible at LDCT(4). These results prompted us to launch in 2013 a prospective screening trial, called bioMILD, to test the efficacy of a combined LDCT-MSC approach as forefront screening tests in a large cohort of 4119 smokers, 50 yrs or older. We succesfully completed the baseline of all the volunteers and executed a LDCT in 11,012 and miRNA test in 9,156 subjects. BioMILD has now reached the 3 yrs follow up for all subjects and 4.2 year median follow up for the all cohort. Analyses of the results are ongoing and will be presented. Concerning the origin of the 24 miRNA, since the classifier was able to identify a risk profile to develop lung cancer up to two years before the radiological diagnosis, we hypothesized that that such circulating miRNAs could be released not merely by cancer cells but rather by the damaged lung microenvironment and the host response that may sustain tumor development. Using *in vitro* models and clinical samples we showed that c-miRNAs originated mostly from blood cells, with activated neutrophils showing modulation of the 24 miRNAs overlapping that observed in plasma of MSC positive subjects(5). The role of immunity in modulating the risk of disease development remains to be elucidated, while it could have enormous impact in terms of prevention and early intervention. Therefore we characterized peripheral blood immune cell profiles as possible complementary biomarkers for risk assessment and analyzed their relationship with MSC. In a case control study of 40 lung cancer patients and 20 controls we found immune cell subpopulations differentially expressed between screening detected lung cancer patients and controls. Of interest an MSC high risk profile in patients was associated with specific circulating immune cell subsets including higher numbers of exausted T cells and monocytes/MDSC and lower cytotoxic T and NK cells. These findings suggest that MSC high risk profile might reflect an immunosuppressive status and prompted us to study the possible utility of MSC in lung cancer immunotherapy settings. Using a prospective cohort of 140 consecutive advanced NSCLC patients treated with immune checkpoints inhibitors we found that MSC either alone or in combination with PD-L1 expression in the tumor was associated with patients survival(6). Therefore, plasma MSC, reflecting an impaired tumor immune contexture, could supplement PD-L1 tumor expression to identify a subgroup of patients who do not benefit from immunotherapy. References: D.R. Aberle, A.M. Adams, C.D. Berg, et al.Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med, 365 (2011), pp. 395-409 Pastorino U, Silva M, Sestini S. et al. Prolonged Lung Cancer Screening Reduced 10-year Mortality in the MILD Trial. Ann Oncol. 2019 Apr 1. GR. Oxnard T. Maddala E. Hubbell et al. Genome-widesequencing for early stage lung cancer detection fromplasma cell-free DNA (cfDNA): the Circulating CancerGenome Atlas (CCGA) study. Paper presented at: 2018 American Society of Clinical Oncology Annual Meeting.June 1–5, 2018; Chicago, IL Sozzi G, Boeri M, Rossi M.et al. Clinical Utility of a Plasma-based microRNA Signature Classifier within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study. 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Keywords: microRNA, Immunity, lung cancer screening

MS18 ROLE OF BIOMARKERS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10 14:30–16:00

MS18.03 AMOLECULAR DIAGNOSTICS, INCORPORATING GWAS AND RISK MODELS: FUTURE APPROACHES TO THE IDENTIFICATION OF HIGH-RISK INDIVIDUALS

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Role of Biomarkers in Lung Cancer Screening As a part of ongoing research to understand the etiology and early detection of lung cancer, the Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) consortium has been genotyping large numbers of lung cancer cases and controls and analyzing biomarkers from case cohort members prior to their diagnosis with lung cancer and matched controls. We are also assembling knowledge about predictors of lung cancer risk to identify biomarkers that will be applied along with radiomic features to select individuals at highest risk for lung cancer to enroll in screening studies and to assist in resolution of cancer risk among those found to have small nodules. To date we have analyzed genetic data from 29,266 patients and 56,450 controls of European descent(1) and curated genotyping information from 20 studies conducted in European descent, 14 from Asian descent and 1 study in African-American Populations(2). Ongoing imputation is allowing us to integrate most of these data for a further analysis that brings together world populations for genetic discovery. Results of these studies have identified 12 strongly replicated loci and an additional 38 loci that are highly significant in some studies but less well replicated. Among the variants that we identified, a variant in BRCA2 (1) is remarkable for conferring over 2 fold increased risk for lung cancer development independent of smoking behavior and thereby indicating a small subset of high risk individuals based on genotype. Further studies to identify rare variants that confer a high risk of lung cancer have identified mutations in ATM and KIAA0930 with odds ratios well over 2. The ATM variant is associated with loss of heterozygosity in tumors but does not cause Ataxia Telangiectasia in homozygotes. We have used genetic information to develop polygenic risk scores and a model that included 221 variants yielded the most improvement in accuracy. Results comparing models to identify individuals at high risk for lung cancer development based on risk scores compared with models based on demographic, clinical and smoking information show a modest increase in prediction accuracy, but identify selected individuals who are at high risk and for whom lung screening would be particularly indicated. The genetic information we have developed and curated can also be used with additional approaches to identify predictors of lung cancer risk using shared heritability and Mendelian randomization analyses. Shared heritability analysis identifies strong genetic correlations

with all measures of smoking behavior and also with primary biliary cirrhosis and schizophrenia. Mendelian randomization, which removes concerns about change in BMI during cancer development, shows that increased BMI is associated with squamous and small cell lung cancer and not associated with adenocarcinoma(3). Mendelian randomization studies found association of increased lung cancer risk with longer germline telomere length and increased risk associated with higher levels of vitamin B12(4). Further Mendelian randomization studies are underway to evaluate other biochemical factors that may associate with increased lung cancer risk. Cohort studies to identify biomarker signatures of risk have identified a reliable panel(5) comprising CEA125, CEA, CYFRA 21-1 and pro-SFTB that along with smoking behavior provide an area under the receiver operator curve of 83%, indicating that a strategy that seeks to identify high risk individuals using data from questionnaires about smoking along with biomarker analysis could substantially improve the yield of low dose spiral CT screening. Further studies of panels of biomarkers including microRNA and circulating cell-free DNA are underway to evaluate the utility of adding additional biomarkers to further identify higher risk individuals. 1. McKay JD*, et al.* (2017) Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nature genetics* 49(7):1126-1132. 2. Bosse Y & Amos CI (2018) A Decade of GWAS Results in Lung Cancer. *Cancer epidemiology, biomarkers & prevention:a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 27(4):363-379. 3. Carreras-Torres R*, et al.* (2017) Obesity, metabolic factors and risk of different histological types of lung cancer: A Mendelian randomization study. *PloS one* 12(6):e0177875. 4. Fanidi A*, et al.* (2018) Is high vitamin B12 status a cause of lung cancer? *International journal of cancer. Journal international du cancer*. 5. Integrative Analysis of Lung Cancer E*, et al.* (2018) Assessment of Lung Cancer Risk on the Basis of a Biomarker Panel of Circulating Proteins. *JAMA oncology* 4(10):e182078.

Keywords: Genetics, Biomarkers, Early Detection

MS18 ROLE OF BIOMARKERS IN LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 10 14:30–16:00

MS18.04 ALTERNATIVE AND PROMISING BIOMARKERS

R. Pio

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Randomized controlled trials have demonstrated that lung cancer screening with low-dose computed tomography (LDCT) in subjects at risk is associated with a decrease in mortality (1-3). However, concerns regarding false positive findings, overdiagnosis, or selection criteria may limit their implementation and sustainability. The use of molecular biomarkers that help to overcome some of these limitations offers great potential. Biomarkers should be non-invasive, reproducible and improve the current standard of care for their intended use. Biomarkers could complement image-based screening in two different ways. First, they may allow refinement of screening selection criteria, independent of age and smoking habits, reducing the numbers of individuals exposed to screening and follow-up interventions. Worldwide collaborative efforts have been implemented to gain insights into the association between SNPs and common cancers (4). Lung cancer-associated single nucleotide polymorphisms (SNPs) identified in these studies may be integrated in risk models to limit the costs of lung cancer screening. Secondly, the combination of radiological findings with molecular biomarkers may facilitate the management of indeterminate pulmonary nodules (IPNs). The implementation of LDCT screening programs is rapidly increasing the detection of IPNs, which too often leads to unnecessary follow-up CTs, or even invasive procedures. Molecular markers may help to differentiate patients with malignant IPNs from the larger number of subjects with benign nodules. At present, no molecular biomarker of lung cancer is being used in routine clinical practice. The tremendous research efforts regarding the development and use of molecular biomarkers in lung cancer screening have recently been reviewed (5). Biomarkers can derive from cancer cells, the tumor microenvironment, or the immune response to cancer. They can be sampled from many different bodily sources, including whole blood, serum, plasma, airway epithelium, sputum, exhaled breath, or urine. Promising molecular candidates include proteins (e.g. cancer-associated antigens, autoantibodies or other immune-related markers), metabolites, microRNAs, epigenetic markers, DNA mutations or RNA signatures. Markers of this kind are at different phases of development, ranging from their analytical validation to the evaluation of their performance in the intended use population. Ultimately, evaluation of the biomarker in real clinical settings will determine its improvement of current standards and cost. Few biomarkers have reached the clinical testing phase. The application of an RNA-based signature in bronchial epithelial cell samples from the AEGIS-1 and AEGIS-2 prospective multicenter observational trials (NCT01309087 and NCT00746759) improved the diagnostic performance of bronchoscopy for the detection of lung cancer (6). In PANOPTIC (NCT01752114), a prospective multicenter observational study, plasma levels of two proteins, LG3BP and C163A, were used to discriminate benign from malignant nodules (7). The bioMILD study (NCT02247453) is prospectively evaluating the efficacy of a plasma microRNA profiling as a first line-screening test for lung cancer detection. The clinical utility of another microRNA-based signature is been validated in blood samples prospectively collected in the COSMOS-II lung cancer screening trial (8). ECLS (NCT01700257) is a randomized study aimed to assess the clinical and cost effectiveness of a test that measures a panel of seven tumor-associated autoantibodies in blood (9). The study has reached its 12,000-participant target, and initial results are expected soon. The DECAMP consortium is conducting two multicenter prospective observational trials (NCT01785342 and NCT02504697) designed to develop an integrated panel of airway and blood-based molecular markers. DECAMP-1 seeks to improve the discrimination between benign and malignant IPNs, whereas DECAMP-2 will test biomarkers to predict the development of lung cancer in screened asymptomatic high-risk individuals. Novel approaches to overcome sensitivity/specificity limitations are also being tested. Host responses to cancer based on activation of the immune system have proved to provide promising diagnostic and prognostic markers applicable in the context of lung cancer screening (10). A diagnostic signature based on the combined determination of complement-activation fragments and cancer-associated proteins has shown a notable capacity to discriminate those patients with malignant IPNs. Next-generation sequencing technologies are also starting to be applied. The CCGA study (NCT02889978) has recently concluded the enrollment of 15,000 participants (more than 10,000 of them with a diagnosis of cancer) from whom longitudinal plasma samples are being collected and analyzed by DNA sequencing and methylation profiling. This study will provide valuable information about the potential application of deep sequencing technologies in circulating cell-free DNA for the early detection of lung cancer. Finally, deep learning approaches will allow the integration of several levels of information (e.g. radiographic features, clinical characteristics and molecular biomarkers) for the generation of more accurate predictive models. In conclusion, molecular biomarkers are potentially useful adjuncts to LDCT screening for lung cancer, either by refining risk prior to LDCT or by assessing malignancy. A remarkable amount of discovery and clinical validation work is ongoing. However, more evidence is still needed to support the implementation of any of the proposed biomarkers in the routine clinical practice. Further development of emerging biomarkers, new technological and integrated approaches, better metrics of clinical utility, and innovative trial designs will be required to speed up the development of lung cancer early detection biomarkers. References: 1. Aberle DR et al. N Engl J Med 2011; 365: 395-409. 2. De Koning HJ et al. IASLC 19th WCLC 2018; Abstract PL02.05. 3. Pastorino U et al. Ann Oncol 2019 [Epub ahead of print]. 4. McKay et al. Nat Genet 2017; 49: 1126-1132. 5. Seijo et al. J Thorac Oncol 2019; 14: 343-357. 6. Silvestri GA et al. N Engl J Med 2015; 373: 243-251. 7. Silvestri GA et al. Chest 2018; 154: 491-500. 8. Marzi M et al. Clin Chem 2016; 62: 743-754. 9. Sullivan FM et al. BMC Cancer 2017; 17: 187. 10. Ajona D et al. J Natl Cancer Inst 2013; 105: 1385-1393.

Keywords: Screening, Molecular marker, early diagnosis

MS18.05 SPUTUM BIOMARKERS, DYSPLASIA AND CHEMOPREVENTION

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The most dramatic improvements in lung cancer survival will emerge from both early detection and the prevention of disease development. Low dose CT screening trials (NLST and NELSON) have shown significant improvements in survival and advances in lung cancer screening will rely on our ability to better define at risk populations and to more personalize the management of indeterminate pulmonary nodules. This includes identifying and validating biomarkers of risk. The NIH defines biomarkers as 'characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathologic processes, or pharmacologic responses to therapeutic interventions'[1]. The ideal biomarker has excellent sensitivity and specificity and applications to lung cancer screening will mostly focus on two specific areas. The first is improving the selection of at-risk subjects to be screened, and the second is to guide the management of screening detected pulmonary nodules. Biomarkers of lung cancer risk can include a variety of potential biospecimens, ranging from sputum and exhaled breath condensates to endobronchial and peripheral lung biopsies. Expectorated sputum has long been viewed as a 'window to the central airways' and cytologic changes have been observed in sputum samples to predict the presence of lung cancer[2]. While sputum cytology can also predict the presence of pre-malignant central airway lesions, sputum collection has largely fallen out of favor due to perceived difficulties in collecting and interpreting specimens, and advances in analyzing other specimens like blood, urine and exhaled breath. Sputum is a readily available resource, and recent methodological advances, most notably automated 3-dimensional morphologic analysis of sputum[3], are currently being studied to determine the presence of cancer or pre-malignant lesions. It may also help risk stratify subjects with suspicious LDCT findings. Additional studies have also focused on sputum samples. For example, selected gene promoter methylation in exfoliated cells from sputum has been shown to predict cancer up to 18 months prior to diagnosis[4]. Other groups have examined sputum miRNA, and their stability make them potentially attractive biomarkers. One study conducted qRT-PCR studies of sputum from subjects with indeterminate pulmonary nodules and found a panel of 3 miRNAs (miRs 21, 31, and 210) with good sensitivity and specificity for identifying malignant nodules[5]. More recently, a pilot study using metagenetic sequencing of the sputum microbiome suggests there may be bacterial biomarkers indicating the presence of lung cancer[6]. Exhaled breath condensate is an additional biospecimen that has been studied as an adjunct to screening protocols, and the subject is extensively reviewed in a recent publication[7]. For NSCLC, specific pre-malignant histologic lesions have been used as biomarkers of risk and modifiable endpoints in chemoprevention trials. For adenocarcinoma, atypical adenomatous hyperplasia (AAH, a lesion more commonly found now that more ground glass opacities are noted during LDCT screening) can progress to adenocarcinoma in situ and eventually adenocarcinoma. Multiple studies are currently profiling AAH lesions with a goal of better understanding those that progress to invasive cancer. Lung squamous cell carcinoma (SCC) develops in the central airways where pre-malignant lesions progress through advancing levels of dysplasia (mild, moderate, and severe), followed by carcinoma in situ and ultimately invasive SCC. Change in endobronchial histology has been the primary endpoint in multiple SCC chemoprevention trials[8], and longitudinal research has revealed an increased cancer risk in subjects with multiple lesions that persist or progress over time[9]. Endobronchial dysplasia that regresses (i.e. fails to become invasive cancer) is associated with specific immune responses and ongoing studies are characterizing the lesional immune microenvironment of bronchial dysplasia. This will allow for a better understanding of progressive lesions and advance the field of precision chemoprevention. 1. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology and therapeutics 2001;69:89-95. 2. Saccomanno G, Archer VE, Auerbach O, Saunders RP, Brennan LM. Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 1974;33:256-70. 3. Wilbur DC, Meyer MG, Presley C, et al. Automated 3-dimensional morphologic analysis of sputum specimens for lung cancer detection: Performance characteristics support use in lung cancer screening. Cancer cytopathology 2015;123:548-56. 4. Leng S, Do K, Yingling CM, et al. 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Cancer Prev Res (Phila) 2016;9:96-104.

Keywords: chemoprevention, endobronchial dysplasia, sputum biomarkers

MS18.06 CAPTIVE AUDIENCE, TEACHABLE MOMENT - INTEGRATING TOBACCO CESSATION IN LUNG CANCER SCREENING

M. Tammemagi

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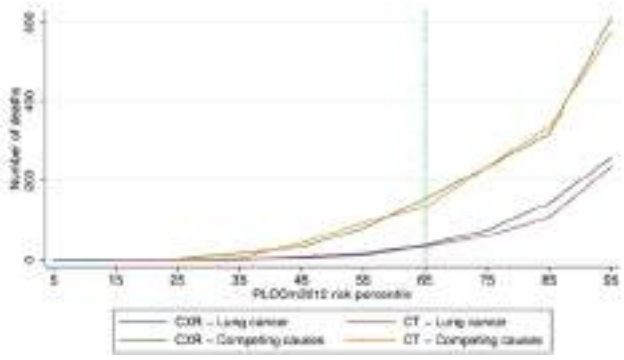
Cigarette smoking causes more than 480,000 deaths each year in the United States.[1]Smoking has been causally linked to cancers of the oropharynx, larynx, esophagus, trachea, bronchus, lung, stomach, liver, pancreas, kidney, ureter, cervix, bladder and colorectum and acute myeloid leukemia, as well as to stroke, blindness, cataracts, age-related macular degeneration, periodontitis, aortic aneurysm, early abdominal aortic atherosclerosis, coronary heart disease, pneumonia, atherosclerotic peripheral vascular disease, chronic obstructive pulmonary disease, tuberculosis, asthma, diabetes, reproductive disorders, ectopic pregnancies, erectile dysfunction, hip fractures, rheumatoid arthritis and immune dysfunction.[1]Lung cancer screening is most effective when applied to individuals at high risk.[2]Using NLST data, Figure 1 describes how the number of competing-causes deaths, primarily smoking related, increases with lung cancer risk, primarily driven by smoking, and how competing-causes deaths exceeds lung cancer deaths. Successful smoking interventions have the potential to greatly reduce morbidity and mortality in lung cancer screenees. It is likely that smoking cessation interventions in lung cancer screening programs will be cost-effective and may lead to health benefits that exceed those of the lung cancer mortality reduction benefits. Current, U.S. guidelines recommend providing smoking cessation interventions for current smokers in lung cancer screening programs. However, which type of smoking cessation program in the lung cancer screening setting is most effective is unknown. Lung cancer screenees generally have longer and more intense smoking histories so they may be more intractable to cessation interventions. On the other hand, screening may provide a *teachable moment*, which may lead to greater rates of cessation.[3]The proportion of current smokers selected for screening is greater when selected by risk prediction model, than when selected by NLST-like criteria. The proportion of current smokers in the NLST was 48.2%, in PLCO NLST-eligible participants was 40.4%, and in the Pan-Canadian Early Detection of Lung Cancer Study and Cancer Care Ontario (CCO) pilot, both of which have eligibility criteria of PLCOm2012 6-year risks ≥2%, were 62.8% and 65.4%, respectively. Two recent reviews concluded that evidence is lacking to recommend specific tailored smoking cessation approach in the lung cancer screening setting and recommend more research.[4,5]Currently, in the U.S., 8 trials in the SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration are underway that are investigating different smoking cessation interventions within lung cancer screening programs.[6]Some of the factor under study in SCALE include the following[6]:participant eligibility criteria, baseline versus annual screen, participant's interest in stopping smoking, treatment delivery method and dose, incorporation of positive and negative screening results, perceived risk of lung cancer, and costs of treatments.Results of SCALE are expected after 2021. Recently, Cadham and colleagues conducted a meta-analysis of smoking cessation interventions in samples that were similar to those in lung

cancer screening programs.[7] At 6-month follow-up, smoking cessation had the following associations with interventions: Electronic/web-based (odds ratio [OR] 1.14, 95% CI 1.03-1.25) Telephone counseling (OR 1.21, 95% CI 0.98-1.50) In-person counseling (OR 1.46, 95% CI 1.25-1.70) Pharmacotherapy (OR 1.53, 95% CI 1.33-1.77). CCO's *Lung Cancer Screening Pilot for People at High Risk*started low dose computed tomography screening in three sites on June 1, 2017. In the first year of screening, 1624 individuals received LDCT scans and current smokers were enrolled in an "opt-out" in-hospital smoking cessation programs. Of scanned participants 88.8% attended in-hospital smoking cessation counselling, and 95.2% were satisfied with their cessation services. In conclusion, several intervention approaches appear to be associated with smoking cessation. Multiple approaches appear better than single approaches. Pharmacotherapy and in-person counseling interventions appear to be superior to electronic/web-based or telephone counseling. Successful enrollment into in-person cessation programs is achievable. 1. United States. Public Health Service. Office of the Surgeon General., National Center for Chronic Disease Prevention and Health Promotion (U.S.). Office on Smoking and Health. *The health consequences of smoking--50 years of progress:a report of the Surgeon General.*Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. 2. Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *The New England journal of medicine.* 2013;368(8):728-736. 3. Taylor KL, Cox LS, Zincke N, Mehta L, McGuire C, Gelmann E. Lung cancer screening as a teachable moment for smoking cessation. *Lung cancer (Amsterdam, Netherlands).* 2007;56(1):125-134. 4. Iaccarino JM, Duran C, Slatore CG, Wiener RS, Kathuria H. Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review. *Preventive medicine.* 2019;121:24-32. 5. Pineiro B, Simmons VN, Palmer AM, Correa JB, Brandon TH. Smoking cessation interventions within the context of Low-Dose Computed Tomography lung cancer screening: A systematic review. *Lung cancer (Amsterdam, Netherlands).* 2016;98:91-98. 6. Joseph AM, Rothman AJ, Almirall D, et al. Lung Cancer Screening and Smoking Cessation Clinical Trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. *American journal of respiratory and critical care medicine.* 2018;197(2):172-182. 7. Cadham C. Systematic Review and Meta-Analysis of Smoking Cessation Interventions for Potential Use in Lung Cancer Screening Settings: 6- and 12-Month Outcomes. American Society of Preventive Oncology Annual Meeting ASPO 2019; Monday, March 11, 2019, 2019; Tampa, Florida. 8. Tammemagi MC, Church TR, Hocking WG, et al. Evaluation of the Lung Cancer Risks at Which to Screen Ever- and Never-Smokers: Screening Rules Applied to the PLCO and NLST Cohorts. *PLoS medicine.* 2014;11(12):e1001764. . Lung cancer and competing causes deaths in the National Lung Screening Trial by PLCOm2012 model risk level (taken from [8])



Keywords: smoking cessation, lung cancer screening

Joint IASLC–CSCO –CAALC Session

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.02 THE OPPORTUNITY OF DRUGS DEVELOPMENT ON IMMUNOTHERAPY IN CHINA

Q. Zhou

Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou/China

Immunotherapy gets the breakthrough after almost 100 years of silence. PD1/PD-L1 inhibitors as the representative have been extensively studied in various human malignant tumors and get promising long term response with relatively fewer adverse events. The first PD1 inhibitor indication was approved for melanoma in Japan on July 2014. Up to now, the US Food and Drug Administration had approved several PD-1 pathway blockade treatments including nivolumab, pembrolizumab and atezolizumab using in first line and second line of NSCLC. In China, nivolumab was approved for second line setting for advanced NSCLC and pembrolizumab combined with chemotherapy were approved for first line setting of advanced NSCLC. Two novel PD-1 inhibitors from Chinese pharmaceutical companies were approved for melanoma and lymphoma by National Medical Products Administration (NMPA) of China. And, a lot of clinical trials about domestic novel PD-1 and PD-L1 inhibitors from Chinese pharmaceutical companies are now ongoing. IO arena faces intense in-class competition from both MNC (Multi-National Corporation) and domestic pharmaceutical company in China. Now there are more than 20 IO antibodies from 10 MNCs and 16 pharmaceutical companies in China. Besides PD1/PD-L1 and CTLA4, other hot IO drugs such as IDO or Lag3 et al are also under investigation. Clinical trials about some novel combination, for example, CMET inhibitor plus IO, anti-angiogenesis drugs plus IO, et al, are also ongoing. There are special questions which need to be settled in China. Chinese population has relatively high rates of hepatitis B virus infection and much higher proportion of EGFR mutation. The delightful changing recently is some studies emerging to consider the characteristics of the Chinese or Asian populations. Some clinical trials are trying to answer these questions. Besides clinical trials for advanced NSCLC, Clinical trials focus on local advanced NSCLC, early stage NSCLC and SCLC are also ongoing. New adjuvant and adjuvant IO trials have started in China. Most importantly, some novel combinations overcoming previous IO resistance are now on the way, which will give more interesting results in the near future. Research about Chinese IO treatment remains in their early stage and further efforts are needed to improve the design of future clinical trials and translational research. Meanwhile, the other hot IO drugs and phase I studies need to speed up in China.

Keywords: Immunotherapy, China, Drugs Development

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.03 ANY DIFFERENCE ON EFFICACY AND TOXICITY BETWEEN EAST AND WEST?

J. Hu

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Lung cancer is now the most commonly diagnosed cancer and the leading cause of cancer related mortality, taking about 1.6 million lives each year. There has been long evidenced that different population display differential sensitivity and safety profiles on different treatment. in addition, many other factors can also influence therapeutic response of patients, such as lifestyle, metabolism, dietary etc. Here we try to explore the impact and underlying mechanism of ethnic difference on response and tolerance of various therapeutic regimens such as cytotoxic chemotherapy, TKIs, antiangiogenic drugs and ICIs. Treatment patterns of lung cancer has been transformed over the years, leading to the better outcomes of patients. The 5-year overall survival (OS) rate of advanced NSCLC is less than 5% in the standard chemotherapy era. Although widely used of tyrosine kinase inhibitors (TKIs) prolonged progression-free survival (PFS) and OS in patients harboring driver gene mutations, the long-time survival rate was still low due to acquired drug resistance. Over the last five years, emergence of immune checkpoint inhibitors (ICIs) has greatly improved outcomes of NSCLC with objective response rate (ORR) about 20% and 5-year OS rate nearly 16% in previous treated patients based on multiple clinical trials data. A retrospective review of the SEER database found that Asian population presented with higher percentage of metastatic lung cancer but significantly greater overall survival rate among nine different ethnic groups. Furthermore, among the total Asian population, Chinese has the highest percentage of adenocarcinomas (69.4%). The latest data show mutation rate of epidermal growth factor receptor (EGFR) in Adenocarcinoma is 40.3-64.5% and 75% in certain clinically enriched population such as non-smoking adenocarcinoma. These data can fully explain the better outcomes of TKIs in Asia population. There has evidence that different population has different sensitivity and toxicity to different anti-tumor regiments. Studies showed that hematological toxicities of docetaxel were more frequently observed in Japanese compared to US/European patients. In addition, it is reported that docetaxel-induced grade 3/4 neutropenia is higher in Asian clinical trials than non-Asian trials. On the other hand, the discrepancy of dosage regimen between Japanese (60 mg/m^2) and western population implies ethnic difference in PK. Similar data of carbo-platin/paclitaxel and irinotecan-based regimens have been reported in many phase 3 or phase 2 trials. Meanwhile, there are many studies compared the adverse events of TKIs in different ethnics and data suggested that incidence of ILD caused by gefitinib and erlotinib is higher in Japan (1.2-5.4%) than in the rest of the world. Despite promising outcomes of ICIs, the clinical trials for Asia population is still rare now. Checkmate 078 was the first trial to predominantly recruit Chinese NSCLC patients, the ORR of Chinese population was 17%, which is in accordance with Caucasian population. However, according to PMS study of Japan and several published meta-analysis results, Asian patients were more likely to develop pneumonitis with the incidence rate 5.7-9.6% in ICIs mono-therapy and these rate would be increased significantly when combined with other drugs. Many genetic studies have revealed the prevalence of genetic polymorphisms (i.e. mutation of SFTPC, ABCA3; telomere-associated genes like TERT, TERC, RTELI, PARN; SNP of MUC5B etc.) was associated with susceptibility to ILD in Japanese. Understanding characteristics of genomic profile will be of no doubt to facilitate the selection of targeted population of ICIs. Except for the toxicity of ICIs, we should pay attention to the drug response of particular groups of population, which were excluded from clinical trials according to the entry criteria of RCT. Among these HBV-infected NSCLC patients seemed to be more emergency as HBV infected population of Asia is accounted for 62% of global HBV burden, therefore, efficacy and toxicity of ICIs on HBV infected NSCLC patients will be discussed based on many clinical trials or real world data. In a word, ethnic difference can influence efficacy and toxicity of different treatment options. More genomic mapping and preclinical research should be implemented to explore the relationship between ethnic diversity and varying degrees of response. Key word: ethnic, efficacy, toxicity, TKIs, ICIs

Keywords: ethnic, efficacy, toxicity, TKIs, ICIs

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.04 NEO-ADJUVANT IMMUNOTHERAPY IN LUNG CANCER

N. Wu

Peking University Cancer Hospital & Institute, Beijing/China

Immune checkpoint inhibitors (ICIs) therapy have been recommended as the standard of care in the first-line treatment strategy of selected advanced non-small cell lung cancer (NSCLC) patients. Effective therapies also needed for NSCLC patients in early-stage, whose failure arises both local relapse and remote metastasis after surgery. Lavin et al revealed that an immunosuppressive microenvironment had developed even in stage I disease, which promoted the investigation of immunotherapeutic regimens in early stage population[1]. The success of ICIs in the metastatic disease has also generated enthusiasm to initiate clinical trials to evaluate the utility

of ICIs as neoadjuvant therapy in the setting of resectable NSCLC[2]. Theoretically, immunotherapy in patients with early-stage NSCLC may have more favorable antitumor effects due to lack of T cell function depletion and less tumor clonal heterogeneity. However, there are lots of details need to be discussed, and this necessitates a review regarding neoadjuvant immunotherapy topic. The fundamental premise on the application of neoadjuvant immunotherapy is the safety and feasibility. In a cohort of 21 patients, Forde et al revealed neoadjuvant nivolumab was associated with well tolerance and few side effects, did not delay surgery and induce a major pathological response (MPR) in 45% of resected tumors[2]. MPR rate is associated with long term survival outcomes, thus it is considered as a surrogate endpoint for recurrence and survival[3].Radiologic assessment of treatment cannot predict pathological response accurately after ICIs therapy. Chest CT might underestimate response rate accurate after neoadjuvant ICIs therapy compared with pathological assessment (10% vs. 45%)[2]. This phenomenon was postulated to be related with T-cell infiltration and peritumoral inflammation during the early stage of treatment, which was defined as "pseudo-progression" by some experts[4]. Bott et al analyzed operative details and postoperative outcomes in this cohort. Unexpected perioperative morbidity and mortality was not observed. The rate of conversion was moderately high because of hilar inflammation and fibrosis, which might develop as a result of response to treatment[5]. The surgical outcomes proved the feasibility and safety of pulmonary resection after neoadjuvant nivolumab monotherapy and encouraged the execution of following neoadjuvant immunotherapy trials relevant to surgical practice. In the setting of resectable NSCLC, what is optimal sequence of immunotherapy and surgery? There is no straight evidence available to clear the issue right now. However, differing from perioperative chemotherapy, the administration of ICIs in the preoperative phase while the tumor is in situ might provide greater therapeutic efficacy in terms of elevated and sustained peripheral tumor-specific immune responses compared with adjuvant immunotherapy[6]. Liu et al proved it through utilizing a murine model of triple-negative breast cancer (TNBC). Therefore, the utilization of ICIs prior to surgery has been presumed to be capable of potentially eliminating micrometastatic disease and thus decrease the risk of recurrence in resectable NSCLC. It was also interesting that mice given neoadjuvant chemotherapy displayed no significant anti-tumor benefit over adjuvant chemotherapy in the same murine model, which was consistent with the results of clinical trials[7]. The optimization of neoadjuvant schemes is underway in resectable NSCLC patients. Since the combination of nivolumab plus ipilimumab showed encouraging clinical activity characterized by a high response rate and durable response in setting of advanced NSCLC[8-9], the combination of double ICIs has been incorporated into the neoadjuvant care of resectable NSCLC patients. The NEOSTAR trial randomized patients to receive nivolumab or nivolumab plus ipilimumab before surgery[10]. The combination therapy was associated with an increased number of tumor-infiltrating lymphocytes compared to monotherapy, suggesting superior therapeutic efficacy in doublet ICIs group. However, higher proportion of patients did not receive scheduled surgery (doublet 23.8% vs monotherapy 8.7%) was a problem need attention. ICIs in combination with chemotherapy (ICI-CT) was another direction of neoadjuvant immunotherapeutic schemes. Safety and tolerability of neoadjuvant ICIs combined with platinum-based doublet chemotherapy has been proved in the KEYNOTE-189 trial[11]and KEYNOTE 407 trial[12]. NADIM trial is an ongoing phase II, single-arm, open-label multicenter study of resectable stage IIIA N2-NSCLC patients with ICI-CT as a neoadjuvant treatment[13]. In NADIM trial, pathological response rate was also higher than that assessed by RECIST. Neoadjuvant ICI-CT yields an unprecedented response rate prompting the regimen as the most promising neoadjuvant scenario. All the oncologists are eager to observe the long-term outcomes of NADIM, which would finally revise the standard pathway of curing early stage NSCLC. In this new era of immunotherapy for NSCLC, multiple questions remain regarding the integration of immunotherapy and traditional therapy protocol. For instance, whether concurrent chemoradiotherapy combined with ICIs could be a neoadjuvant regimen for resectable stage IIIA (N2) NSCLC? Accrued evidence indicates that radiation could stimulate the immune system via upregulating tumor-associated antigens, augmenting MHC class I surface expression, increasing T-cell tumor-specific CD 8+ T cells, et al[14]. PACIFIC trial has delineated ICI significantly prolonged overall survival among patients with stage III, unresectable NSCLC following concurrent chemoradiotherapy[15]. If irradiation could produce systemic effects under ICI and contribute to the development of a broader range of cancer treatments[16], surgery would be asked to perform a better local tumor control. Surgery for advanced NSCLC are increasingly expanding in setting of partial or complete treatment response after immunotherapy[17]. It will indeed take years before we exactly know how to most effectively incorporate ICI into other traditional therapies, including surgery. It is always attractive to predict which individuals will have a long-lasting response. Fortunately, neoadjuvant therapy allows for an assessment of treatment effect, as well as pathological response due to the convenience of specimencollection after surgery. Optimal biomarkers should be capable to improve patient selection for ICI treatment. Therapeutic selection based on actionable genomic alterations can clearly delineate patients who will receive survival benefit from a given therapy. However, the same scenario cannot certainly happen for immune-based biomarkers. Some experts deem deescalating therapy of single agent checkpoint blockade should be approached with caution regarding the lack of transformative immune-based biomarker[18]. Except PD-L1 express and TMB, dynamics of the immune system need to be standardized to ensure the accuracy of results and uniformity across clinical trials[19]. To capture a perfect biomarker to predict clinical responses to ICIs is an unrealistic goal in the short-term. Further studies are desiderated to identify biomarkers associated with improved survival.

Keywords: neoadjuvant immunotherapy, Lung cancer, Resectable

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.05 BIOMARKER IN IMMUNOTHERAPY: MYTH OR REALITY?

A. Addeo

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Background: NSCLC treatment landscape has rapidly evolved with several immune checkpoint inhibitors (ICIs) approved initially in second line as monotherapy and subsequently in first line as either monotherapy or in combination with chemotherapy. The recent presentation at the ASCO 2019 of the 5 years overall survival (OS) of the Keynote 001 has further strengthened the importance and impact of ICIs on patients with NSCLC, showing unprecedented 5 years overall OS. However up to 50-60% of NSCLC patient does not benefit from such a treatment. The need to validate and find out new effective biomarker (BM) remains crucial. Discussion: PD-L1 expression is the only approved BM in NSCLC that proved to be predictive of better OS for anti-PD1 (Pembrolizumab). Despite several advantages such as short turnaround time (TAT), relatively simple IHC assay (gone through an harmonized process in the blueprint2) there are several limitations: PD-L1 non expresser could still be responders and benefit form ICIs or in driven mutated NSCLC the PD-L1 level might be very high, generally mediates by the JAK3 pathway, but not being responsive to ICIs for the rarity of T cell infiltrations. A new promising BM is the tumour mutation burden (TMB). The prevalence of somatic mutation varies between 0.01 mut/Mb to 400 mutations/Mb. Some of these mutations led to the translation of novel peptide epitopes or neoantigens that should enhance the immunogenicity of the tumour by eliciting T cell repertoire. The hypothesis then is that in case of high TMB ICIs should work better than chemo. So far this has been partially seen in some studies in term of response rate (RR) an progression free survival (PFS) but no study has been designed yet as having primary endpoint better OS in High TMB patients. Furthermore there are several aspects to consider about TMB: TAT is at least 2 week (it the first studies were conducted by using whole exome sequencing), high cost, no clear cut-off, unclear if it should be performed on cancer tissue or circulating tumour DNA (ctDNA) and the most important one the prospective trial has ever validated TMB as predictive of better OS compared to chemotherapy. There are several new BM in embryonic phase: role and importance of TILs, immune gene signature, INFgamma relatedmRNAbased signatures, myeloid-derived suppressor cells(MDSCs) or the neutrophil-to-lymphocyte ratio (NLR) at baseline. None of them is ready for prime time but there are ongoing studies that hopefully will validate useful BM to adopt in clinical practice Conclusion: are BMs reality? Yes we already have a reliable predictive BM which remains PD-L1 expression. TMB might represent a possible alternative to identify a different subgroup of NSCLC patients. PD-L1 high and high TMB might partially overlap but they highly likely correspond to 2 different patients populations. There is indeed room for improvement and more BMs are needed: possibly simple to adopt in clinical practice, with short TAT and most important showing OS benefit, to definitively move from the myth to the reality.

JCSE01.06 NEW ERA BEYOND PD-1/PD-L1

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Over the past few years, targeting immune checkpoints such as PD-1/PD-L1 (and in some extend CTLA-4) has changed the landscape of lung cancer therapy and largely impacted patients with notable therapeutic benefits. However, not all lung cancer patients respond to immune checkpoint inhibitors and actually only some 15-20% of those with metastatic disease achieve long term survival, reflecting to the complexity of immune checkpoints and daunting tumor resistance. In order to broaden the possibilities of lung cancer immunotherapy, we need to seek alternative immune checkpoints beyond PD-1/ PD-L1, test novel combination strategies of immune checkpoint inhibitors and more conventional treatments, and increase the predictive potential of biomarkers to optimally guide clinical practice. Meanwhile, there are a number of unsolved questions that may require our attention for future better clinical performance. The wide range of immune-related adverse effects (irAEs) that accompany immune checkpoint inhibitors can complicate this efficacious immunotherapy and restrict its use in cancer patients. The precise pathophysiology underlying irAEs is frequently unknown, but may be related to breaking the balance of immunologic homeostasis. Although any organ system is possibly influenced, irAEs most commonly involve the gastrointestinal tract, endocrine glands, and skin. Most of the toxic effects are reversible, but deaths due to severe irAEs such as myocarditis and pneumonitis can occur. The serious problem of irAEs particularly requires to define optimal strategies for multidisciplinary and collaborative management, and ad-hoc education programs. Of note, recent data suggest that prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. The clinical therapeutic efficacy of immune checkpoint inhibitors remains controversial. Tumor resistance, primary and acquired, is a daunting challenge that limits the responsiveness to immunotherapy, and deserves intensive investigation. Hyperprogressive disease (HPD) following immunotherapy also deserve adequate attention. Evidence suggests that MDM2 family amplification or EGFR, KEAP and LKB1 aberrations may lead to poor clinical outcomes on IO treatment and may account for the risk of HPD. Preclinical and clinical testing of alternative immune checkpoints is mandatory, particularly in programs that coupled a biomarker driven strategy. It is noteworthy that tumor infiltrating T cells can simultaneously express PD-1/ PD-L1 along with other immune checkpoints. Also, evidence has delineated that upregulation of compensatory inhibitory molecules such as LAG-3, VISTA, and TIM-3 may mediate tumor resistance to immune checkpoint inhibitors. Understanding the precise molecular mechanisms of different immune checkpoints will benefit the design of effective combination therapies and overcome potential resistance. More well-designed combination strategies (antiangiogenics, targeted therapies, chemotherapeutics,..) that can yield remarkable and synergistic clinical benefits are critical for immune checkpoint therapy. To optimize the combination therapies, we should carefully explore effective and safe doses of treatments, sequencing of the agents, appropriate timing, and so on. There is a pressing need to study the indepth mechanisms of the interaction between chemo-radiotherapy or targeted therapy and the immune system. In addition, identifying more combinations of immune checkpoint inhibitors and new treatment approaches such as by-specific antibodies, chimeric antigen receptor T cell (CAR-T) immunotherapy, TILs, modulating the microbioma and tumor vaccines is a tantalizing option. Finally, due to the complexity of the immune system, developping and validating a multiparametic model of predictive biomarkers is much required. As mentioned earlier, PD-L1 expression can inform treatment decisions, but its clinical value still needs confirmation in different patient cohorts. Meanwhile, certain genomic tumor aberrations, TMB and TME are future directions for routine clinical practice. Different TIL phenotypes, diverse TCRs, immune gene signatures, and genetic features derived from blood monitoring or TME hold high potential, but are ready for clinical use as yet. References Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clin Cancer Res. 2017; 23: 4242-4250. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–68. 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Keywords: Beyond PD-1/PD-L1, Adoptive cell therapy, bi-specific antibodies

JCSE01.09 A PHASE II UMBRELLA STUDY OF CAMRELIZUMAB IN DIFFERENT PD-L1 EXPRESSION COHORTS IN PRE-TREATED ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER

Y.-L. Wu[1], C. Huang[2], Y. Fan[3], J. Feng[4], H.-M. Pan[5], L. Jiang[6], J.-J. Yang[7], X.-Y. Li[8], X.-Q. Liu[9], J.-P. Xiong[8], Y.-Q. Zhao[10], Y. Cheng[11], R. Ma[12], J. Wang[13], Y.-N. Wang[14], Y.-H. Liu[15], D.-M. Lin[16], W. Shi[17], X. Lin[17]

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Background: The role of PD-L1 expression in 2nd line and beyond non-small cell lung cancer (NSCLC) remains controversial. Camrelizumab (SHR-1210) is a potent anti-PD-1 monoclonal antibody and has shown promising activity in NSCLC in Phase I studies. We report results from the SHR-1210-201 study (NCT03085069), a phase II umbrella

study of camrelizumab monotherapy in different PD-L1 expression cohorts in Chinese patients with previously treated advanced or metastatic NSCLC. **Method:** Patients who progressed during or following platinum-based doublet chemotherapy were enrolled and assigned to one of 4 cohorts based on PD-L1 expression. Patients with EGFR or ALK genomic alterations were eligible provided they had disease progression with at least one approved tyrosine kinase inhibitor and with ≥50% PD-L1 expression in tumor. All enrolled patients received camrelizumab at 200 mg IV Q2W until loss of clinical benefit. The primary endpoint was objective response rate (ORR), other endpoints included progression-free survival (PFS) and overall survival (OS). **Result:** As of Aug 1st 2018, of all the 259 patients who underwent screen, 229 cases could be pathologically evaluated. PD-L1 expression were 47.6% (109/229) in PD-L1 < 1%, 27.1% (62/229) in PD-L1 ≥1-<25%, 8.7% (20/229) in ≥25-<50% and 16.6% (38/229) in ≥50%. A total of 63.8% (146/229) patients were enrolled. 89.0% of patients had stage IV NSCLC and 54.8% had non-squamous tumor histology. ORR was 18.5% (95%CI: 12.6%–25.8%) in ITT population. Subgroup analysis showed increased PD-L1 expression was associated with better response rate (Table 1). No response was observed in patients with EGFR mutation. The responders had durable response (median: 15.1 months; 95%CI: 5.5–not reached). Median PFS was 3.2 months (95%CI: 2.0–3.4) and median OS was 19.4 months (95%CI: 11.6–not reached) (Table 1). Treatment-related adverse events (AEs) occurred in 87.7% of patients (all Grade); 20.5% had ≥G3 related AE; and 15.8% had related SAE. 21.2% of AEs led to dose interruption and 7.5% led to treatment discontinuation.

Conclusion: In Chinese patients with previously treated advanced/metastatic NSCLC, camrelizumab demonstrated improved ORR, PFS, and OS compared with historical data of the 2nd line chemotherapy. The efficacy in patients with PD-L1 <1% is similar as the 2nd line mono-chemotherapy, while patients with higher PD-L1 expression derived greater benefit from camrelizumab, the ORR, PFS and OS in patients with PD-L1 ≥25% was comparable to the 1st line doublet chemotherapy in advanced NSCLC. Camrelizumab was well tolerated. This phase 2 data warrant further clinical studies of camrelizumab in NSCLC.

Keywords: advanced/metastatic non-small cell lung cancer, camrelizumab, PD-L1 expression

Table 1 - Efficacy data in subgroups

Population	No of pts	ORR, % (95%CI)	PFS (month), median (95%CI)	1YOS, % (95%CI)	OS (month), median (95%CI)
PD-L1<1%	74	12.2% (5.7%, 21.8%)	2.1 (1.9, 3.2)	47.1% (33.8%, 59.2%)	11.6 (7.8, NR)
PD-L1 ≥1% and < 25%	31	19.4% (7.5%, 37.5%)	3.1 (1.8, 4.9)	76.7% (57.2%, 88.2%)	NR (NR, NR)
PD-L1 ≥25% and < 50%	11	45.5% (16.7%, 76.6%)	6.0 (1.9, NR)	81.8% (44.7%, 95.1%)	NR (2.9, NR)
PD-L1 ≥50% (without EGFR mutation)	25	28.0% (12.1%, 49.4%)	7.6 (3.3, 11.4)	55.2% (32.3%, 73.2%)	NR (8.6, NR)
PD-L1 ≥50% (with EGFR mutation)	5	0	1.7 (1.2, NR)	40.0% (5.2%, 75.3%)	10.3 (1.2, NR)
ITT	146	18.5% (12.6%, 25.8%)	3.2 (2.0, 3.4)	56.6% (47.3%, 64.9%)	19.4 (11.6, NR)

Abbreviation: NR, Not Reached

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.10 EFFICACY AND SAFETY OF NEOADJUVANT PD-1 BLOCKADE WITH SINTILIMAB IN RESECTABLE SQUAMOUS NON-SMALL CELL LUNG CANCER (SQNSCLC)

N. Li[1], J. Ying[1], X. Tao[2], F. Zhang[2], Z. Zhao[2], Y. Ling[2], Y. Gao[1], J. Zhao[3], Q. Xue[1], Y. Mao[1], W. Lei[2], N. Wu[4], S. Wang[2], J. Duan[5], Y. Gao[1], Z. Wang[6], N. Sun[1], J. Wang[7], S. Gao[1], J. He[1], H. Zhou[8], S. Wang[9]

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Background: NSCLC patients who have potentially resectable disease often subsequently relapse after surgery. New therapy that prevents relapse after surgery is desperately needed. In this study, we tested the efficacy and safety of neoadjuvant sintilimab, an anti-PD-1 antibody, for patients with resectable sqNSCLC in China. **Method:** All patients had treatment-naïve resectable sqNSCLC (stage IB-IIIA) that was confirmed by histopathology. Patients received two cycles of sintilimab (200 mg IV) on Day 1 and 22. Surgery was performed between Day 29-43. An enhanced PET/CT was obtained at baseline and seven days prior to surgery. Preliminary analysis of safety profile and efficacy was planned after at least 20 patients had received operation. **Result:** As of Jan. 28, 2019, 22 patients (20 males and 2 females) with sqNSCLC received two doses of sintilimab followed by radical resection. The median age was 61.5 yr (range, 48 to 70). Six (27.3%) and four (18.2%) patients experienced neoadjuvant treatment emergent adverse events (TEAEs) and neoadjuvant treatment-related AEs (TRAEs), respectively. Most of the TEAEs and TRAEs were grade 1 or 2. Three patients achieved radiological partial response: an ORR of 13.6% based on RECIST 1.1. Ten patients (45.5%) achieved a major pathologic response (MPR, ≤10% viable tumor cells), including four (18.2%) had complete pathologic response (no viable tumor cell). There was a direct correlation between pathological response and decrease in the standardized uptake values (SUV) in the primary tumor. Among nine patients with > 30% decrease of SUV, eight had MPR, compared with no MRP response in the 11 patients with ≤30% decrease of SUV. **Conclusion:** Neoadjuvant sintilimab for sqNSCLC patients was tolerable and the 45.5% MRP rate is encouraging. A decrease in SUV may be predictive of pathologic response after PD-1 therapy in sqNSCLC.

Keywords: squamous NSCLC, Sintilimab, neoadjuvant

JCSE01.11 EFFICACY AND SAFETY OF SINTILIMAB WITH ANLOTINIB AS FIRST-LINE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

B. Han[1], T. Chu[2], R. Zhong[2], H. Zhong[2], B. Zhang[1], W. Zhang[3], C. Shi[1], J. Qian[2], Y. Han[2]

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Background: Given the synergy effect of immunotherapy and anti-angiogenic therapy in advanced NSCLC, FDA approved atezolizumab plus bevacizumab and chemotherapy as first-line treatment. However, chemo-free first-line strategy of PD-1/PD-L1 inhibitor combining angiogenesis modulator remains to be explored. This is the first trial evaluating sintilimab (anti-PD-1) plus anlotinib (multi-target TKI against tumor angiogenesis and proliferation) in treatment-naive advanced NSCLC patients and is one arm of Phase II anlotinib-based trial (NCT03628521). **Method:** Treatment-naive, stage IIIB/IV NSCLC patients aged 18-75 with ECOG PS 0-1 were eligible. Patients with EGFR, ALK or ROS1 mutations were excluded. Participants were given intravenous sintilimab (200mg q3w) and oral anlotinib (12mg/d 2 weeks on/1 week off) until progression or unacceptable toxicity. The primary endpoints were ORR and safety. The secondary endpoints included DCR, PFS and OS. AEs were graded according to CTCAE v4.0. **Result:** From Septembe-2018 to February-2019, 22 patients were enrolled. All are under treatment and have received at least one tumor assessment as of Apr-8th-2019. Most were male (95.5%), former/current smokers (63.6%) and squamous cell histology (54.5%). 4 had baseline brain metastases. Among all, 15 achieved PR (7 confirmed, the rest waiting for next assessment), 7 achieved SD, ORR was 68.2% and DCR was 100%. Two grade 3 TRAE occurred with no grade 4/5 observation. The most common TRAE were hematuria, hyperuricemia, hypertension, increased ALT and rash, etc. No unexpected AE observed. Of 21 PD-L1-evaluable patients, 13 (61.9%) were PD-L1+ and showed higher ORR than PD-L1- patients. 16 patients got TMB status (details in table). Notably, 7 of 9 patients achieved SD developed cavities, suggesting a synergetic anti-tumor effect from combination regimen.

Table 1. Response rates

Best Overall Response	Overall (n=22)	PD-L1 + (n=13)	PD-L1 - (n=6)	TMB ≥ 10 (n=6)	TMB <10 (n=10)
CR, n (%)	0	0	0	0	0
PR, n (%)	15 (68.2%)	9 (69.2%)	5 (62.5%)	5 (83.3%)	5 (50%)
SD, n (%)	7 (31.8%)	4 (30.8%)	3 (37.5%)	1 (16.7%)	5 (50%)
PD, n (%)	0	0	0	0	0
ORR, n (%)	15 (68.2%)	9 (69.2%)	5 (62.5%)	5 (83.3%)	5 (50%)
DCR, n (%)	22 (100%)	13 (100%)	8 (100%)	6 (100%)	10 (100%)

Conclusion: In this interim analysis, sintilimab plus anlotinib showed high ORR (68.2%) and DCR (100%) with good tolerability, supporting worthy of further development from this convenient usage of chemo-free regimen in first line setting.

Keywords: PD-1 inhibitor, multi-target angiogenesis agent, advanced NSCLC

JCSE01.14 HIGHER PREVALENCE OF EGFR MUTATIONS SIGNIFICANTLY CORRELATES WITH LOWER PD-L1 EXPRESSION IN CHINESE LUNG ADENOCARCINOMA

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Background: *EGFR* mutations are more prevalent in lung adenocarcinoma compared with other non-small cell lung cancer and are more prevalent in East Asians compared with the other populations. At the same time, we observed lower PD-L1 Tumor Proportion Score (TPS) in Chinese lung adenocarcinoma patients (pts) compared with that in Chinese lung squamous cell carcinoma pts and we also observed the proportion of PD-L1 positive (TPS >= 1%) in Chinese lung adenocarcinoma pts was lower than that in other multicenter cohorts. Then we hypothesize that the higher prevalence of *EGFR* mutations in Chinese lung adenocarcinoma pts correlates with lower PD-L1 expression. **Method:** The Origimed-based lung adenocarcinoma cohort was a retrospective cohort consisted of more than one thousand Chinese lung adenocarcinoma pts who underwent both NGS panel sequencing and PD-L1 immunohistochemistry (IHC) in a College of American Pathologists (CAP) certified and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory during the year 2017 and 2018. Antibodies used in the PD-L1 IHC assay included 28-8 (sample size = 883) and 22C3 (sample size = 158). Tumor Proportion Score (TPS) was applied. All the slides were reviewed by the same senior pathologist. All the *EGFR* mutations were manually reviewed in Integrated Genomics Viewer for confirmation. After confirmation, each pts was assigned to *EGFR* positive group or *EGFR* negative group. Fisher' s exact test and Student' s t-test were applied. **Result:** For antibody 28-8, PD-L1 IHC was positive (TPS >= 1%) in 18% (66/370) *EGFR* positive pts and was positive in 35% (180/513) *EGFR* negative pts (fisher exact test p value = 1.6e-5). For antibody 22C3, PD-L1 IHC was positive (TPS >= 1%) in 14% (9/64) *EGFR* positive pts and was positive in 45% (42/94) *EGFR* negative pts (fisher exact test p value = 3.8e-3). And we observed a significantly lower PD-L1 TPS in *EGFR* positive pts for both antibodies (t-test p value = 3.5e-11 for PD-L1 antibody 28-8; t-test p value = 6.0e-5 for PD-L1 antibody 22C3). **Conclusion:** The observation demonstrated that lower PD-L1 TPS in Chinese Lung Adenocarcinoma pts was significantly correlated with East-Asian-specific high prevalence of *EGFR* mutations. The observation reassured that *EGFR* mutation status should be examined simultaneously with PD-L1 IHC in lung adenocarcinoma pts because it was a confounding factor for predicting immunotherapy outcome using PD-L1 TPS. The observation partly explained the generally higher PD-L1 TPS in Chinese lung squamous carcinoma pts compared with that in Chinese lung adenocarcinoma pts.

Keywords: PD-L1, EGFR, IHC

JCSE01.15 LIVER METASTASES PREDICTS POORER PROGNOSIS IN ADVANCED NSCLC PATIENTS WHO RECEIVING NIVOLUMAB MONOTHERAPY

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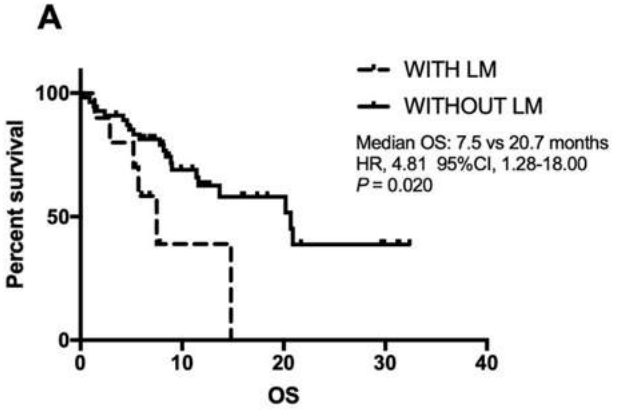
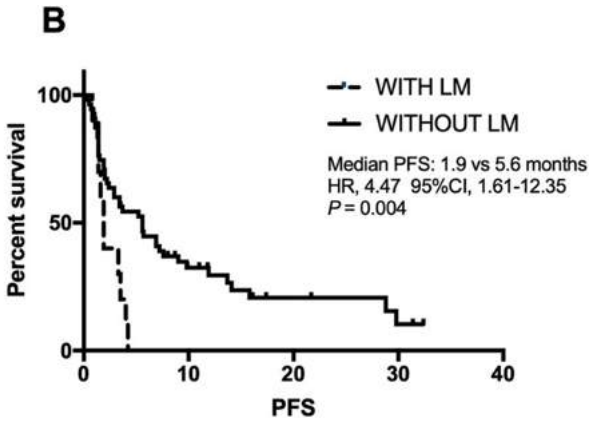
Background: Nivolumab is a fully human IgG4 monoclonal antibody targeting the programmed death-1 (PD-1). It's a standard second-line treatment for advanced NSCLC. Liver metastases(LM) is one of the worst prognostic NSCLC metastatic sites, but the attention to LM is far lower than brain metastases and bone metastases. **Method:** Patients with stage IIIB-IV NSCLC treated with second-line or later nivolumab monotherapy were retrospectively collected from January 2016 to July 2018. The patients were divided into two cohorts based on the presence or absence of LM at the time of first dose. Study endpoints included OS and PFS. **Result:** 65 patients

were included, including 10 patients with and 55 patients without LM. Baseline characteristics of the two cohorts were comparable, as shown in the below table.

Characteristic	*All*	*LM (n=10)*	*Without LM (n=55)*	*P-Value*
Sex(Female/Male)	16/49	2/8	14/41	0.999
Mean age (years)	59.0±10.2	60.1±8.0	58.8±10.5	0.713
ECOG PS				0.999
0-1	59	9	50	
≥2	6	1	5	
Histologic subtype				0.203
Squamous carcinoma	26	2	24	
Adenocarcinoma	36	7	29	
Others	3	1	2	
Stage				0.999
IV	62	10	52	
IIIB/IIIC	3	0	3	
Lines of therapy				0.673
2nd Line	53	9	44	
≥3rd Line	12	1	11	
Driver gene status				0.580
EGFR mutations	4	0	4	
KRAS mutations	4	1	3	
Other mutations	5	0	5	
Driver gene negative	27	6	21	
Unknown	25	3	22	
Other metastatic sites				0.958
Central nervous system	24	4	20	
Bone	20	2	18	
Adrenal gland	6	0	6	
Intrathoracic	47	6	41	
Other/unspecified	9	1	8	

The median OS of the patients with and without LM was 7.5 and 20.7 months, respectively(HR =4.81;95%CI, 1.28-18.00;p=0.020). Their median PFS was 1.9 and 5.6 months, respectively(HR =4.47;95%CI, 1.61-12.35;p=0.004). COX multivariate regression analysis suggested LM was an independent prognostic factor. Kaplan-Meier curves of OS and PFS were shown in the below figure.





Conclusion: The outcome of advanced NSCLC patients with LM treated with Nivolumab monotherapy is relatively poor compared with those without LM.

Keywords: liver metastases, nivolumab, Non-Small Cell Lung Cancer

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
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JCSE01.16 METASTATIC LYMPH NODES AS HIGH IMMUNOGENICITY MEDIA FOR PERIOPERATIVE IMMUNOTHERAPY IN LOCALLY ADVANCED NSCLC

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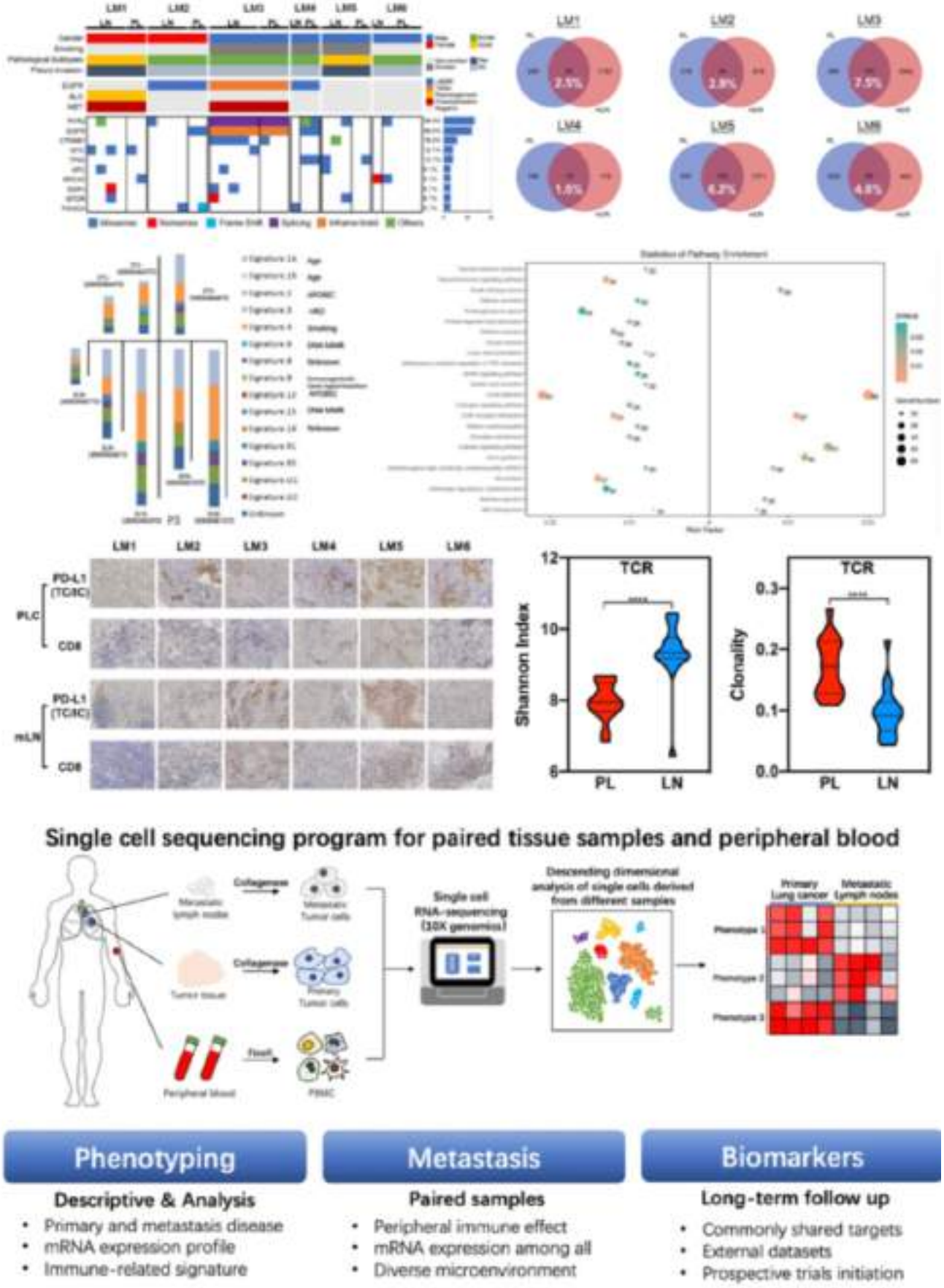
Background: Perioperative chemotherapy showed limited survival benefit and increased toxicities while neoadjuvant immunotherapy achieved great success in early phase trials. Both inter/intra-tumoral heterogeneity (ITH) between primary lesion and metastatic lymph nodes (mLNs), and rationale of superior efficacy for immunotherapy remained poorly explored in locally advanced non-small cell lung cancer (NSCLC). **Method:** We retrospectively collected 6 locally advanced lung adenocarcinoma (LUAD) patients. 15 tissue samples were performed multi-region whole exosome sequencing and TCR repertoire analysis as well as 18 matched metastatic lymph nodes (mLNs). **Result:** 290 somatic mutations in average were identified in primary LUAD (PL) and 441.6 for mLNs. Tumor mutation burden as well as tumor neoantigen burden was significant higher in mLNs than in primary LUAD (median value, 6.6mut/Mb vs. 3.4mut/Mb, P=0.0376; 229.5 neo counts vs. 165 neo counts, P=0.0287). Increased transversion ratio was found in mLNs compared to primary lesions. The genomic concordance between primary lesions and mLNs was 58.4%±12.5% and 33.3% for EGFR-mutation. 87 copy number variants were detected in 14 samples with 3q, 8q and X chromosome as frequently mutated cytobands. Small cell lung cancer functional pathway was enriched in mLNs exclusively. Both expression of PD-L1 and CD8 revealed high level (median value 20% and 40%) and consistence (5/6, 83.3%) between primary and metastatsis lesions. TCR clonality was 17.2% and 9.1% for primary and metastasis lesions, respectively with higher T cell diversity and intra-tumoral heterogeneity of TCR found in mLNs.



Conclusion: Extensive genomic and TCR ITH was found between primary LUAD and mLNs which may lead to mixed response to perioperative treatment. mLNs may serve as a better immunogenicity media for perioperative immunotherapy suggesting a potential adjuvant modality of immunotherapy performing lymph nodes sampling during surgery. Results of an initiated single cell sequencing program including paired samples were pending to further provide insights of diverse immune-microenvironment.

Keywords: locally advanced lung cancer, intra-tumoral heterogeneity, perioperative immunotherapy

JCSE01.17 MODELLING THE IMMUNOSUPPRESSIVE DIFFERENCE OF SBRT AND CRT BY SIMULATING THE DOSE TO CIRCULATING LYMPHOCYTES IN NON-SMALL CELL LUNG CANCER

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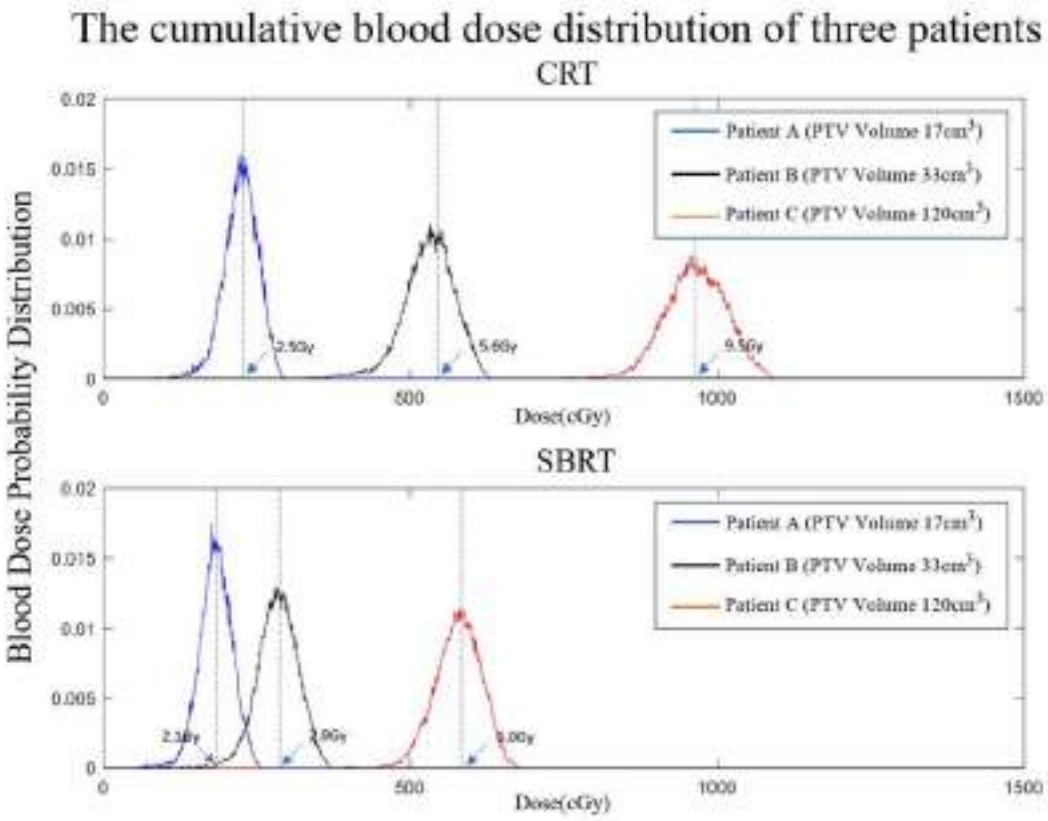
Radiation Oncology Institute of Enze Medical Health Academy, Affiliated Taizhou Hospital of Wenzhou Medical University, Taizhou/China

Background: Radiation-dose delivered to circulating lymphocyte (CL) has detrimental effect on immune system for cancer patients. Our study established a model to compare the cumulative dose on CL of patients with conventional fractionation radiotherapy (CRT) and stereotactic body radiation therapy (SBRT) in lung cancer with different target volume. **Method:** The improved model is based on convolution algorithm suggested by Yovino(Cancer Investigation, 2013). The current blood DVHs of each organ were multiplied with treatment field DVH to generate original DVHs. During one second, 0.6% of whole-body blood circulates through each organ and rest body according to blood circulating pattern and then new DVHs of organ were generated. The new DVHs would be used for next second's calculation with treatment field DVH. Conventional fractionated non-small cell lung cancer plan 60Gy (30 fractions*2.0Gy) and SBRT plan 50Gy (5fractions*10Gy) are constructed for three patients with different target volumes. The primary endpoint is peak cumulative blood dose (PCBC). **Result:** PCBC of three patients with CRT and SBRT were calculated as Figure 1. PCBC with CRT to circulating lymphocyte (CL) were 2.5Gy, 5.6Gy, 9.5Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively. And PCBC with SBRT to circulating lymphocyte (CL) were 2.1Gy, 2.9Gy, 6.0Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively. PCBC gap of SBRT to circulating lymphocyte (CL) was decreased 0.4Gy, 2.7Gy, 3.5Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively.



Conclusion: An improved simulation-model was established, SBRT, compared to CRT, will lead to decreased cumulative dose on CL, which may cause less impact on immune system with the enlargement of PTV-volume.

Keywords: Stereotactic body radiation therapy (SBRT), Conventional fractionation radiotherapy (CRT), Immunosuppressive

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
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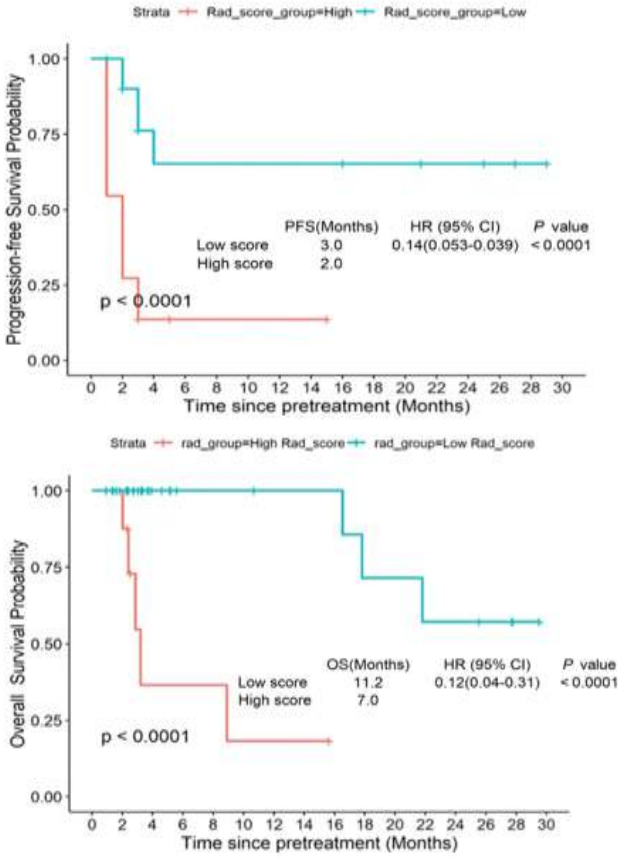
JCSE01.18 A CT-BASED RADIOMICS APPROACH TO PREDICT PD1 INHIBITOR RESPONSE IN NON-SMALL-CELL LUNG CANCER

J. Wang, S. Wang, H. Yu, C. Liu, X. Zhao, S. Sun, J. Chang, J. Qiao, X. Wu

Fudan University Shanghai Cancer Center, Shanghai/China

Background: The purpose of this study was to investigate the use of radiomics features as predictive parameters of clinical outcomes of non-small-cell lung cancer (NSCLC) patients treated with PD1 inhibitor. **Method:** Forty-three stage IIIB/IV NSCLC patients without EGFR mutation or ALK rearrangement who received nivolumab were enrolled between Apr 2016 and Jan 2019. High-dimensional quantitative feature analysis via Pyradiomics was applied to extract 852 radiomics features of pre-anti-PD1 treatment CT. A radiomic score model was constructed from these features with the use of least absolute shrinkage and selection operator (LASSO) Cox regression. The radiomic score for each patient was computed using an equation in which the coefficients were derived from the LASSO Cox model to subgroup patients by progression-free survival (PFS). The median value of radiomic score was used as the cut-off value to cluster patients into high or low score groups.



Result: We developed a radiomic signature for PFS that included seven variables. The median value of radiomic score was 0.23. The objective response rate (ORR) was 16.3% (7/43), the median PFS was 2 months and median overall survival (OS) was 3.2 months of all 43 patients. A low radiomic score was associated with a higher ORR (33.7% vs 0%, p= 0.0036), improved PFS (median: 3 months vs 2 months; HR 0.14, 95% CI 0.053-0.39, P<0.0001) and longer OS (median: 11.2 months vs 7.0 months; HR 0.12, 95%CI 0.04-0.31, p < 0.0001). Multivariate analysis also showed that a low radiomic score was related to better PFS (HR 0.12, 95% CI 0.041-0.32, P<0.0001) and OS (HR 0.11, 95%CI 0.03-0.28, p < 0.0001). **Conclusion:** The radiomic signature as an imaging predictor provided a promising way to predict clinical outcomes for NSCLC patients treated with PD-1 inhibitor.

Keywords: Non small cell lung cancer, PD1 inhibitor, CT-based radiomics approach

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
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JCSE01.19 TUMOR MUTATION SCORE IS MORE POWERFUL THAN TUMOR MUTATION BURDEN IN PREDICTING RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

Y. Li[1], Z. Chen[2], L. Wu[3], W. Tao[3]

[1]*Fudan University Shanghai Cancer Center, Shanghai/China,* [2]*Tongji Hospital, Huazhong University of Science and Technology, Wuhan/China,* [3]*Renmin Hospital of Wuhan University, Wuhan/China*

Background: Tumor mutation burden (TMB) and PD-L1 expression are the two important biomarkers for immune checkpoint inhibitors (ICIs) in lung cancer. However, growing evidences are showing that not all mutations, such as EGFR mutation, are favorable factors in predicting clinical outcome of ICIs and the power of TMB, which is unselective, might be attenuated. Therefore, we developed tumor mutation score (TMS) as better biomarker for response of ICIs in non-small cell lung cancer (NSCLC). **Method:** TMS was defined as the number of genes with nonsynonymous somatic mutations. Mutations were detected by targeted next-generation sequencing (NGS) in 240 NSCLC patients treated with anti-PD-(L)1 monotherapy or in combination with anti-CTLA4. Durable clinical benefit (DCB) was defined as complete response (CR)/partial response (PR)/stable disease (SD) that lasted 6 months. TMS, TMB and PD-L1 expression were compared among DCB and no durable benefit (NDB) NSCLC patients. **Result:** The total TMS was significantly correlated with TMB (R=0.98, P<0.001) and performed almost equally to TMB in the analysis. 12 genes and 11 genes (5 sharing genes) were significantly associated with longer progression-free survival (PFS) and response (DCB vs NDB), respectively. The number of mutated genes within these 18 genes were defined as TMS18. In the survival analysis of PFS, the HRs of the high group were TMS19 (HR=0.307, P<0.001), TMB (HR=0.455, P<0.001), and PD-L1 expression (HR= 0.403, P=0.02), separately. Moreover, patients with DCB had significantly higher TMS18 (P<0.001), TMB (P=0.006), and PD-L1 expression (P=0.032). High TMS18 group had highest proportion of CR/PR/SD patients, which was 74.1% (CR/PR/SD: 3/17/20), especially in distinguishing CR patients. Taken together, TMS18 was more powerful than TMB and PD-L1 in predicting response of ICIs in NSCLC. **Conclusion:** Simple transformation from unselective TMB to selective TMS greatly enhanced the power of mutations-based biomarkers. TMS in combination with PD-L1 expression might yield better efficiency in predicting response of ICIs in NSCLC with future validation in larger cohorts.

Keywords: Tumor Mutation Score, Tumor Mutation Burden, PD-L1

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.20 PILOT STUDY ON THE TUMOR IMMUNE MICROENVIRONMENT BETWEEN NON-SMALL CELL LUNG CANCER (NSCLC) AND SMALL CELL LUNG CANCER (SCLC)

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Background: Tumor immune microenvironment plays an important role in immunotherapy and prognosis. However, the differences and the clinical significance between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) is still largely unknown. **Method:** Resected lung cancer FFPE specimens and matched peripheral blood mononuclear cells (PBMC) from six patients with NSCLC (three adenocarcinoma, three squamous cell carcinoma) and three patients with SCLC were collected. All of the nine patients underwent stage III disease. Tumor mutation burden (TMB) was evaluated by hybridization capture based next-generation sequencing with 1021 cancer associated genes. Tumor infiltrating lymphocytes (TILs) were assessed by immunohistochemistry using multiple immune markers and meanwhile the intratumoral T-cell repertoires were analyzed via high-throughput sequencing of TCR β-chain. **Result:** Typical EGFR mutations in adenocarcinoma (2 in 3), NSCLC and RB1

mutations in SCLC (3 in 3) were observed. SCLC patients showed significantly higher TMB than NSCLC. Regarding to the tumor immune microenviroment, SCLC tumors exhibited lower infiltration of CD3+ and CD8+ TILs (P< 0.05). Furthermore, we found that SCLC patients tended to have lower TCR Shannon index (P= 0.167) and higher Clonality index (P= 0.095). Interestingly, patients with higher Shannon index exhibited better Overall Survival (OS) while Clonality was potentially associated with decreased OS. However, further study with more patients is needed to confirm the results. **Conclusion:** Tumor immune microenvironment varies between NSCLC and SCLC patients. Specifically, less prevalent and lower diversity of TILs were observed in SCLCs. This might potentially influence survival outcomes.

Keywords: Lung cancer, T-cell receptor repertoire

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.21 CHANGES OF PERIPHERAL BLOOD SPD-L1 IN PATIENTS WITH SMALL CELL LUNG CANCER DURING CHEMOTHERAPY AND ITS CLINICAL SIGNIFICANCE

H. Tian[1], X. Kang[2], L. Yang[1], H. Zhu[2], W. Guo[3], X. Song[2]

[1]*Shanxi Medical University, Taiyuan, Shanxi/China,* [2]*Shanxi Tumor Hospital, Taiyuan, Shanxi/China,* [3]*National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/China*

Background: As a new immunotherapeutic target, the inhibitors of programmed death 1 (PD-1) and programmed death ligand-1 (PD-L1) pathway have been used to treat a variety of tumors including small cell lung cancer (SCLC). However, the biomarkers now used to predict the efficacy of SCLC immunological checkpoint inhibitors are still in the exploratory phase. The aim of this prospective study was to investigate the prevalence and prognostic roles of soluble PD-L1(sPD-L1) protein in the blood of patients with lung cancer. **Method:** A total of 94 patients with SCLC who were diagnosed by histopathology or cytopathology between March 2018 to November 2018 were enrolled. Blood samples plasma were collected at the time of diagnosis. 17 samples of healthy subjects matching in sex and age from the Health care Center of the hospital were also studied as control. The level of sPD-L1 protein in the blood was measured using an enzyme-linked immunosorbent assay (ELISA). And the correlation of sPD-L1 expression with tumor stage, distant metastasis, and pro gastrin releasing peptide (ProGRP) was analyzed. **Result:** Expression of sPD-L1 in SCLC patients was significantly higher than healthy people(P<0.05).A cut-off value of 1.362ng/ml was distinguished in patients according to Receiver operating characteristic curve (ROC). Dynamic changes of sPD-L1 are associated with progressive disease(PD)[a], partial response(PR)[a] and stable disease(SD)[b] in SCLC patients([a] P<0.01,[b] P>0.05).The expression of sPD-L1 in serum was positively correlated with ProGRP.

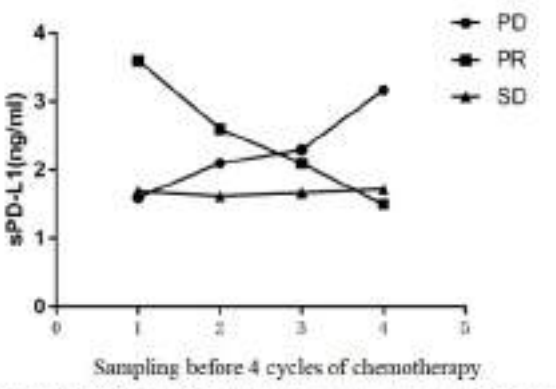

Figure 1 Trend of sPD-L1 in patients with small cell lung cancer during treatment

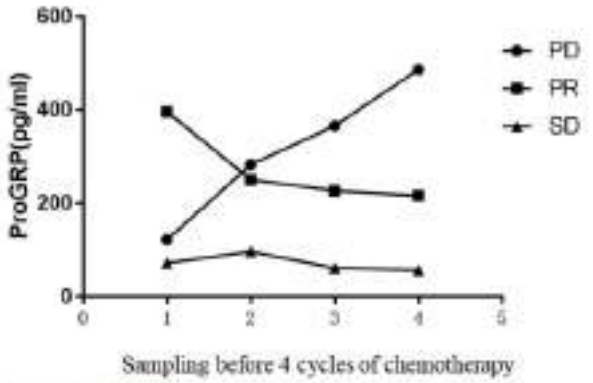

Figure 2 Trend of ProGRP in patients with small cell lung cancer during treatment

Conclusion: Our results indicated that changes of plasma SPD-L1 levels in SCLC patients are associated with prognosis. Plasma sPD-L1 protein is a great biomarker in SCLC and may play an important role in sifting the beneficiaries of immunotherapy.

Keywords: small cell lung cancer (SCLC), soluble programmed death ligand 1 (sPD-L1), pro gastrin releasing peptide (ProGRP)

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.22 TUMOR MICROENVIRONMENT IS ASSOCIATED WITH EFFICACY OF PD-1/PD-L1 INHIBITORS IN PATIENTS WITH PRIMARY PULMONARY LYMPHOEPITHELIOMA-LIKE CANCER

K. Yin[1], Z. Xie[2], Z. Lv[2], J.-J. Yang[3], X.-N. Yang[4], Q. Zhou[5], W.-Z. Zhong[6], L.-L. Li[2], H.-B. Feng[2], W.-B. Guo[2], D.-X. Lu[2], Y. Chen[2], W.-Q. Yan[2], Y.-L. Wu[7], X.-C. Zhang[2]

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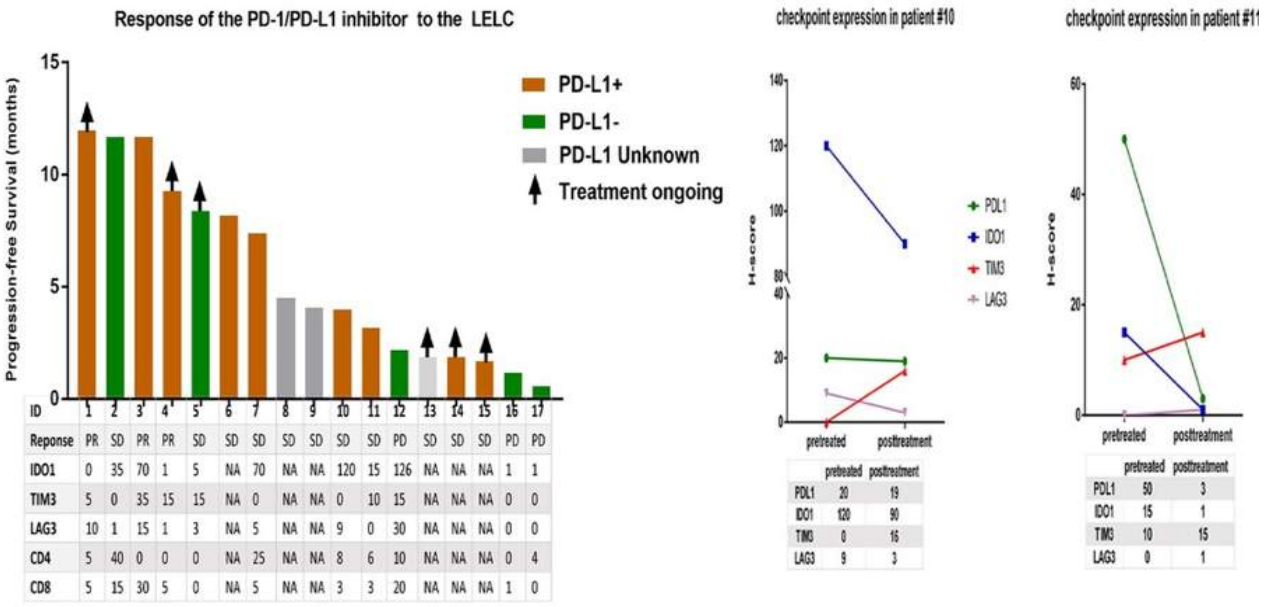
Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is Epstein-Barr (EB) virus related subtype of non-small-cell lung cancer. Evidence of immunotherapy in LELC is scarce. The role of immune markers in tumor microenvironment and their relation with the efficacy of PD-1/PD-L1 inhibitors in LELC remain poorly explored.Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is Epstein-Barr (EB) virus related subtype of non-small-cell lung cancer. Evidence of immunotherapy in LELC is scarce. The role of immune markers in tumor microenvironment and their relation with the efficacy of PD-1/PD-L1 inhibitors in LELC remain poorly explored. **Method:** A total of seventeen patients treated with PD-1/PD-L1 inhibitors in Guangdong Lung Cancer Institute were enrolled. We detected multiple immune markers including PD-L1, IDO1, TIM3, LAG3, CD4 and CD8 by immunohistochemistry in eleven of these patients. Dynamic changes of the checkpoint biomarkers in two patients (#10 and #11) treated with PD-1 inhibitors were analyzed. Tumors with 1% TPS (tumor proportion staining) were defined as PD-L1 positive. H-score of PD-L1, IDO1, TIM3 and LAG3 was calculated by multiplying percentage of positively stained cells and intensity score (0, absent; 1, weak; 2, moderate; 3, strong). For CD4 and CD8, the H-score equals the percentage of staining positive lymphocytes among all nucleated cells.



ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Reponse	PR	SD	PR	PR	SD	SD	SD	SD	SD	SD	SD	PD	SD	SD	SD	PD	PD
IDO1	0	35	70	1	5	NA	70	NA	NA	120	15	126	NA	NA	NA	1	1
TIM3	5	0	35	15	15	NA	0	NA	NA	0	10	15	NA	NA	NA	0	0
LAG3	10	1	15	1	3	NA	5	NA	NA	9	0	30	NA	NA	NA	0	0
CD4	5	40	0	0	0	NA	25	NA	NA	8	6	10	NA	NA	NA	0	4
CD8	5	15	30	5	0	NA	5	NA	NA	3	3	20	NA	NA	NA	1	0

	pretreated	posttreatment
PDL1	20	19
IDO1	120	90
TIM3	0	16
LAG3	9	3

	pretreated	posttreatment
PDL1	50	3
IDO1	15	1
TIM3	10	15
LAG3	0	1

Result: In the 17 patients, most of them suffered from lines of chemotherapy (only two patients (2/17, 11.8%) received PD-1/PD-L1 inhibitors as the first line therapy). There are eight males and nine females. The median age was 47 years (range from 13 to 63). All of them were stage IIIB and IV. Thirteen of seventeen patients received single agent PD-1/PD-L1 inhibitor. PD-1/PD-L1 inhibitor showed an 82.4% disease control rate and 17.6% objective response rate. The median progression free survival was 7.4 months. The overall survival was not reached. Biomarkers of IDO1, LAG3, and TIM3 were not mutually exclusive with PD-L1, and could be highly expressed in responder patients to PD1/PD-L1 inhibitors. Notably, TIM3 expression was up-regulated at disease progression in two patients treated with PD-1 inhibitor. **Conclusion:** PD-1/PD-L1 inhibitors had preliminary good activity, and TIM3 up-regulation might be a mechanism of resistance to PD-1 inhibitors in advanced pulmonary LELC.

Keywords: lymphoepithelioma-like carcinoma, PD-1/PD-L1 inhibitors, Tumor micro environment; TIM3

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.23 SPECIFIC TP53 MUTATION SUBTYPES AS BIOMARKER FOR RESPONSE TO PD-1/L1 BLOCKADE IMMUNOTHERAPY IN NSCLC

H. Sun[1], S.-Y. Liu[2], J.Y. Zhou[3], M. Zheng[2], J.J. Huan[4], Y.F. Guan[4], R. Gao[4], X. Yi[5], Y.-L. Wu[6]

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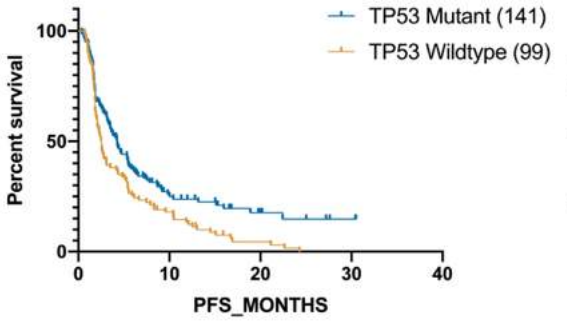
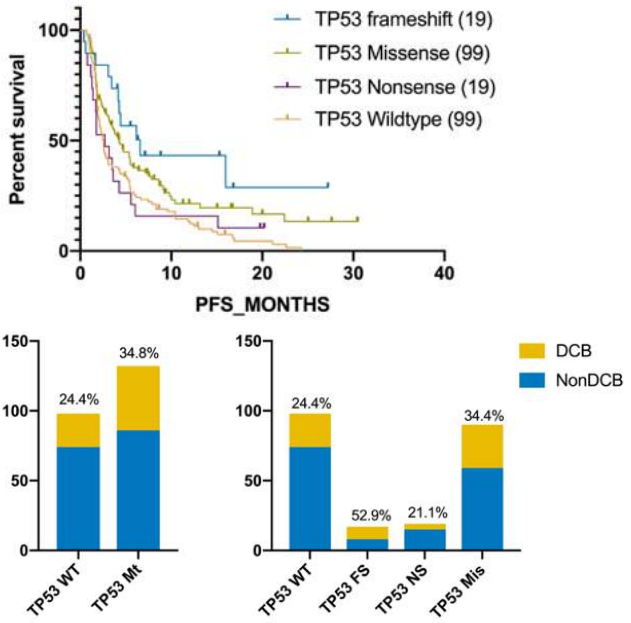
Background: Although TP53 co-mutation with KRAS have been proved to have predictive value for response to PD-1/L1 blockades, not all TP53 mutations are equal in this context. TP53 subtypes as independent factors to predict the response to PD-1/L1 blockade have not yet reported. **Method:** We performed an integrated analysis on the multiple-dimensional data types including genomic and clinical data from cohorts of NSCLC public (240 from MSK database) and local databases (224 patient with PD-L1 IHC score, 1986 NSCLC with TMB data). Durable clinical benefit (DCB) was defined as partial response/stable disease that lasted more than 6 months. **Result:** The presence of mutant TP53 was associated with longer median progression free survival (mPFS) in NSCLC taking PD-1/L1 blockade therapy compared with TP53 wild-type group in the MSK-cohort (4.3 *vs*2.6 months, P=0.0027, HR=0.6409, 95%CI, 0.49 to 0.88). TP53 frameshift seemed to predict longer mPFS (6.6 months, P=0.0159, HR= 0.41, 95%CI, 0.26 to 0.65) than TP53 wild-type, TP53 missense (mPFS=4.27 months, P=0.17) and TP53 nonsense status (mPFS=2.7 months, P=0.002).NSCLC with TP53 frameshift mutation had a 52.9% rate of DCB, which was higher than TP53 missense (34.4%) and nonsense (21.1%) group. Besides, in the MSK cohort, five of six patients with TP53 truncated mutation in proline-rich (PR) domain (residues 58--101) achieved DCB, and one patient achieved 5.5 months of PFS and did not progress. Fractions of PD-L1 low-positive (1% - 49%) and PD-L1 high-positive (≥50%) tumors between each TP53 mutation subtype and wild-type groups are analyzed based on local data. The TP53 mutation rate was significantly higher in NSCLC with PD-L1 score >50% (P=0.004). But NSCLC with TP53 frameshift showed lower fractions of PD-L1 high-positive (12.5%, 2/16) compared with TP53 missense group (27.5%, 33/120) and TP53 nonsense group (25.8%, 8/31). PD-L1 low-positive rate is also lower in TP53 frameshift group (25.0%, 4/16) than TP53 missense (30.8%, 37/120) and nonsense group (29.0%, 9/31). Among 1986 NSCLC patients with TMB data, each TP53 mutation subtype is associated with significantly higher TMB than TP53 wildtype, especially among NSCLC with TP53 truncated mutation in PR domain (median TMB= 9 mut/Mbs). But no significant difference was found between TP53 mutation subtypes in TMB.





Conclusion: Our study demonstrated heterogeneity among TP53 mutations in predicting the response to PD-1/L1 blockade therapy. TP53 frameshift mutation may contribute to better PD-1/L1 blockade therapy response beyond PD-1/L1 IHC status. And the truncated TP53 mutation in PR domain may contribute to DCB.

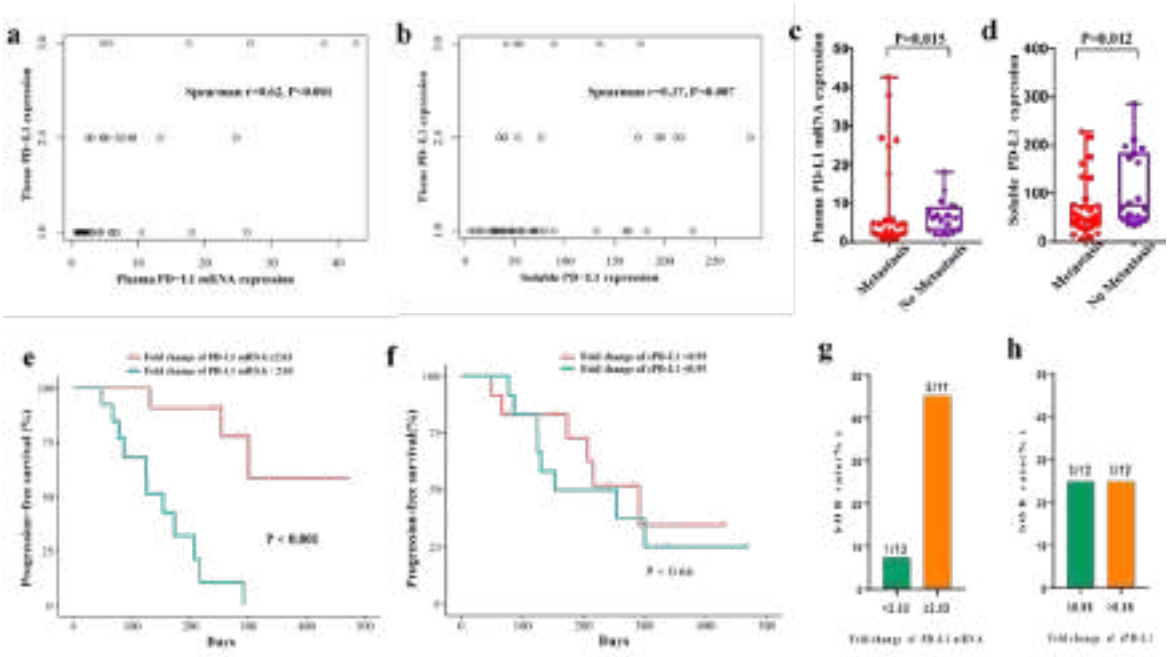
Keywords: TP53 subtype, NSCLC, PD-1/L1 blockade

JCSE01.24 DYNAMIC CHANGES OF PLASMA PD-L1 MRNA EXPRESSION PREDICT RESPONSE TO ANTI-PD-1/ANTI-PD-L1 TREATMENT IN MALIGNANCIES

J. Sun, Q. Yang, M. Chen, J. Gu, L. Zheng, Y. Yu, F. Li, L. Zhang, K. Niu

Cancer Institute of People's Liberation Army, Chongqing/China

Background: PD-L1 expression in malignant tumor tissues is a rational biomarker to predict the efficacy and prognosis of anti-PD-1/anti-PD-L1 treatment, but few studies focus on the role of blood PD-L1 expression. **Method:** Fifty-one paired tissue samples and blood samples, as well as clinicopathologic features, were collected from patients with diverse malignancies to investigate the correlation among tissue PD-L1 (tPD-L1) expression, plasma PD-L1 mRNA expression, soluble PD-L1 (sPD-L1) expression and clinicopathologic features. Tissue PD-L1 were measured by immunohistochemistry. PD-L1 mRNA and self-designed plasma inner reference PLACON were measured by quantitative real-time PCR. Soluble PD-L1 were detected by ELISA kit. Then, dynamic changes of blood PD-L1 expression (at baseline and within 2 months) were measured to evaluate the efficacy of patients with malignancies (n=24) who received anti-PD-1/anti-PD-L1 treatment. **Result:** Moderate correlation between tPD-L1 and PD-L1 mRNA (r=0.62, *P*<0.001), weak correlation between tPD-L1 and sPD-L1 (r=0.37, *P*=0.007) and weak correlation between PD-L1 mRNA and sPD-L1 (r=0.32, *P*=0.02) were found. Most clinicopathologic features had no significant correlation with PD-L1 mRNA and sPD-L1 expression. Interestingly, patients without metastasis had higher PD-L1 mRNA and sPD-L1 expression than counterparts. Further, patients with over 2.03-fold PD-L1 mRNA increase (n=11) during treatment experienced improved progression-free survival (PFS) than those with less than 2.03-fold increase (n=13), these patients also had higher best overall response (bOR) rate (45.45% vs. 7.69%). By comparison, the dynamic changes of sPD-L1 expression had no significant correlation with PFS and bOR.



a, The correlation between tPD-L1 and plasma PD-L1 mRNA (n=51). b, The correlation between tPD-L1 and sPD-L1 (n=51). c, Plasma PD-L1 mRNA expression in patients with (n=33) and without (n=18) metastasis. d, sPD-L1 expression in patients with (n=33) and without (n=18) metastasis. e, Kaplan–Meier PFS of patients with high (n = 11) and low (n = 13) fold changes of plasma PD-L1 mRNA within 2 months. f, Kaplan–Meier progression-free survival of patients with high (n = 12) and low (n = 12) fold changes of plasma sPD-L1 within 2 months. g, bOR rate for patients with high and low fold changes of plasma PD-L1 mRNA . h, bOR rate for patients with high and low fold changes of plasma sPD-L1. tPD-L1, tissue PD-L1; sPD-L1, soluble PD-L1; PFS, progression-free survival; bOR, best overall response.
* Tissue PD-L1 expression were measured by immunohistochemistry with SP142 (1.0 : <1%, 2.0 : 1%–49%, 3.0 : ≥ 50%). Plasma PD-L1 mRNA and self-designed plasma inner reference PLACON (Reference: 10.16016/j.1000-5404.201812172) were detected by quantitative real-time PCR. Plasma soluble PD-L1 expression were measured by ELISA kit.

Conclusion: Our study demonstrates that plasma PD-L1 mRNA expression was significantly correlated with tissue PD-L1 expression, and provides proof for the application of plasma PD-L1 mRNA as a predictor for anti-PD-1/anti-PD-L1 treatment.

Keywords: dynamic changes, anti-PD-1/anti-PD-L1 treatment, PD-L1 mRNA

JCSE01.25 TP53/KMT2C CO-MUTATION AS A NOVEL BIOMARKER FOR IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS

Q. Zhou[1], X. Peng[1], W. Wang[2], W. Wang[2], L. Zhang[2], K. Wang[2], S. Zhang[2]

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Background: Immune checkpoint inhibitors (ICIs) have shown remarkable antitumor effects in non-small cell lung cancer (NSCLC), however only a subset of patients respond. Genomic alterations (GAs) detected by targeted next-generation sequencing (NGS) is increasingly used in clinical practice, but its correlation with recognized immune biomarkers and predictive value for ICIs response in NSCLC is unclear. **Method:** FFPE tumor and matched blood samples of 637 NSCLC patients (84 squamous cell and 553 non-squamous cell) were collected for targeted NGS panel sequencing from December 2017 to January 2019. GAs including single nucleotide variations, short and long insertions/deletions, copy number variations and gene rearrangements were assessed. TMB high (TMB-H) was defined as ≥10 muts/Mb. Positive PD-L1 expression was defined as ≥1% of tumor cells with membranous staining (22C3/28-8, DAKO). Genomic data and ICIs treatment outcome from a 240 NSCLC patient cohort was derived from cBioPortal (MSKCC, J Clin Oncol 2018). **Result:** In 637 NSCLC patients, the prevalence of PD-L1≥1% was 26.5% and the median TMB was 4.6 muts/Mb (IQR, 2.3-10). Recurrent *TP53*, *KRAS*, *LRP1B* and *KEAP1* mutations were significantly correlated with higher TMB (p value). *TP53*, *KRAS* and *KEAP1* mutations were significantly enriched in the TMB-H/PD-L1+ subset while *STK11* mutations were enriched in TMB-H/PD-L1- subset (p value). *KMT2C*, also known as *MLL3*, belongs to the mixed-lineage leukemia (MLL) family of histone methyltransferases and its GAs was found in 5% of our cohort. Tumors with *KMT2C* and *TP53* co-mutations (co-MUT) had a significantly higher TMB (15.1 muts/Mb) than *TP53/KMT2C* single-MUT (8.7 muts/Mb) and *TP53/KMT2C* co-WT (3.1 muts/Mb) tumors. Moreover, TMB-H/PD-L1+ subset was enriched in *KMT2C* and *TP53* co-MUT (25%) comparing to *TP53/KMT2C* single-MUT (14.7%) and *TP53/KMT2C* co-WT (3.3%) tumors. Survival analysis from public clinical trials confirmed that patients with *TP53/KMT2C* co-MUT had remarkable clinical benefit to ICIs in both progression free survival (PFS) and durable clinical benefit (DCB). The median PFS was 7.3, 4.2 and 2.5 months for *TP53/KMT2C* co-MUT, *TP53/KMT2C* single-MUT and *TP53/KMT2C* co-WT patients, respectively (p=0.0032). *TP53/KMT2C* co-MUT was an independent variable of PFS (*TP53/KMT2C* co-MUT vs. *TP53/KMT2C* co-WT, HR: 0.47, 95%CI: 0.25-0.89, p=0.0199). Furthermore, *TP53* with *KMT2C* or *KRAS* co-MUT expanded the patient population benefiting from ICIs (mPFS = 7.2 months, p=0.00042; DCB = 51.2%, p= 0.0195). **Conclusion:** This study provides evidence that *TP53/KMT2C* co-MUT may serve as a predictive biomarker for ICIs in NSCLC. GAs detected by targeted NGS could illuminate insight for immunotherapy.

Keywords: Non-Small Cell Lung Cancer, KMT2C, Immunotherapy

JCSE01.26 PD-1 INHIBITOR PLUS CHEMOTHERAPY AS 2ND/SUBSEQUENT LINE SETTING DEMONSTRATE SUPERIOR EFFICACY OVER PD-1 INHIBITOR ALONE IN PTS OF ADVANCED NSCLC

S. Ren[1], Y. Liu[2], F. Zhou[3], T. Jiang[4], C. Su[4], X. Chen[5], C. Zhou[6]

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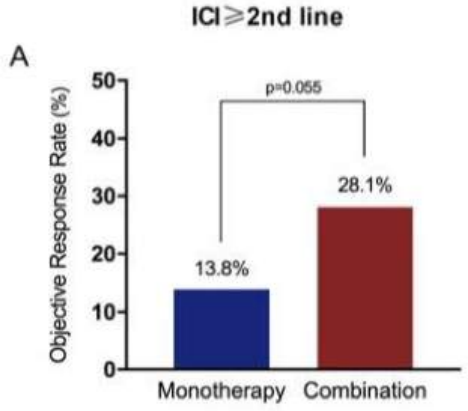
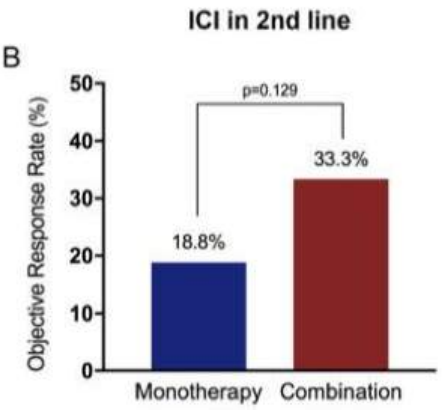
Background: PD-1/PD-L1 inhibitors have become standard of care as the 2nd-line setting and also approved as 1st line setting when combined with doublet chemotherapy in patients with advanced NSCLC. This study aims to compare the efficacy of PD-1 inhibitor plus chemotherapy with PD-1 inhibitor alone as 2nd/subsequent lines setting in patients with advanced NSCLC **Method:** Patients who received PD-1 inhibitor monotherapy or PD-1 inhibitor plus chemotherapy as 2nd/subsequent lines setting in Shanghai Pulmonary Hospital, Tongji University were retrospectively collected. Detailed clinicopathologic characteristics and therapeutic outcomes were analysis. **Result:** From January 2016 to February 2019, 148 patients who meet the criteria were included. Among them, 116 were in PD-1 inhibitor monotherapy group and 32 were in PD-1 inhibitor plus chemotherapy group. Chemotherapy regimens were pemetrexed(n=9), docetaxel(n=2), nab-paclitaxel(n=18) and gemcitabine(n=3). The baseline characteristics such as age, gender, smoking status, histology, PD-1 mono-antibodies, line of therapy were similar in the 2 groups. Combination group showed a favorable ORR (28.1% vs. 13.8%, p=0.055) and a significantly longer PFS(median 4.9 vs 2.5 months, p=0.005) compared with ICI monotherapy. Overall survial (OS) data was immature in the cutoff date of follow up. In the subgroup of 96 patients (monotherapy group n=69/ Combination group n=27) who were included as 2nd line setting, PD-1 inhibitor plus chemotherapy had significantly higher ORR(ORR:33.3% vs 18.8%, p=0.129) and longer PFS(median PFS: 4.9 vs 2.9 months, p=0.041).





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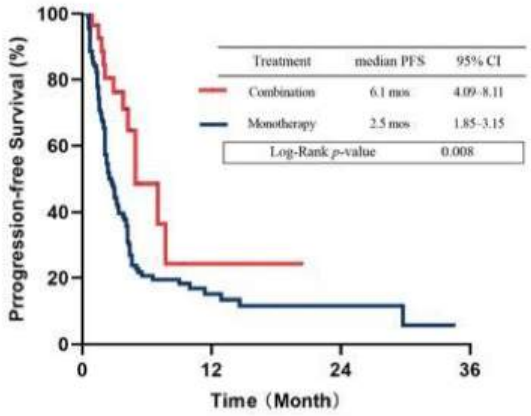

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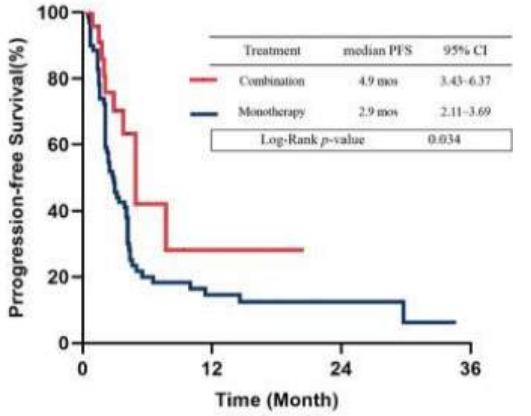

Conclusion: PD-1 inhibitor plus chemotherapy as 2nd/subsequent lines setting demonstrated superior efficacy over PD-1 inhibitor alone in patients with advanced NSCLC.

Keywords: Chemotherapy, NSCLC, Immunotherapy

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.27 A NOVEL NON-INVASIVE BIOMARKER BASED ON PERIPHERAL PD-1+CD8+T CELL RECEPTOR REPERTOIRE PREDICTS CLINICAL OUTCOMES OF IMMUNOTHERAPY IN NSCLC

J. Han[1], Z. Wang[2], Y. Wang[3], J. Li[4], J. Duan[5], H. Bai[5], J. Wang[6]

[1]*Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/China,* [2]*National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing/China,* [3]*Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou/China,* [4]*Geneplus-Beijing Institute, beijing/China,* [5]*Molecular Oncology, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing/China,* [6]*Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing/China*

Background: To investigate the potential value of peripheral blood programmed cell death 1 (PD-1)$^{+}$CD8^{+}Tcell receptor (TCR) repertoire profiling in predicting the clinical outcomesof immune checkpoint blockades (ICBs) for patients with non-small cell lung cancer (NSCLC). **Method:** The study comprised two independent cohorts (A and B). Cohort A (n=25) was used for the discovery of TCR diversity in the prediction of response to ICBs, and cohort B (n=15) was used as an independent validation set. A total of 40 out of 51 patients with stage IIIB-IV NSCLCs undergoing anti-PD-1/PD-ligand 1 (PD-L1) therapy between March 14th, 2017 and May 2nd, 2018were ultimately recruited.Pre- and post-ICB (4-6 weeks from the timepoint of the first imaging evaluation) peripheral blood samples were prospectively collected, and PD-1^{+}CD8^{+}T cells were isolated by flowcytometry for TCR sequencing. The diversity and clonality of the TCR repertoire were calculated for biomarker exploration. **Result:** In cohort A, patients with a high pre-ICB PD-1^{+}CD8^{+}TCR diversity had better response rate and longer progression-free survival (PFS) to anti-PD-1/PD-L1 therapythan those with a low diversity (6.4 months vs. 2.5 months, HR, 0.39, 95% CI, 0.17-0.94,*P*= 0.021), which was validated in cohort B. In a merged dataset from cohorts A and B, pre-ICB PD-1^{+}CD8^{+}TCR diversity achieved an optimal Youden's index of 0.81 with a sensitivity of 0.87 and a specificity of 0.94 in stratifying clinical response of ICBs [partial response (PR) + stable disease (SD) vs. progressive disease (PD)]. Patients with an increased PD-1^{+}CD8^{+}TCR clonality after treatment demonstrated significantly improved PFS (7.3 months vs. 2.6 months, HR, 0.26, 95% CI, 0.08-0.86,*P*= 0.002) compared to those with a decreased TCR clonality. Interestingly, two patients with initial pseudo-PD exhibited similar changes of TCR clonality and expansion of dominant TCR clones with those with PR but not PD. **Conclusion:** Pre-ICB TCR diversity and early change of TCR clonality after treatment based onperipheral PD-1^{+}CD8^{+}TCR repertoire sequencing are biomarkers to predict the response and survival to anti-PD-1/PD-L1 therapy, which provide a promising non-invasive approach to stratify NSCLC patients for ICB treatment.

Keywords: TCR, NSCLC, Immunotherapy

JCSE01 JOINT IASLC-CSCO-CAALC SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–11:15

JCSE01.28 CHANGES OF BRAIN STRUCTURE IN ADVANCED NSCLC PATIENTS RECEIVING EGFR-TKIS: DYNAMIC ANALYSIS BASED ON SERIES MRI IMAGES

C. Luo[1], B. Yang[2], X. Zhou[3], L. Zhou[3], Y. Zhou[3], J. Zhu[3], M. Huang[3], F. Peng[3], Y. Liu[3], Y. Wang[3], Z. Li[4], Y. Lu[3], S. Lui[2], Y. Gong[5]

[1]*West China Hospital, Sichuan University, Chengdu, sichuan province/China,* [2]*Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province/China,* [3]*Department of Thoracic Oncology and State Key Laboratory of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, sichuan province/China,* [4]*Department of Radiation Oncology, West China Hospital, Sichuan University, Chengdu, Sichuan Province/China,* [5]*Cancer Center, West China Hospital, Sichuan University, chengdu/China*

Background: EGFR-TKI was the standard care for metastatic NSCLC patients harboring positive EGFR mutation, which might inhibit EGF signaling pathway and consequently have effect on differentiation, maturation and rehabilitation of neural cells. For the first time, we evaluated the dynamic changes of white matter lesion (WML) and gray matter volume (GMV) among such patients based on series of MRI images. **Method:** We retrospectively identified 778 patients with pathologically diagnosed advanced NSCLC receiving first-generation EGFR-TKIs in our hospital from 2010 to 2017, and 75 patients without brain metastasis and else comorbidity (hypertension, *etc.*) were analyzed. The modified Scheltens visual scale were performed to evaluate the changes of WML based on the series (baseline, 12 months' point and 24 months' point) of MRI images, and CBM (cluster-based morphometry) method based on SPM12 were adopted to identify GMV loss. The statistical methods were performed using SPSS software 22.0. **Result:** During the 24-month EGFR-TKI treatment, the patient's WML visual scores showed a progressive worsen. Comparing to the baseline (6.680±3.636), the scores were significantly changed at the 12 months' point (8.650±3.857; Mean scores increasing 1.973, 95% CI 1.595-2.352, p<0.001) and changed more obviously at the 24 months' point (10.110±3.854; Mean scores increasing 3.427, 95% CI 2.979-3.874, p<0.001), respectively. Also, the significant GMV loss were found in subregions of the right occipital lobe (mean decrease 76.714, 95% CI 40.739-112.690), left occipital lobe (mean decrease 93.476, 95% CI 37.483-149.469) and left basal ganglia (mean decrease 37.571, 95% CI 21.576-53.567), respectively (all *p*<0.005, the cluster level FDR<0.05). **Conclusion:** Dynamic structural analysis of series brain MRI images showed the significant worsen of the WML and GMV loss in patients with advanced NSCLC receiving EGFR-TKIs chronically. Perspective studies are warranted to verify its impact on the cognitive deficiency and hypomnesis among these patients in future.

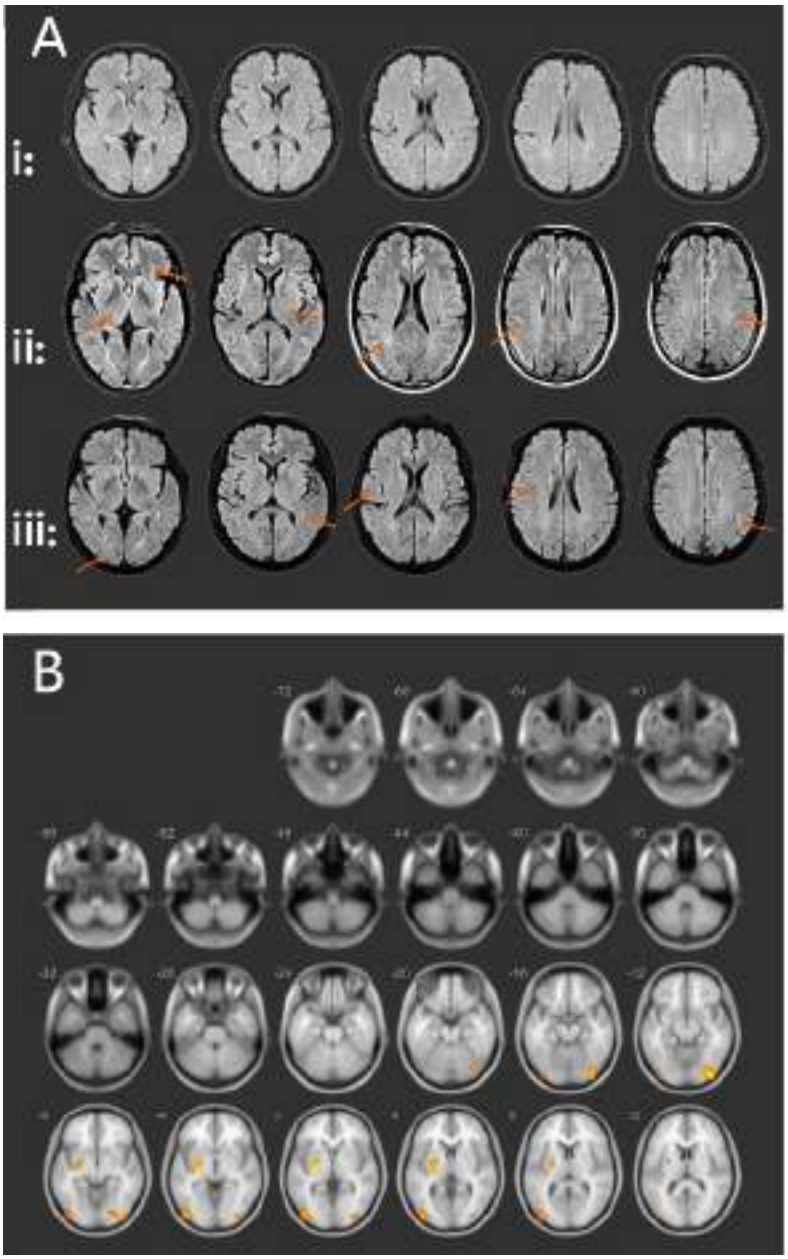

Figure. A. Series MRI images of one representative patient receiving long-term EGFR-TKI. (i. Baseline; ii. 12 months' point; iii. 24 months' point). New white matter lesions were identified in T2 FLAIR images (with yellow arrows). B. Significant loss of gray matter volume (colored areas) was identified by cluster-based morphometry method in the brain subregions among the studied population.

Keywords: NSCLC, EGFR-TKI, Brain MRI

Symposia

S01 IASLC CT SCREENING SYMPOSIUM: FOREFRONT ADVANCES IN LUNG CANCER SCREENING (TICKETED SESSION)
SATURDAY, SEPTEMBER 7, 2019 07:00–12:00

S01.02 INTRODUCTIONS & WELCOME

J. Mulshine[1], J. Field[2]

[1]*Rush University, Chicago/United States of America,* [2]*The University of Liverpool, Liverpool/United Kingdom*

The Five-year Vision for Lung Cancer Screening

The goal of lung cancer screening is to increase the detection of asymptomatic, localized cancers that can more frequently be cured. Given this prospect, it is with a sense of urgency that we explore strategies that allow us to benefit as many willing candidates to receive this service. In addition, there is an obligation to ensure that this cancer detection service is delivered in a fashion that conveys maximal benefit while minimizing harms. Thinking strategically, what steps and in what sequence should we pursue implementation of lung cancer screening to optimize improvement of lung cancer outcome in the five-year window? First, we expect results from a number of currently ongoing studies of smoking cessation studies integrated into lung cancer screening to be completed which may provide insight how to enhance cessation rates long-term smokers. This would be critical information to rapidly disseminate as risk of smoking harms rise so steeply in later life and since tobacco causes not only premature death but also profound economic costs (1, 2). Resources to accelerate screening research are currently an intense focus of developmental efforts. Over the next five years, collaborative mechanisms such as the IASLC's Early Lung Imaging Confederation will be fully functional and providing imaging cases with associated metadata to allow a robust number of research questions to be rapidly addressed (3). Many believe that from an outcome's perspective that "you get what your measure". Currently, there are no established panel of metrics that define excellence in screening. This must be rapidly addressed. A strong measure of screening success would be the reality within five years that clinicians and subjects have easy access to information regarding critical outcomes at a lung cancer screening facility. Such annual metrics for a screening facility may include, screening number, rate of lung cancers detected in screening, frequency of Stage I/II/III/IV, frequency of symptom-detected lung cancer, frequency of true positive lung case detection, operability rate, non-malignant thoracic resection rate, surgical morbidity/mortality rate, compliance with subject follow-up and smoking cessation rate. Armed with such information, subjects as well as clinicians can make well-informed decision about selection of site of care. Five years from now the clinical community may also come to consensus on a reliable and economical approach to access the biological potential of a resected tumor from a screen-identified cancer patient. The goal being to identify aggressive Stage I lung cancers based on mechanistic signatures derived from molecular analysis of the resected tumors identifying cancers that are unlikely to be cured with surgery alone. Appropriate target therapy can be match based on tumor characteristics so that immediate adjuvant therapy may be administered to preserve the possibility of a curative option for that subset of screen-detected cancers. The key to the remarkable progress in lung cancer screening outcomes has been fueled by the rapid advances in reliably imaging of small non calcified lung nodules. Further progress in improving the efficiency of lung cancer screening management has been made possible by actually measuring changes in the volume of lung nodules over time to specifically identify clinically aggressive lung nodules. Reliably measuring lung nodule volume in the range of 6 mm in diameter is a challenging task, but the work of the Quantitative Imaging Biomarker Alliance (QIBA) has worked out a quality conformance process that greatly improved the reliability of using imaging as a quantitative biomarker in this context (3). As screening is rolled out, the QIBA quantitative measurement can be disseminated through a cloud-based infrastructure such as the environment being developed by IASLC to support the imaging quality aspect of lung cancer screening (4, 5). A key to sustain innovation in this regard is to continue to cultivate collaborative efforts in an open research environment so that investigators from many nations can participate and innovate, as IASLC has demonstrated with its impressive contributions to both lung cancer pathology and staging.

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Keywords: Lung cancer Screening,

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S01.03 SESSION I: 2019 STATUS OF THE INTERNATIONAL MATURITY OF CT TRIAL OUTCOMES AND THEIR IMPLICATIONS

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[1]*Rush University, Chicago/United States of America,* [2]*The University of Liverpool, Liverpool/United Kingdom*

Outstanding issues in lung cancer screening: Implementation Research Programmes The Lung cancer community now have the results from two large international RCTs, NLST and NELSON (1, 2), recent confirmatory data from the MILD trial (3), as well as from large international cohort studies (4-7) and smaller RCTs in Europe (8), all of which provide evidence to start the implementing lung cancer. The recent European consensus statement on lung cancer screening provides a very strong argument for the implementation of lung cancer screening (9). However, the actual implementation a cancer screening modality quite often only occurs 10-15 years after the large clinical trials, due to a range of issue which includes the allocation of long term funding, approval from national organisations, clinical agreement regarding the screening protocol and design of the implementation programmes, as well as national service delivery and staffing issues. All the evidence indicates that one would start to save lives now if lung cancer screening was implemented and even though there are acknowledged harms, the benefits outweigh the harms, as recently demonstrated in the NLST infographic (10). The number of deaths per year from lung cancer is still a major public health issue and has to be tackled with a well -structured and integrated smoking cessation and lung cancer screening programmes. This does not infer we are currently in a position to undertake lung cancer screening to its optimum, we still have a great deal to learn and we need to plan for future 'Implementation Research Programmes'. Figure 1 provides the basis for continued improvements in screening over the next 20 years and are the subject of this presentation." We need to have conversations with the public, as to who benefits from lung cancer screening and discuss the basic concept of 'early detection with early treatment, saves lives'. Future Implementation Projects. • Patient engagement / compliance.• Identification of patients in primary care- availability of risk data, integrated Information technology development.• Quality assurance of imagining CT platforms. • Use of liquid biopsies / breath tests in remote populations. • Patient selection utilising risk prediction models – optimising risk models. • Risk of lung cancer in females – re-evaluate based on NELSON mortality data. • Lung cancer Risk in non-smokers, new approaches required. • LDCT scans utilising volume & VDT – improve methodology / reporting. • Coronary Calcium assessment, working with cardiology on treatment pathways. • Use of AI reading of scans - quality control and future Radiology reporting. • Central CT Screening scans reading nationally / internationally. • Identification of the Indeterminate nodules – care pathway utilising integrated radiomics and biomarkers. • Referral to MDT in centers of excellence – potential for spoke & hub care with far-reach communities. • Treatment options / non-surgical – required clinical trials for small CT Screen detected nodules. • Developing new innovative interventive treatment trials in the lung cancer screening pathway, which will be required over the future 20-year

screening programmes. • Continuously monitor mortality and cost effectiveness to improve the service. • Significant other findings/ unexpected findings, integrated pathway of care with primary care for CT screened patients. • Annual / biannual repeat screening based on initial CT Scan reports and patient underlying risks – re-evaluate with new data. • Smoking cessation programmes – review success and adapt for differing populations.

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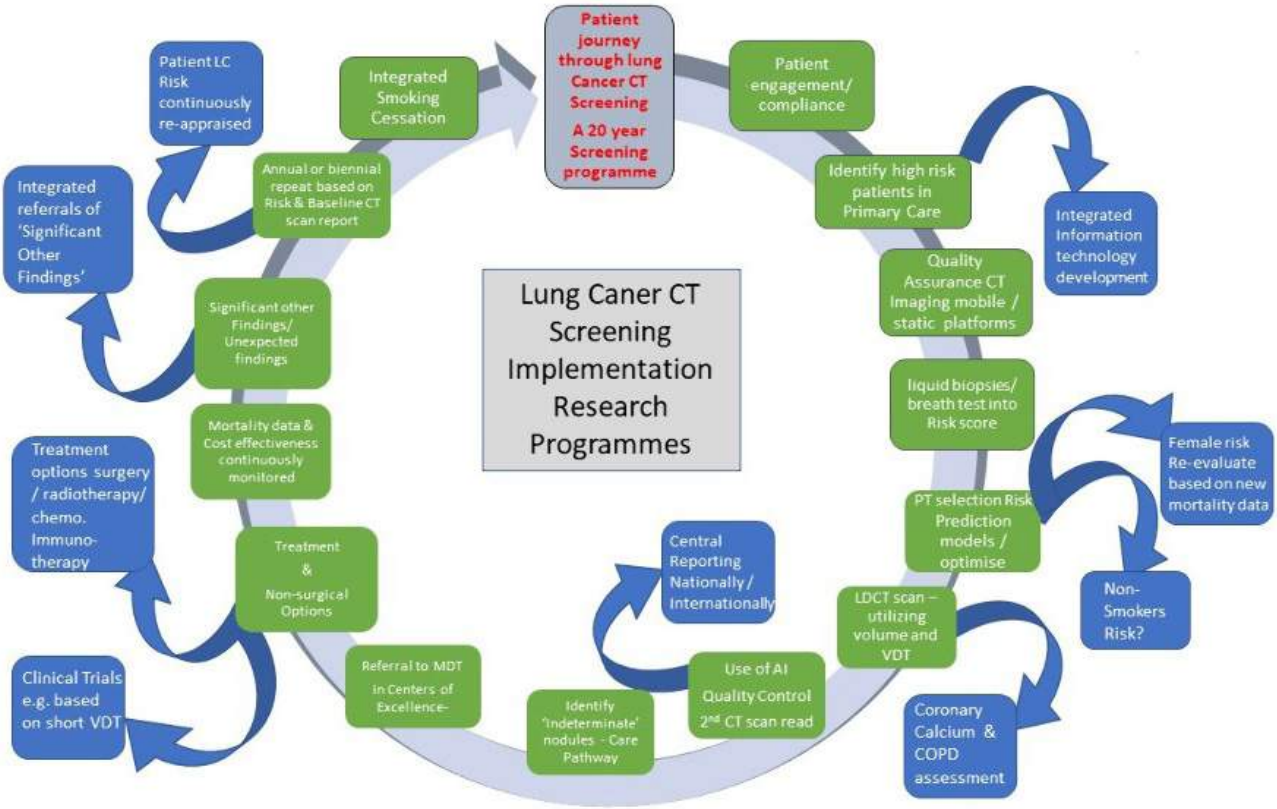
Keywords: Lung Cancer Screening: Implementation research



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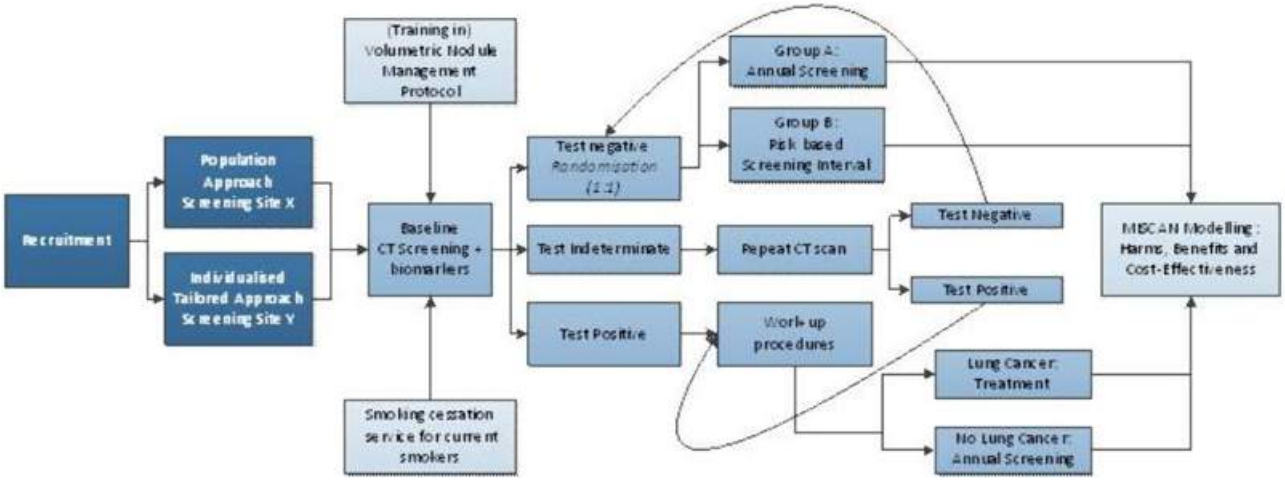
S01.04 LUNG CANCER SCREENING: 2019 – TAKING GLOBAL IMPLEMENTATION FORWARD

H.J. De Koning, C. Aalst

Public Health, Erasmus Mc University Medical Centre Rotterdam, Ca/NL

With 338,000 EU-deaths annually, lung cancer is a devastating problem. Computed Tomography (CT) screening has the potential to prevent ten-thousands of lung cancer deaths annually. The positive results of the Dutch-Belgian screening trial (NELSON), with relatively low referral rates, and the NLST in the USA provided conclusive evidence. However, implementation is likely to be limited, slow and of variable quality throughout Europe, and current guidelines could easily require up to 25 million CT screens annually. The most optimal strategy in risk-based lung and thoracic screening is still unknown regarding the optimal and most cost-effective (e.g., targeted) strategy 1) to recruit, 2) to include smoking cessation and co-morbidity-reducing services in the context of screening, and 3) to determine the (risk-based) screening interval. Personalised regimens based on the baseline CT result can potentially retain 85% of the mortality reduction achievable through screening at 45% less screens, thus potentially saving much unnecessary harm associated with screening, and 0.5-1 billion Euros per year. But we do not know whether it is safe to have risk-based less intensive screening intervals after a negative baseline CT. Various methods to improve participation of hard-to-reach individuals have to be assessed in different healthcare settings. Innovative co-morbidity reducing strategies have to be tested including other markers on CT imaging, as Calcium Score and COPD. Such implementation research is needed to form the evidence base for risk-based lung cancer screening with huge benefits for the EU, on health outcomes, cost savings, and innovation in the long run.



Keywords: implementation, trial, Screening

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S01.07 THE U19 PLANS FOR INTEGRATION OF BIOMARKERS INTO FUTURE LUNG CANCER SCREENING

C. Amos[1], R.J. Hung On Behalf Of The International Lung Cancer Consortium[2], P. Brennan[3]

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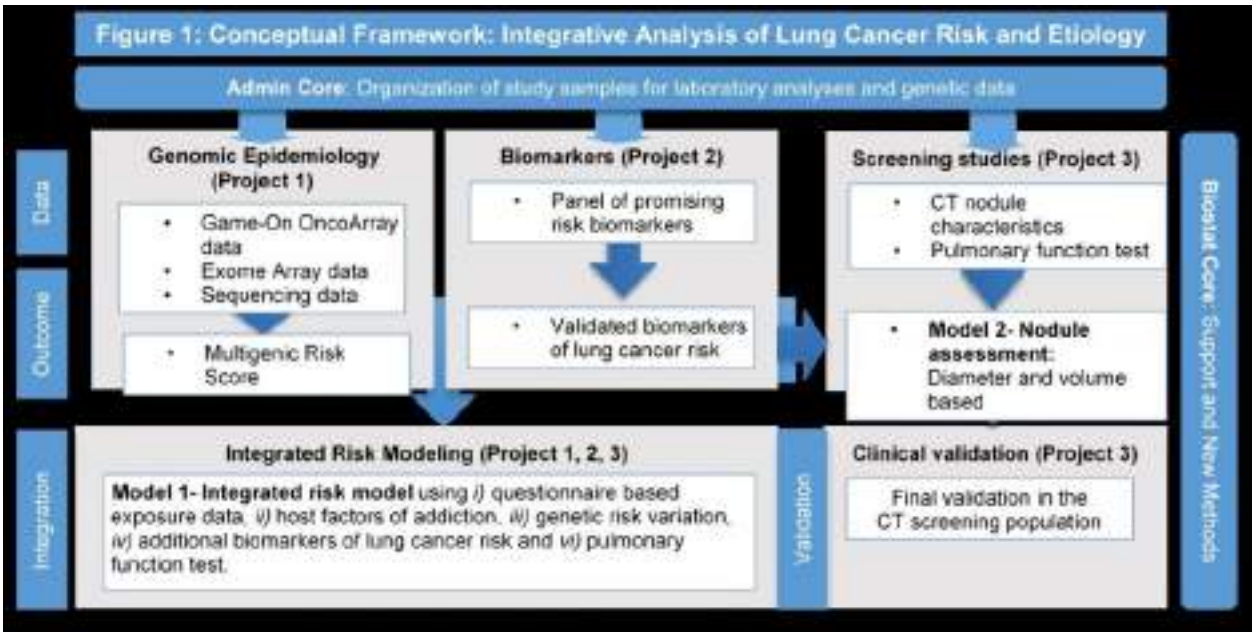
The goal of the U19 Integrative analysis of Lung Cancer Etiology and Risk (INTEGRAL) consortium is to develop biomarkers that characterize individual risk for development and progression from lung cancer. We are using a comprehensive strategy, depicted below in Figure 1, for this analysis and we are drawing on world-wide resources and expertise. There are three projects focusing on i) genetics of smoking behavior and lung cancer risk, ii) biomarker discovery and validation for identifying individuals at highest risk for developing lung cancer and iii) evaluation of these biomarkers in screening cohorts along with radiographic analaysis to evaluate risk for lung cancer development and nodule behavior. There are also administrative and biostatistics cores. We will discuss strategies and novel findings from these projects. For Project 1, to assist in genetic analysis, we have reimputed all the available data from lung cancer cases and controls using the haplotype reference consortium to bring together a data lake comprising data from over 100,000 individuals. The consortium provides data to its members and to collaborators who would like to evaluate hypotheses related to lung cancer by providing access for analyses and we currently are supporting 107 projects evaluating lung cancer risk. Additionally, consortium members from the University of Laval have performed transcriptomic analysis of normal lung tissue from over 500 participants undergoing surgery for lung cancer treatment. We are also studying the role that genetic factors have in influencing smoking behavior by collaborating with other large consortia and by studying multiethnic variation using Hawaiian multiethnic populations. Analyses of the genetic data and further extension to the UK Biobank have identified novel genetic loci that contribute to risk. Interaction analysis of the *CHRNA3/A5/B4* cluster with all other genomic regions identifies interactions with the 15q25.1 nicotinic receptors that influence lung cancer risk. Results identified genes in the neuroactive ligand receptor interaction pathway as playing a key role in increasing lung cancer risk. A cross-ethnicity analysis identified genetic factors in the major histocompatibility complex (MHC) that affect risk for lung cancer. We imputed sequence variation for 26,044 cases and 20,836 controls in classical HLA genes, fine-mapped MHC associations for lung cancer risk with major histologies and compared results among ethnicities. Independent and novel associations within HLA genes were identified in Europeans primarily affecting risk for squamous cell histology including amino acids in the HLA-B*0801 peptide binding groove and an independent HLA-DQB1*06 loci group. In Asians, associations are driven by two independent HLA allele sets affecting adenocarcinoma risk primarily that both increase risk in HLA-DQB1*0401 and HLA-DRB1*0701; the latter was better represented by the amino acid Ala-104. These results implicate several HLA-tumor peptide interactions as the major MHC factor modulating lung cancer susceptibility. A rare variant analysis yielded a mutation of the ATM gene that is rare in all populations except individuals of Jewish descent that primarily increase risk for adenocarcinoma and has highest risk in nonsmoking women. Analyses of smoking and genetic data have identified gene-smoking interactions that contribute to lung cancer risk, and particularly several genes that protect at-risk smokers from lung cancer development. Mendelian randomization and mediation analyses are underway to evaluate novel biomarkers that can be further studied in project 2. This effort found a surprising result that elevated levels of vitamin B12 increase risk for lung cancer development. Project 2 has been bringing together an approach to analyzing biomarkers using data from existing cohort consortia, which have collected samples prior to the clinical presentation of lung cancers. Results of an initial study showed that analysis of 4 circulating proteins (CEA125, CEA, CYFRA 21-1 and pro-SFTB) yielded an area under the receiver operator curve accuracy of 83%. This level of accuracy is sufficient to consider the panel for recruitment of individuals for screening studies, but we anticipate that adding additional biomarkers will further improve the accuracy of risk prediction. Biomarkers that are being further considered include additional protein markers along with micoRNA species, the inclusion of polygenic risk scores and additional serum-derived biomarkers like vitamins B-6 and B-12 that have been shown in mendelian randomization studies to help in identifying high risk subjects. Project 3 is focused on the establishment and validation of the models in the LDCT screening programs. In collaboration with National Lung Screening Trial, Canadian LDCT screening programs, NELSON and United Kingdom Lung Study (UKLS), we have begun the data harmonization across LDCT studies, including clinic-epidemiological data as well as nodule characteristics. We have established a pipeline of feature extractions for the radiomics analysis and compared the inter-reader variability. The intraclass correlation coefficients are >0.75 for the majority of the radiomics features extracted. We will conduct cross-study validation for the model building to ensure the maximum generalizability of the model. We will start the work on biomarkers and assess their added values in these models.



Keywords: biomarkers, genetics, early detection

S01.11 FRAMING CURRENT STATUS

D. Yankelevitz

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CT screening has gained increased acceptance due to results from recently reported randomized controlled trials. Nevertheless, there continues to be concerns regarding the benefits. Articles continue to appear describing a very marginal benefit versus harms. This concern has likely impacted its uptake both in the US and globally. There is a strong need to rethink what is the relevant information to provide to a person interested in screening. The most obvious answer would related to their frequency of being diagnosed with a potentially life threatening cancer and then how curable it would be if found early by screening versus later when symptom prompted. Without knowing these specifics there is no rational way to make a decision. Nevertheless, this type of information is not routinely available and is commonly misrepresented in the literature. It is vital that people understand that lung cancer can be found early in the majority of cases and that surgery is curative in the majority of them as well. Another aspect of screening that directly affects the overall usefulness relates to the management of screen detected findings. Currently there are several different protocols that are being used. It will be important to be able to learn from each of these how well they perform and in particular, which aspects of the protocols work best. Some standardized measure that compares their efficiency would be useful. This not only would apply to the management schemes but also to the various software that is being applied. The use of volumetrics has been gaining continued acceptance, but it has different roles, it can be used for setting size thresholds and also looking for change over time. Each of these represent important areas that can have a large impact and both aspects need to be studied separately. Finally there is continued advancement in our ability to look for other findings on the same basic scan. The overall benefits that are likely to come about as a result of the screening process will extend to other illnesses and how this will be integrated into an overall assessment of benefit should be a high priority for those interested in screening.

Keywords: Protocols, Screening, volumetrics

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S01.14 LUNG CANCER MDT

D. Baldwin

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The Lung Cancer MDT David R Baldwin Consultant Respiratory Physician and Honorary Professor of Medicine Nottingham University Hospitals and University of Nottingham, UK Multidisciplinary Team (MDT) meetings or “Tumour Boards” are increasingly becoming a central component of lung cancer services. Management of lung cancer patients through diagnosis, staging, fitness assessment and treatment is a multidisciplinary endeavour. Good communication between disciplines means that the goal of personalised treatment can be realised because of the complexity of modern management, not least the rapid change in treatments. Many lung cancer services have a meeting of professionals at key points along the clinical pathway that is commonly at the point of decision to treat and where diagnosis and/or staging is complex. There are a number of documents that describe the membership of the MDT and how the meetings should function. Key is that all relevant professional groups are represented and that there is a clear record of the discussion. Despite the widespread adoption of MDT meetings, there remains limited evidence for their effectiveness. This is because the integration of MDTs into the lung cancer services has evolved as management has become increasingly complex. It would be difficult to devise an experiment to test the efficacy of the MDT as they are now so embedded in services. With respect to lung cancer screening, it is important that MDTs adhere to guideline-driven management so as to reduce the harms that may accrue. The place of the lung cancer MDT is in relation to a high probability of cancer. In screening it is probably better to have a separate MDT to advise on the management of nodules and incidental findings, again using guideline-driven management. All MDTs should record data for audit, quality improvement and research.

Keywords: Guideline-driven, Multiprofessional, multidisciplinary team

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S01.15 SERVICE REQUIREMENTS; STAFF AND PLATFORMS AVAILABILITY

H. Schmidt

University Health Network, Alberta/Canada

Lung cancer screening encompasses a pathway that includes several integral elements. It starts with the active recruitment of individuals and their risk assessment. The pathway continues into radiology, with the actual scanning using low dose computed tomography (LDCT), as well as standardized reporting that focuses on the follow up of both lung nodules and incidental findings. At the end of the pathway is the seamless integration into a diagnostic assessment program for confirmation and timely and appropriate treatment of the detected lung cancer. High quality, and quality assurance of the radiology performance is the central piece in this pathway, to decrease the harm from radiation and false positives. Since lung cancer screening is most often a newly established program in an institution, this presents a unique opportunity to build robust quality standards for radiology. Radiology quality assurance comes with requirements regarding acquisition, interpretation and reporting of the low-dose computed tomography (LDCT) scans. The facility standards need to provide equipment that does allow low dose data acquisition. Scanning protocols need to be defined, and protocol compliance needs to be assured, radiation exposure needs to be regularly measured with phantoms, and image storage needs to be properly identified. Personnel requirements cover both the technologists and the reporting radiologists. Both have to provide the necessary training and certification. Radiologists need to document their ongoing experience in chest reporting, participate in a workshop or alternative training regarding nodule follow up, and get familiar with the respective reporting template. Radiologists training programs have received positive feedbackon content, their goal is to increase confidence in reading lung cancer screening LDCTs and appropriate recommend follow up for screen-detected nodules. Complex cases are collected and their discussion fosters mutual learning. Ongoing quality assurance measures include peer review and double reads, to minimize false positive. An adjudication process can provide expert opinion and support learning where consensus can not initially be reached. Report completeness should be confirmed with regular audits. All these requirements should be available and met by a facility planning to engage in lung cancer screening using LDCT. All above standards are available; they need to be monitored, must be met at baseline and during tailored annual assessments, ensuring compliance across screening sites. In summary, the implementation of a robust quality assurance program assures a high standard around the radiology workflow, from LDCT scanning to image interpretation and follow up recommendations. Radiologist training programs, centre minimum requirements, and standardized reporting can ensure that quality standards are consistently high

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S01.17 SMOKING CESSATION

R. Murray

University of Nottingham, Nottingham/United Kingdom

More than 85% of cases of lung cancer are caused by tobacco smoking, and stopping smoking, at any age, significantly reduces lung cancer risk. Despite positive findings reported by the National Lung Screening Trial (NLST) and the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON), a number of important questions remain regarding the best way to implement lung cancer screening (LCS), including how most effectively to embed smoking cessation interventions (SCI) into these programmes. One concern that has been raised around LCS for current smokers is the potential 'moral hazard' arising from a negative (i.e. reassuring) screening result, which may reduce motivation to quit. Conversely, attendance at a lung cancer screening programme offers a 'teachable moment' for smoking cessation, occurring at a time when participating smokers may be particularly receptive to offers of help to quit. Indeed, a negative screen result has been reported as being perceived as a 'clean slate' as a motivator to stop smoking. Evidence suggests that smoking cessation and low dose computed tomography (LDCT) screening have additive effects on survival; an analysis of participants in the NLST reported a 38% reduction in lung cancer mortality with the combination of smoking abstinence at 15 years with LDCT screening. Further, research has indicated that adding SCIs to LCS improves the cost effectiveness of such programmes. It is, therefore, essential that any lung cancer screening programme provides smoking cessation support for participants. Clinical guidelines regarding delivery of smoking cessation interventions in the context of LCS have been produced by the Association for the Treatment of Tobacco Use and Dependence and The Society for Research on Nicotine and Tobacco, but this document acknowledges the paucity of data and need for future research specific to this patient population. Participants in LCS are unlikely to be representative of the general population of smokers, and evidence regarding smoking cessation outcomes in a lung cancer screening (LCS) context is variable. There is some evidence to suggest that participation in LCS alone may increase smoking cessation rates above that of the general population, influenced by screening outcomes. However, comparisons between smoking cessation outcomes in screened and control populations in a number of studies have reported inconsistent findings. There is limited proven effectiveness of low intensity SCIs delivered as part of LCS programmes. When comparing such interventions delivered to smokers attending for LCS, there appears to be no difference between standard written advice, internet resources, quitline details or brief advice. However, more intensive interventions such as telephone-based counselling sessions have been shown to be more effective than self-help cessation resources and a combination of cognitive behavioural therapy and pharmacotherapy have shown further promise. Little research exists as to the potential benefits of e-cigarettes for cessation in this setting but given their increasing popularity as a cessation aid this requires further attention. Delivery of a more intensive intervention at the time of screening may be viable; one recent study reported that it was feasible to deliver a single tailored session of motivational interviewing counselling on the day of screening. Smoking cessation studies from other settings mayprovide learnings transferrable to the LCS setting. Personalised interventions for smoking cessation are generally more effective than standard approaches. the presence of emphysema and coronary artery calcification may be incidental findings from LDCT scans that could be used as part of an SCI in the LCS setting. This may be particularly pertinent where participants are fit, relatively asymptomatic and hence potentially more susceptible to a message that lung damage had already occurred but clinical impact could be reduced by stopping smoking (as may be the case in LCS attendees). Relatively few studies have tested interventions for smoking cessation in LCS settings, and are subject to large variations in timing, setting, participants, SCI and outcome measures which does not allow direct comparison between studies and makes it difficult to draw conclusions regarding optimal interventions. However, it is likely that higher intensity interventions will be more effective and the use of incidental scan findings should be considered. Much research into the best way to integrate SCIs into LCS is now ongoing in an attempt to answer the outstanding implementation questions. The SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration in the US consists of eight clinical trials which seek to build an evidence base for effective interventions in LCS, using a common core of data collection measures to allow pooling of data and comparison across studies. In the UK, the Yorkshire Enhanced Stop Smoking study (YESS) seeks to test the delivery of an intensive SCI, co-located with the Yorkshire Lung Screening Trial (YLST) and personalised to the LCS result. Data from these studies will hopefully add clarity to the question of how best to reduce morbidity and mortality amongst those presenting for LCS.

Keywords: smoking cessation, lung cancer screening

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S01.18 COST EFFECTIVENESS

B. Pyenson

Milliman, Inc., New York City/United States of America

There is broad consensus that lung cancer screening with low-dose CT is cost-effective. However, there has been slow take-up in the US where it is covered by commercial insurance and by the federal Medicare program. One way to optimize LC screening is to consider screening as part of an integrated program that specializes in population health for the cluster of smoking-related illness. There are four components of this, LC screening centers can provide high-quality screening and systematic follow-up and appropriate referrals Imaging for LC screening can quantify cardiac calcification, COPD, and osteoporosis, all of which may be associated with smoking LC screening centers can operate as a center for smoking cessation, exercise counseling, and adherence support For the 1.5 million annual indeterminant pulmonary nodules in the US, LC screening centers can provide appropriate follow-up. The vast majority of such cases receive no follow-up. There are both economic and financial consequences for integrated screening. The economic consequences are measured in cost-effectiveness. The financial consequences are attracting high-utilizing people away from lower-quality providers, which can offset the loss of income from treating late stage lung cancers.

Keywords: screening cost-effectiveness financial

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S01.19 BIOMARKERS

P. Brennan, M. Johansson, H. Robbins

International Agency for Research on Cancer, Lyon/France

Improved risk stratification has the potential to enhance the ratio of benefit to harm for lung cancer screening. Risk biomarkers for lung cancer have been identified that have the potential to contribute to risk stratification, and efforts in this area are ongoing, although whether they are practical or cost-effective remains to be clarified. Recent progress in the use of biomarkers for lung cancer risk stratification and their cost-effectiveness will be discussed. References Guida F, et al. .Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer, Assessment of Lung Cancer Risk on the Basis of a Biomarker Panel of Circulating Proteins. JAMA Oncol. 2018 Oct 1;4(10) Robbins HA, et al. .Benefits and harms in the National Lung Screening Trial: expected outcomes with a modern management protocol. Lancet Respir Med. 2019 May 7

Keywords: Lung cancer, biomarkers, risk

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S01.20 HOW WILL SUCCESS WILL BE JUDGED

K. Fong[1,2], H. Marshall[1]

[1]*University of Queensland, Chermside/Australia,* [2]*The Prince Charles Hospital, Chermside/Australia*

For instance, for a screening proponent, the implementation of a population based CT screening program may signify success, whereas the opposite conclusion will be drawn by those not swayed by the available evidence on lung cancer screening. From a technical viewpoint, as screening refers to the application of a test to a population which has no overt signs or symptoms of the disease in question, to detect disease at a stage when treatment is more effective. The technical effectiveness of CT screening can be viewed as its ability to detect the presence or absence of lung cancer, sensitivity, specificity, True and False positives, True and False negatives. From a CT screening program perspective, the metrics may include: · Participation (where it relates to an appropriate level of access and participation of people in the target and eligible population) · Cancer detection rates · Safety and harm minimisation (potential harm, either physical or emotional, is minimised) · Timeliness (providing access to screening and assessment services in a timely and efficient manner) · Client focused From an economic point of view, success may be a measure of the balance of the costs of screening (costs of the test and subsequent diagnostic tests and the costs associated with any hazard of the test as well as the costs of over-treatment) to reduced costs of therapy (costs associated with less expenditure on the treatment of the advanced disease, and the economic value of the additional years of life gained) For the policy maker, the metrics of success will include budgetary management, degree of realised benefit for the population targeted in the context of health care funding for other conditions (eg incidence and mortality), opportunity costs and population health measures, and adherence with their national screening policy Here we discuss the nuances of selecting metrics for lung cancer CT screening to inform our considerations for the multiple circumstances that make up the pragmatisim of real life.

Keywords: Lung cancer, Screening, metrics

S01 IASLC CT SCREENING SYMPOSIUM: FOREFRONT ADVANCES IN LUNG CANCER SCREENING (TICKETED SESSION)
SATURDAY, SEPTEMBER 7, 2019 07:00–12:00

S01.23 EVOLUTION OF ELIC

R. Avila

Accumetra, LLC, Clifton Park/United States of America

The Early Lung Imaging Confederation (ELIC) Hub & Spoke Environment (H&SE) is a new globally distributed and open source lung cancer imaging database and computational analysis environment designed to significantly improve the cost, time, and quality of lung cancer imaging research. This IASLC led initiative and computational infrastructure project, when fully deployed, will allow clinical research groups (Spokes) to securely make their locally stored de-identified lung cancer imaging collections available for computational analysis by other research groups (Clients), all coordinated by a central IASLC managed server (Hub). Clinical sites will be able to make lung cancer imaging data available for specific types of computational analysis without transmitting the imaging data over national boundaries to other groups and losing control over how the data is used and further distributed. This allows lung cancer screening research groups to more easily make available datasets to large global lung cancer imaging research studies with far more control over data use. This federated data storage and analysis approach will allow the ELIC H&SE to scale to much larger data sizes than a traditional centralized database, one day allowing lung cancer imaging researchers to quickly and easily perform quantitative analysis on global lung cancer imaging studies with larger collections of high quality, standardized data than is attainable today. This is viewed as a critical next step for the development of next generation Artificial Intelligence algorithms for lung cancer imaging, which require large amounts of data for algorithm development and performance evaluation. In preparation for the 2018 IASLC WCLC meeting in Toronto, Canada, a proof-of-concept ELIC Hub and Spoke Environment was developed and set up using Amazon Web Services (AWS) cloud resources. A hub was set up on a Virginia AWS cloud instance and 10 spokes, each pre-populated with an identical set of 100 de-identified CT lung scans, were set up at 10 globally distributed AWS cloud locations including Mumbai, London, Frankfurt, Montreal, Sydney, Tokyo, Paris, Seoul, Sao Paulo, and Virginia (on a separate cloud instance). Two open source lung cancer imaging algorithms, one that automatically computes lung volume for a thoracic CT scan and another for volumetric measurement of small lung nodules, were made available for use by the 10 spoke instances. Live demonstrations of the proof-of-concept system were shown at the 2018 WCLC meeting including the ability to launch computational experiments and receive back quantitative results from the 10 globally distributed spokes. Figure 1 shows the global distribution of the hub and spokes for the 2018 WCLC ELIC proof of concept demonstrations. The live demonstrations showed that the ELIC H&SE could be used to select globally distributed datasets available on the spokes for analysis, run specific computational algorithms on those datasets, and have all of the results aggregated in real-time for viewing on the hub, as shown in Figure 2. The ELIC

H&SE infrastructure is now undergoing further development in 2019 to bring it from a proof-of-concept demonstration to a functional globally distributed database and computational environment capable of performing useful quantitative lung cancer imaging studies. References to tools and resources for performing data de-identification and encryption are being added to support research groups that will be uploading lung imaging datasets and metadata into the ELIC H&SE. Standards for lung cancer screening data representation, starting with a lung cancer screening data dictionary developed by the VA-Partnership to increase Access to Lung Screening (VA-PALS) project, are also being added to ensure that global analyses can be performed with common terminology and data formats. In addition, the Radiological Society of North America's Quantitative Imaging Biomarker Alliance (QIBA) small lung nodule conformance certification phantom, specifications, and methods are being used to help lung cancer screening sites prospectively collect, monitor, and optimize lung cancer imaging studies for high quality volume measurements. All of these resources and formats are planned to be reviewed with all ELIC stakeholders on a quarterly basis to receive feedback and refine the systems and methods. There are numerous functionality advantages for spokes that use local cloud computing resources including significantly improved security for both clients and spokes, improved computational efficiency through on-demand cloud resourcing, and continuously updated hardware and infrastructure. Additional software development is underway that will allow ELIC to achieve these advantages for cloud-based deployments. Live demonstrations are again planned for the 2019 IASLC WCLC meeting in Barcelona, Spain showing an early demonstration of a new iaslc-elic.org website capable of supporting both spokes and clients performing globally distributed lung cancer imaging research studies.

Figure 1: The global distribution of the hub and spokes for the 2018 WCLC ELIC proof-of-concept demonstrations.

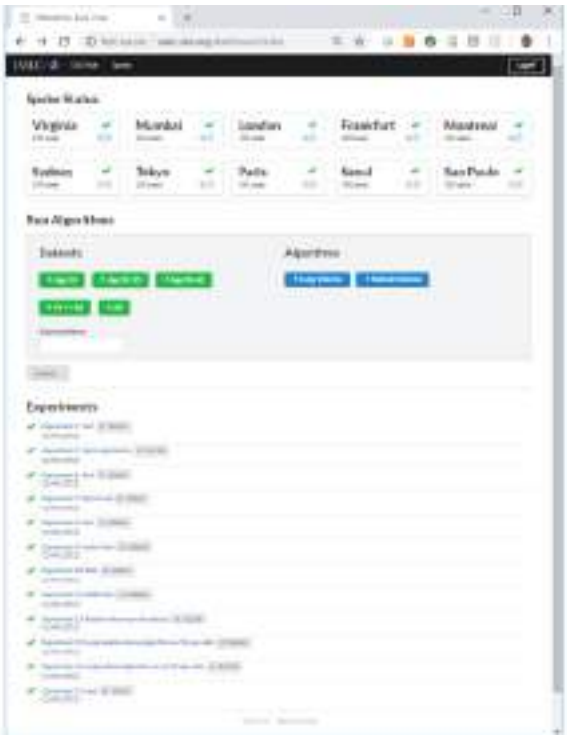


Figure 2: ELIC H&SE live demonstration screenshots showing the ability to view spoke status, select globally distributed datasets for analysis, and view a list of completed experiments (left) as well as drill down and view statistical experiment results including computationally generated images (right).

Keywords: Lung Cancer Imaging, lung cancer screening, Computed tomography

S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.01 INTRODUCTION

I. Wistuba

The University of Texas MD Anderson Cancer Center, Houston/United States of America

Dr. Adi Gazdar was a scientific pioneer, a groundbreaking pathologist, loyal friend and inspiring mentor. Dr. Gazdar was born in India; he earned his medical degree from Guy's Hospital Medical School at the University of London and completed residencies in pathology at Peter Bent Brigham Hospital and New England Deaconess Hospital in Boston before joining the NCI in 1968. During his remarkable five-decade career, Dr. Gazdar served 23 years with the National Cancer Institute (NCI) a senior scientist and section head. His NCI experience included initially leading its Viral Pathology Section; the Human Tumor Cell Biology Laboratory for the NCI's VA Medical Oncology Branch from 1975 to 1981; and then the Human Tumor Cell Biology Section for the NCI-Navy Oncology Branch from 1981 to 1991. His team collected, cataloged, and analyzed thousands of human cancer specimens with an emphasis on lung cancer and lymphomas. In 1991, he joined his long-time colleague Dr. John D. Minna at the University of Texas Southwestern Medical Center, Dallas, Texas, where he had a distinguished 27-year career as professor of pathology as the W. Ray Wallace Distinguished Chair in Molecular Oncology Research, and deputy director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research. Dr. Gazdar's efforts in the laboratory yielded the first large panel lung and breast cancer cell lines, used by investigators around the world, and he developed molecular methods for detecting early lung tumors. Dr. Gazdar also identified several genes involved in the pathogenesis of different cancers. In lung cancer, he uncovered mutated genes dysregulated by mutation and DNA methylation, provided some of the first work characterizing neuroendocrine cancers such as small cell lung cancer, and played a major role in the discovery of the mutated epidermal growth factor

receptor (*EGFR*) gene as a therapeutic target in lung cancer arising in never-smokers. During his long career, Dr. Gazdar published about 800 articles, book chapters and commentaries, and has been cited over 110,000 times, ranking him among the top 1% of scientists in the biomedical field. His numerous honors and recognitions include a 2004 award from the prestigious Jacqueline Seroussi Memorial Foundation for Cancer Research in Israel and the 2003 Mary J. Matthews Pathology/Translational Research from the International Association for the Study of Lung Cancer (IASLC). Dr. Gazdar was an inspirational role model for many young scientists mentoring over 100 post-doctoral fellows from around the world. IASLC established the Adi Gazdar Translational Research Fellowship Award on 2017 to honor his legacy in lung cancer training.

Keywords: Pathology, Molecular Pathology, Legacy

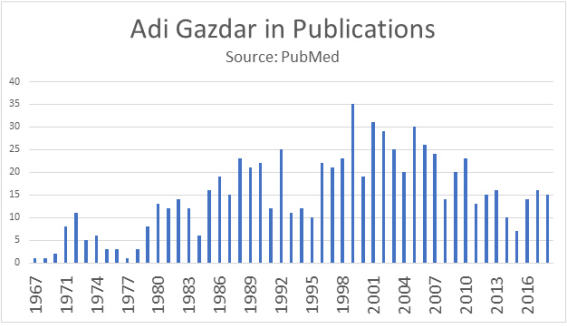
S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.02 ADI GAZDAR'S LEGACY

P. Ujhazy[1], M. Antman[1], C. Burgess[1], J. Mulshine[2]

[1]*National Cancer Institute, Rockville/United States of America,* [2]*Rush University, Chicago/United States of America*

Adi F. Gazdar (1937-2018) belongs to the 150 most successful scientists of all time. His impact in cancer research, virology, molecular pathology, cell biology, and many other disciplines was immense. A giant in lung cancer research, Dr. Gazdar pioneered numerous concepts and his work was seminal in the establishment of the current standard of care. He will be remembered as a prolific innovator, respected mentor, valued collaborator, and an altruistic human being. Here we will quantify the scientific legacy of Dr. Gazdar using various bibliometric analyses. The impact of Dr. Gazdar's work was evaluated with the use of a panel of bibliometric tools including PubMed, iSearch, iGrants, iCite, Google Scholar, Web of Science, Clarivate Analytics, and Dimensions. Adi Gazdar has published more than 700 scientific publications that were cited more than 120,000 times, his H index is 171, and his most cited paper has more than 4000 citations (see Figure 1).



His Weighted Relative Citation Ration (RCR) since 1994 is 1,283 with a mean RCR of 2.78 and median 1.33 per publication. By disciplines, most of his publications are in oncology, followed by studies on the respiratory system, cell biology, pathology, biochemistry and molecular biology, experimental medicine research, genetics, internal medicine, and biology. By scientific topics Dr. Gazdar published on lung cancer (small cell and non-small cell), tumor suppressor genes, viruses, breast cancer, allele loss, DNA methylation, risk factors, T cells, colorectal carcinoma, model systems, and growth factors and others. Many of his papers are related to drug development and testing and he published more than 10 papers on each of the following agents: decitabine, cisplatin, gefitinib, azacytidine, etoposide, insulin, doxorubicin, erlotinib, levodopa, tretinoin, and cyclophosphamide. Perhaps the most impact of Dr. Gazdar's work had the creation and distribution of cell lines and models that allowed to characterize the retroviral particles in patients with T-cell lymphoma, test virtually all current chemo and targeted therapy agents used in the treatment of lung cancer, and define molecular subtypes of small cell and non-small cell lung cancers that are currently used in diagnosis. The National Cancer Institute US in collaboration with a team at the University of Texas Southwestern are currently assessing the tremendous impact that these cell lines had on all aspects of lung cancer research and standard of care. This Stewardship Project is led by Dr. James Mulshine from Rush University.

The preliminary data generated by this project indicate that Dr. Gazdar's 278 lung cancer cell lines led to 33,207 publications, which were cited 2,968,974 times, referred by 4,700 patents, linked to 422 clinical trials, and produced 14,057 supporting grants by 1,019 funders world wide. An example for the most cited cell line H460 is in Figure 2. This cell line itself had 11,124 publications cited 347,117 times, was mentioned in 1,564 patents, was linked to 118 clinical trials and 4,890 grants funded by 717 organizations. Doctor Adi F. Gazdar left behind an immense wealth of work that has changed cancer research and standard of care.

Keywords: Gazdar, bibliometrics, Lung cancer

S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.03 THE IMPACT OF CELL LINE DEVELOPMENT IN LUNG CANCER RESEARCH

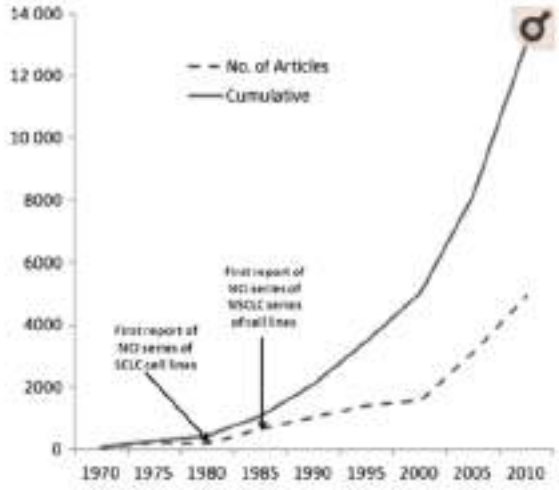
P. Bunn, Jr

Univ. of Colorado Cancer Center, Aurora/United States of America

Advances in Lung Cancer Research using patient derived cell lines and xenografts In the 1970s there were few lung cancer preclinical models and therapy selection was generally empiric. When the NCI established a branch to specifically study lung cancer (the NCI-VA Medical Oncology Branch) a systematic effort to establish permanent lung cancer cell lines with orthotopic implantation into athymic mice was implemented. The branch was led by Dr. John Minna and the cell line efforts were led by Dr. Adi Gazdar. The cell lines were given sequential numbers starting from NCI-H1 indicating the NCI origin and that they were human cell lines. Figure 1 shows how often these lines have been use in publications on lung cancer. These lines were initially used to study various chemotherapy agents and combinations such as the etoposide/cisplatin in small cell lung cancer (SCLC) xenografts. The expression of multiple proteins such as CD56 and many neuropeptides distinguished these SCLC cell lines from NSCLC cell lines. Originally it was recognized that most SCLC cell lines grew as floating aggregates but that s minority grew attached to the plastic. These later cell lines were termed "variant" lines were as the floaters were called "classic". Essentially all of the lines had p53 mutations and loss of Rb. More recent studies indicated that the classic lines highly expressed neuroendocrine features. The variant lines more often had amplified myc. a new model of SCLC subtypes defined by differential expression of four key transcription regulators: achaete-scute homologue 1 (ASCL1); neurogenic differentiation factor 1 (NeuroD1), yes-associated protein 1 (YAP1) and POU class 2 homeobox 3 (POU2F3). These high NE SCLC cell lines and tumors also expressed *NKX2-1*, the entire range of NE markers, and lacked expression of the neuronal and NE repressor REST. The low NE subtype had undergone epithelial mesenchymal transition (EMT) and had activated the Notch, Hippo and TGFβ pathways and MYC oncogene. Recent studies found that 16% of human SCLC tumors and 10% of SCLC cell lines were of the low NE subtype, as well as cell lines from the GEM model. Synaptophysin was a more commonly expressed marker for variant SCLC cell lines, which rarely showed Dopa decarboxylase activity. These cell lines and patient samples were also used to describe the expression of N-Myc and L-Myc in small cell lung cancers. Reports demonstrated that 6 of 31 independently derived human small-cell lung cancer (SCLC) cell

lines had 5- to 170-fold amplified N-myc gene sequences. A third myc-related gene (L-myc) cloned from SCLC DNA with homology to a small region of both the c-myc and N-myc genes. SCLC cell lines may prove useful in defining patients most likely to benefit from immunotherapy. For example, human SCLC cells, in contrast to other lung cancer types, are characterized by greatly reduced transcription of HLA-A,B,C and beta 2m genes, which suggests the existence of a mechanism for evading the host immune response to the tumor and of an E1a-like product in this type of tumor cell. Cell lines with myc amplification were shown to be especially sensitive to aurora kinase inhibitors. The human lung cancer cell lines were also used to define many of the genetic, proteomic and transcription features of lung adenocarcinomas, squamous carcinomas and large cell carcinomas. Early studies demonstrated a significant correlation between EGFR gene copy number, EGFR gene mutations, and gefitinib sensitivity. EGFR protein was necessary but not sufficient for predicting sensitivity. Gefitinib-sensitive lines showed a G(1) cell cycle arrest and inactivation of downstream signaling proteins; resistant cell lines had no changes. The in vivo effects mirrored the *in vitro* effects. Cell lines have also been used to study EGFR exon 20 mutations and HER2 mutations. HER2(YVMA) mutations were shown to activate cellular substrates more potently than HER2(WT); and that lung cancer cells expressing this mutation remain sensitive to HER2-targeted therapies but insensitive to EGFR TKIs. HER2 mutations were in-frame insertions in exon 20 and target the identical corresponding region as did EGFR exon 20 insertions.HER2 exon 20 insertions were shown to be sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. EGFR-mediated bypass signaling has been reported after ALK and ROS1 blockade as well as RET and NTRK1 blockade. EGFR signaling provided a critical adaptive survival mechanism that allows cancer cells to evade oncogene-specific inhibitors, providing a rationale to co-target The RAS-MAPK dependence was shown to be a hallmark of EML4-ALK lung adenocarcinoma and provided a rationale for the upfront inhibition of both ALK and MEK to forestall resistance and improve patient outcomes. Dr. Gazdar and colleagues also developed a method to reproducibly generate continuously replicating human bronchial epithelial cell (HBEC) lines that provide a novel resource to study the molecular pathogenesis of lung cancer and the differentiation of bronchial epithelial cells. In summary, human lung cancer cell lines have contributed greatly to the development of novel biomarkers and therapies for lung cancer and much of the work stemmed from early development by Dr. Gazdar and his team at the NCI.

Figure 4



Number of citations for human lung cancer cell lines. Data were obtained from a search of the PubMed database from within the EndNote program by use of the medical search heading terms "lung neoplasms", "cell line, tumor", and "humans." The cumulative number of citations and the number of citations per 5 years are shown. The results are from a search performed in June 2010. NCI = National Cancer Institute; NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer.

Keywords: lung cancer cell lines, targeted therapy, molecular drivers

SYMPOSIA

S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.04 DR. GAZDAR AS A MENTOR

T. Mitsudomi

Kindai University Faculty of Medicine, Osaka-Sayama/Japan

It was September in 1989 when I joined the NCI-Navy Medical Oncology Branch as a postdoctoral fellow. At that time, I was in my 10th year as a surgeon. The reason why I wanted to join the NCI-Navy was that I was greatly fascinated by the book entitled "The Biology of Lung Cancer" published by Marcel Dekker authored by many of the NCI-Navy MOB investigators. Especially, I was attracted by experimental works that used many lung cancer cell lines established by Adi's group. When I first met Adi, my impression was that he was a calm and quiet person. My first project was to characterize peripheral airway cell phenotype in the adenocarcinoma cell lines by examining the expression of surfactant proteins as well as class II MHC. But I did not like this project and after 2 months or so, he agreed to change my theme to KRAS or TP53 mutations in lung cancer cell lines. He never pushed me to do or not to do something and never became emotional. I was deeply immersed in the research to look for the clinical and pathologic significance of those genetic abnormalities in lung cancer. This was what is called "translational research" today. I thought I could find what I should pursue throughout my life as a lung cancer doctor. It is obvious that without this experience and Adi, my life would have been so different. In addition, human network owing to Adi has been a precious treasure for me. One day in 1990, he gave me a paraffin block of bronchial biopsy sample and told me to search for TP53 mutation. It is currently a routine diagnostic workup to examine genetic alterations in the biopsy samples when you see lung cancer patients. It was as if he had known what would be the future diagnostic workup before 30 years. During this fruitful time of my life, I am so proud that I was able to co-authored 18 papers with Adi. After coming back to Japan, I saw Adi occasionally but periodically at various meetings such as the AACR, ASCO, ELCC and especially WCLC. Every time, he encouraged me to pursue my goal and gave some suggestions on my experiments. When Adi was to edit a special issue on Lung Cancer in Never Smokers in Translational

Lung Cancer Research in 2018, he invited me to write about GGO lesions in never smokers. It was the last homework that he assigned to me. I am going to organize the Annual meeting of the Japanese Lung Cancer Society in December 2019. When I talked to him and his wife Celia at the Toronto WCLC meeting in 2018, Adi promised me to come to Japan to give a lecture. That was our last conversation. The promise has been broken and I really miss him. Adi. Please rest in peace. There are many of your children all over the world who have inherited your spirit as a lung cancer researcher.

Keywords: Translational research, mentor

S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.05 THE IMPORTANCE OF ELUCIDATING GENOMIC EVENTS IS LUNG PREMALIGNANCY

K. Fong

The Prince Charles Hospital, Chermside/Australia

In contrast to the dramatic explosion of knowledge for cancer genomics such as trunk/branch; driver/passenger; intrinsic/acquired mutations from rapid technological developments, much work is still needed in the study of preneoplasia. Very sadly, lung cancer research around the world in 2018 lost a legend in preneoplasia research, Dr Adi Gazdar, who has either trained or worked with many of the scientists contributing to recent lung preneoplasia research. This is in addition to his enduring contributions establishing globally used lung cancer cell line resources and making lung cancer pathology discoveries. This research area owes much to pioneering work started over 20 years ago when Dr Gazdar, Dr John Minna and colleagues started thinking about preneoplastic molecular changes and field cancerisation (Smith, Hung et al. 1996, Yashima, Litzky et al. 1997). Subsequently, he and his former-post-doctoral Fellow Igancio Wistuba, another world renowned pathologist, summarised the main morphologic forms of preneoplastic lung lesions recognize then; squamous dysplasias, atypical adenomatous hyperplasia, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, and highlighted different molecular pathways for adenocarcinoma: smoking-associated activation of RAS signaling, and nonsmoking-associated activation of EGFR signaling; the latter is detected in histologically normal respiratory epithelium (Wistuba and Gazdar 2006). It is clear that there has been steady progress in lung preneoplasia research, with the hope of translation to human benefit through prevention and/or early diagnosis. Many scientists in the field of lung preneoplasia have been influenced by the foundational work from Dr Adi Gazdar, scientist, pathologist, teacher and friend to many of us. The ability to diagnose pre- neoplasia at its earliest stages will help enable the development of novel diagnostic, prevention strategies and therapeutics during the process of carcinogenesis when clinical intervention could be curative; a laudable goal in lung cancer where most cancers are now clinically diagnosed in advanced stages.

Keywords: lung cancer, preneoplasia, Adi Gazdar

S02 SYMPOSIUM HONORING DR. GAZDAR'S LEGACY
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 17:30–19:00

S02.06 NEW DEVELOPMENTS IN SCLC AND NEUROENDOCRINE TUMORS

L. Byers

The University of Texas MD Anderson Cancer Center, Houston/United States of America

In an IASLC memorial earlier this year, Dr. Gazdar was very appropriately described as "a true giant in the field of lung cancer." Dr. Gazdar's profound impact on our field continues to be felt both in the clinic and at the bench. As a world-renowned molecular and clinical pathologist, he played a key role in setting the standards for classifying human lung cancers. As a scientist, he established ~400 human cancer cell lines. These included a large number of molecularly-annotated non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) cell lines that have led to countless, practice-changing biological discoveries. As a founding-father of lung cancer research, he had a remarkable depth of knowledge in lung cancer biology and pathology. He shared his expertise through hundreds of publications. However, he also gave generously of himself (and his knowledge) to collaborators and mentees – serving as an advisor and teacher to almost everyone in the field who had the opportunity to be around him. Having contributed to key discoveries over five decades, Dr. Gazdar intuitively understood which new developments were likely to make the biggest impact and what questions we should be asking next. This was especially true for small cell lung cancer (SCLC) and other neuroendocrine tumors, where despite years of research there had been relatively few advances in the clinic. In a review published a year before his death, Dr. Gazdar and his co-authors shared their excitement for the recent worldwide resurgence of SCLC research – which they describe as "The Second Golden Age" of SCLC research.1 Several new developments in SCLC and neuroendocrine tumors have contributed to a better understanding of the disease and have shown promise for translational application. These include the discovery of (1) significant heterogeneity between patients with SCLC, (2) the plasticity of SCLC over time, (3) the role of intra-tumoral heterogeneity in metastasis and resistance, and (4) the identification of new therapeutic targets, immunotherapy approaches, and candidate biomarkers for SCLC. Going forward, opportunities and unmet needs in SCLC include enrolling patients onto clinical trials that can identify therapeutic vulnerabilities among specific SCLC subtypes; deeply profiling relapsed SCLC (through new models and patient specimen profiling); and extending our understanding of the immune microenvironment in SCLC. Given the pace and impact of recent discoveries in SCLC, it is no surprise that Dr. Gazdar and his co-authors concluded that "...while the past has been bleak, the future offers great promise." 1. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer 2017;17:725-37.

Keywords: SCLC, Heterogeneity, biomarkers

Young Investigator Session

YI01 FIRST TIME ATTENDEE SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–08:30

YI01.01 PLANNING AN ACADEMIC CAREER IN LUNG CANCER

D. Gandara

UC Davis Comprehensive Cancer Center, Sacramento/United States of America

For those graduating from training in oncologist specialties worldwide in 2019, never have there been so many and such diverse opportunities, including Industry-related and Governmental positions. While the term "private practice" has specific connotations for oncologists in the USA that may no be applicable elsewhere in the world, the requisites for a career in academic medicine are uniform on a global basis. For example, it is often stated that that for clinical investigators a career in academic medicine is like a 3 legged stool, supported equally by clinical care, research and teaching. Some would add that administration is the fourth leg of an academic career, since it is often a significant component of time-spent. For those in a purely laboratory-based academic career, clinical care may be replaced by other activities. Assuming that you choose to be an academic physician with clinical care responsibilities, there are 3 broad categories of effort: clinical educator/administrator, clinical investigator and clinician-scientist. Making the decision on which career pathway to follow is often not easy, and may be influenced by your country of origin and associated opportunities and challenges for different specialties in oncology where you intend to work. In fact, changing the decision between academic and non-academic career pathways have never been easier. There are many examples today of oncologists moving back and forth between academics and industry, with equal success in both venues. This presentation will give a "personalized" approach to career planning taken from my own and other shared experiences. Since the ratio of pros/cons for academic medicine are largely applicable on an individual basis, this presentation mode will hopefully provide young investigators attending WCLC 2019 with personal insight and position them well for making this career-defining decision.

Keywords: academic career

YI01 FIRST TIME ATTENDEE SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–08:30

YI01.02 WHY TO BECOME A MEMBER OF THE IASLC

G. Scagliotti

University of Turin; San Luigi Gonzaga Hospital, Orbassano/Italy

Since the 1970s, the International Association for the Study of Lung Cancer (IASLC) has promoted research and education into all aspects of lung cancer and other thoracic malignancies, as well as encouraged worldwide cancer prevention efforts. According to its mission statement the International Association for the Study of Lung Cancer (IASLC) must embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment and all other aspects of lung cancer and other thoracic malignancies; provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public; use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world. In the last ten years those goals have been embraced by a growing number of members worldwide and now the association counts on approximately 7.000 members with a large portfolio of scientific and educational activities, being now IASLC the premiere society in the field of thoracic oncology. Beyond this bold statement the really question here is why me? While IASLC in the context of many other offers coming from other scientific organizations? The answer comes from one of our members "Being a member helped me in many, many ways. First coming to the IASLC World Conference on Lung Cancer. I was a resident and presenting in front of 100 people [....] that helped me secure my fellowship position. The IASLC helped me with great networking opportunities to interact with many members of the lung cancer community". That is really the key message. Inclusivity and multidisciplinary. The composition of our Board and committees reflect this sense of inclusivity. We want all the players in the thoracic oncology arena to have the appropriate voice, and the younger generation at the foremost. IASLC mentors and support younger people in the context of several activities within the organization. IASLC has a wide range of fellowships that support people to travel and present at meetings, to get involved in research, and more importantly to get a research grant to make your ideas a reality, and to meet people who can help you further in boosting your career. Our annual meeting is a reference meeting and every year the most relevant scientific research results have been constantly presented. The targeted therapy meeting held every year at the end of February in Santa Monica remains a unique forum of scientific exchange between researchers and pharma not paired by any other type of meeting throughout the world. Equally relevant are the regional meetings that are mainly educational but are also offering the opportunity to report about your own research. One of the main duties of a membership association is to provide value to its members, through high quality and relevant offerings and deeper, more efficient mechanisms for engagement. Creating a robust experience for IASLC members and honoring our commitment to geographic and discipline diversity is our goal The most challenging part for any scientific society is to understand the differences in generational needs. We need to identify the best new talents, the rising stars in our field, who will not only disrupt conventional thinking; they will lead the IASLC in the future. Specific actions will be considered and others are already in place to convince younger generations to see themselves in the IASLC mission. We want you joining us in the fight against tobacco, we want you to be the ambassadors of our organization for the present and, more importantly, the future of our patients with the ultimate goal to be part of a dream:the eradication of thoracic malignancies

Keywords: thoracic malignancies, fellowship, membership

YI01 FIRST TIME ATTENDEE SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–08:30

YI01.03 MAKING THE MOST OF WCLC: A GUIDE FOR FIRST TIME ATTENDEES

H. Wakelee[1], B. Bunn[2]

[1]*Stanford University, Stanford/United States of America,* [2]*IASLC, Denver/United States of America*

Congratulations on making the decision to attend the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC)! This is the largest meeting in the world focused entirely on thoracic malignancies and is truly an international and multidisciplinary event. However, it is possible to get lost with so many concurrent sessions and in the sea of thousands of delegates. So having a game plan is critical. You will want to have a roadmap and plan for each day but also allow time for networking and to have some fun. With the virtual meeting available afterwards do not worry too much if you want to be in two places at once. You can be... "virtually." Check out the "First Time WCLC Attendees" tab on the IASLC WCLC2019 conference website for great guidance from Dr. Anne-Marie Baird. To paraphrase her: #1 Prepare #2 Attend the Young Investigators Symposium #3 Check out the Posters #4 Network #5 Engage with Social Media. These are all outstanding suggestions! To help you prepare be sure to look at the program in advance and get a sense of the conference center layout. Each morning there is a Plenary session highlighting key topics with talks given by world leaders. These can be amazing! The top abstracts of the meeting will be presented in the Presidential symposium on Monday morning Sept 9. The conference app (available a week or so before the start of WCLC2019) is a great way to keep track of everything. With so many concurrent sessions it will be important to have the info at your fingertips. There is a daily press conference that you can attend or review in the press and media section of the WCLC website. Highlights of the day (HOD) will be presented Mon Sept 9 and Tues Sept 10 from 10:30-12 of the conference and also included in emails and on the website. Checkout the daily newspaper (WCLC Daily News) for more highlights. Also you may want to follow everything that is happening on social media! IASLC

is active on: Twitter, Facebook, LinkedIn, YouTube, Instagram Important Hashtags for lung cancer #LungCancer, #CureMESO, #NSCLC, #SCLC, #CancerResearch, #Oncology, #clinicaltrials IASLC 2019 World Conference on Lung Cancer – Social Details: • Official Conference Hashtag: #WCLC19 • Official Hashtag of Lung Cancer Social Media Community: #LCSM The IASLC operates a social media booth at each WCLC for new users to learn about social media, get a tip-sheet and take photos with special branded backdrop (which is really fun)! As you look at the program you will see there is a great mix of education sessions, workshops and new data presentations. You will likely want to attend a mix of all of these. The education sessions may be a focus since those will include global experts summarizing particular topics and future predictions. It can be a bit tricky to understand the significance of some of the new data without knowing the background and the education sessions will help with that knowledge. It is also great to go to some of the mini-orals (MA) and oral (O) sessions to hear the latest research, particularly in your areas of interest. The mini-orals can be tricky as each one goes by fast so be ready! Again, plan in advance. As Dr. Baird points out, the poster/networking sessions are really wonderful. A lot of critical data that might not be as "flashy" is buried in the posters and you are likely to learn a lot. Even more importantly you will have a chance to network and find out who around the world is focusing in the same areas where you have interests. There are 2 poster sessions each day. The poster sessions are particularly great because you actually get to interact with people. If you see someone you want to talk to at the poster session do not be intimidated if they happen to be a "name" you have read multiple times in key papers. Everyone is excited to meet eager people working to help fight lung cancer! The importance of networking cannot be over-emphasized. Getting to know the field and others who share your passion for fighting lung cancer and other thoracic malignancies can make a tremendous impact on your future academic career. Branch out and meet people in other disciplines and from other parts of the world. Having a common interest in fighting lung cancer can lead to some strong connections and it is incredibly fun to attend future conferences knowing that you will get to connect with friends you met at your first IASLC WCLC. Important collaborations can also be started including international efforts. If you are still in training this networking time is also critical to your future job hunting! Remember to have FUN! Sign up and attend the IASLC social events. These involve good food, great music and sometimes dancing and most importantly a real opportunity to network. Saturday – Opening Ceremony and Welcome Reception Monday - IASLC Foundation Road to Hope gala Tuesday - Closing Ceremony After running around at the conference there will be times you just want to sit and relax. Fortunately there is an IASLC membership lounge in the exhibit hall open during exhibit hours. All members are invited to use the space for meetings, to sit for a few minutes, and to learn more about the IASLC and its committees. More details can be found here: https://wclc2019.iaslc.org/networking_opportunities/ Also, make some time before or after the conference to be a tourist in the local region. Most convention centers are fairly similar, but thinking about the last 3 IASLC WCLC conferences you can imagine how Yokohama, Toronto and Barcelona are all very different and fabulous places to explore. Enjoy your first IASLC WCLC and hopefully you will plan to make it an annual event!

Keywords: Networking, young investigators, Social Media

YI01 FIRST TIME ATTENDEE SESSION
SATURDAY, SEPTEMBER 7, 2019 07:00–08:30

YI01.04 CONGRATULATIONS, YOUR ABSTRACT HAS BEEN ACCEPTED, AND NOW? - TIPS AND TRICKS TO PREPARE A PRESENTATION FOR WCLC

B. Solomon

Peter MacCallum Cancer Center, Melbourne/Australia

This presentation will provide a practical guide about how to prepare and deliver an effective and engaging presentation at WCLC. Tips and suggestions will be provided for oral presentations, miniorals, posters and E-posters.

YI02 CLINICAL TRIALS
SATURDAY, SEPTEMBER 7, 2019 09:00–10:30

YI02.02 BASKET AND UMBRELLA TRIAL DESIGNS IN ONCOLOGY

J. Menis

University of Padova, Istituto Oncologico Veneto (IOV), Padova/Italy

Cancer treatment has made gigantic improvements in patients' prognosis in multiple cancer types, by virtue of major steps forward in the concept of personalized medicine. This involves scientific progress in tumour biology, genomics technology, computational analysis and drug discovery that has propelled advances in both translational and clinical cancer research. In particular, rapid development, decreased cost, and increased availability of next-generation genomic sequencing and other methods for both molecular and, more recently, immunological tumor classification have changed the paradigm for understanding and treating cancer. Until recently, drug development has been conducted separately for different histological tumor types since the histological type was the primary known determinant of drug efficacy. However, this histology focus has been integrated by new knowledge on genomic alterations and immunological profile. Therefore, clinical trials have been evolving in parallel, from the traditional two-arm comparison of an experimental treatment vs. a control, to accelerate identification of promising therapies, to increase throughput and to allow for the increasing use of molecular and immunological classification of patients into smaller sub-groups. Also cost-efficiency need to be considered: classical phase I, II and III models for drug development require large resources, limiting the number of experimental agents that can be tested and making the evaluation of targeted agents inefficient. On the other hand, methodology and quality assurance need to be preserved since the validation of biomarkers is generally affected by several challenges, such as the multitude of assessment methods (i.e. immunohistochemistry, fluorescence in situ hybridisation, next-generation sequencing, etc.), reliability in terms of sensitivity and specificity, reproducibility of the test, feasibility of obtaining an adequate and representative tumour sample and, finally, the overall related costs. All these considerations, added to the strong collaboration with the regulatory agencies, approving novel agents based on data obtained from phase 1/2 trials, have led to an evolution in the design of early-stage clinical trials. The enrichment design can require many fewer patients, i.e. only those patients hypothesized to benefit, to be randomized relative to the "all comers" randomized design. The choice between an unselected versus enriched design should always be made also based on the existing level of evidence for the predictive biomarker. Two main enrichment strategies can be used to avoid over-treatment and save valuable resources, by matching the right drug to the right subgroup of patients. They can be defined as: basket trials and umbrella trials. Basket trials allow patients with multiple diseases and one or more target to be enrolled in cohorts or groups in one trial (the basket). They are often viewed as parallel phase II trials within the same entity, designed on the basis of a common denominator. Researchers are therefore allowed to separately analyse the patients' responses as each tumour type can be put in one cohort, and assess the impact of the drug on all of the patients as one group. If one group shows a good response, this group will be expanded to immediately assess whether others could benefit from the new therapy. If another group does not show evidence of effectiveness, this group may be closed and the other cohort can continue the recruitment. Basket trials can be further sub-classified in three groups: basket trials on one drug in several tumour types (1), basket trials on one drug for one molecular alteration in several tumour types (2), and basket trials on one drug in several molecular alterations in several tumour types. Umbrella trials are built on a centrally performed molecular portrait and molecularly selected cohorts with matched drugs, and can include patients' randomisation and strategy validation. In the umbrella design, a separate enrichment trial is conducted for each bio- marker stratum. The enrichment design for a given stratum uses as the test regimen a drug expected to be active for the alteration defining that stratum. Beyond new designs, new end-points and new evaluation techniques are also warranted to finally achieve methodology and clinical improvements, in particular within immunotherapy trials. As clinicians continuously learn from their patients, applying knowledge gained from one set of patients to their forthcoming patients, in adaptive designs, modifications of some aspects of the trial can be prospectively planned so that changes (''adaptations'') may take place while the study is ongoing (for example: a treatment arm or a subgroup of patients could be dropped; the trial size could be

increased, etc). Planning for such types of studies would allow to overcome the challenge related to the limited available information in the literature describing the targeted sub-populations. Alongside the growing complexity of these clinical trials, new frameworks for stronger and faster collaboration between all stakeholders in drug development, including academic institutions and frameworks, clinicians, pharma companies and regulatory agencies, has to be further encouraged. In the current era, the main goal should be to identify large and meaningful differences in small, molecularly and immunologically selected groups of patients and to develop rapidly new compounds. Basket and umbrella trials respond to the need of ''trials designed to learn'', that can evolve into ''trials designed to conclude''. Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev 2014; 23: 367–78 Simon R. Critical Review of Umbrella, Basket, and Platform Designs for OncologyClinical Trials. Clin Pharmacol Ther. 2017; 102(6):934-41 Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol. 2017;28(1):34-43 Garralda E, Dienstmann R, Piris-Giménez A, Braña I, Rodon J, Tabernero J. New clinical trial designs in the era of precision medicine. Mol Oncol. 2019;13(3):549-57 Renfro LA, Mandrekar SJ. Definitions and statistical properties of master protocols for personalized medicine in oncology. J Biopharm Stat. 2018;28(2):217-228 Rashdan S, Gerber DE. Going into BATTLE: umbrella and basket clinical trials to accelerate the study of biomarker-based therapies. Ann Transl Med. 2016;4(24):529 Morrell L, Hordern J, Brown L, et al. Mind the gap? The platform trial as a working environment. Trials. 2019; 20(1):297

Keywords: design, basket, umbrella

YI02 CLINICAL TRIALS
SATURDAY, SEPTEMBER 7, 2019 09:00–10:30

YI02.03 STATISTICAL PITFALLS IN CLINICAL TRIAL DESIGN

U. Dafni

University of Lausanne, Athens/Greece

This topic will be discussed in the context of the following principles that clinical trials should adhere to. A *clinical trial* is an experiment testing medical treatments on human subjects. The process of evaluating medical treatment in humans starts with a Phase I clinical trial, followed by a Phase II and a Phase III trial towards regulatory approval. *Phase III* Phase III clinical trials are the gold standard for the evaluation of therapeutic interventions' efficacy. The goals of a Phase III clinical trial include minimization of random error, elimination of systematic error (bias) and ensuring the generalizability of study results. The clinical trial design is the methodology for achieving these goals. Randomization, always present in phase III trials, provides a treatment assignment that is independent of outcome and patient/disease features, thus balancing treatment groups on known and unknown factors associated with outcome. Further, the intention-to-treat (ITT) analysis approach is the gold standard for all phase III randomized, controlled clinical trials. It analyzes all patients in the treatment groups as randomized without regard to treatment actually received. The systematic error (Bias), which is any effect rendering the observed results not representative of the treatment effect, is addressed through randomization and corresponding ITT analysis. Minimization of random error is addressed through the use of adequately large sample size. *Phase II* Phase II clinical trials can be either randomized (screening, selection, randomized discontinuation designs) or non-randomized. The latter may be seriously misleading since the impact of prognostic factors is usually far larger than that of treatment, while known prognostic factors may explain little variance. Randomized phase II trials allow control of selection bias and simultaneous testing of several new treatments, combinations, doses etc. They are preferable than non-randomized trials (some degree of control is better than none!) but they could be misleading due to the small sample sizes. They cannot replace phase III trials. In Phase II trials, the objective is to select active drugs for further testing and document toxicity, but not to provide definite estimate of new drugs' efficacy, wh8ch is achieved only though a well-powered Phase III clinical trial. *Hypothesis Testing* In any experiment, two hypotheses covering all possible outcomes are pitted against each other. Only one of them can be true. The *alternative hypoth*esis is the statement we would like to prove, and the *null hypothesis,* the statement we would like to reject. The only possible conclusions in hypothesis testing are: 1. *Reject the Null Hypothesis*, and thus prove the desired alternative hypothesis (positive trial), or 2. *Not able to reject the null hypothesis* (negative trial). Any trial needs to be designed in such a way that it is known a-priori what the errors relative with each of the two possible conclusions will be. Rejecting the null wrongly (false positive result), is subject to *Type-I error (alpha)*, or *significance level*, while not rejecting the null hypothesis wrongly (false negative result), is subject to *Type-II error (beta)*. The *sample size* of the trial is decided at the design stage to guarantee that these two errors remain below pre-defined bounds. These bounds are usually 5% for Type-I error, and 20% for type II error. One more important design characteristic is *power*, which is equal to (1-beta) and it is the probability of correctly rejecting the null hypothesis (values usually set above 80%). *Superiority vs Equivalence/Non-inferiority* Clear distinction should be made between superiority and equivalence/non-inferiority Phase III trials, with each testing a different type of null hypothesis. In a superiority trial we aim to reject a null hypothesis of "*no effect*" or "*no difference*", while in an *equivalence* trial we aim to reject a null hypothesis of "*different effect*". More particularly, in a superiority trial we aim to demonstrate the superiority of a new therapy compared to an established therapy or placebo. In this case, the determination of the sample size takes into account the *clinical significance* (by how much the new therapy should be better than the established one), the *power* and the *significance level* of the test, as well as the magnitude of the variation of the corresponding measure of interest. In equivalence trials, the objective is to demonstrate that a new treatment is equivalent to a standard therapy with regards to a specific clinical end point, while it has an intrinsic benefit for other clinical end points, while in non-inferiority trials, to evaluate whether the new treatment is not inferior to or as effective as the standard therapy for a particular end point. In this case, a *tolerance and a non-inferiority margin* must be predefined, along with the *power* and the *significance level* of the test. Failure to reject the Null hypothesis should not be confused with acceptance of the Null hypothesis. *Subgroup Analysis* Another issue that should be taken into account in the design of a trial is subgroup analysis, involving multiplicity issues. It is common practice to perform multiple subgroup analyses, but the probability of a false positive finding (type-I error) increases as the number of subgroup analyses increases (*curse of multiplicity*). *Prognostic vs Predictive Marker* The correlation between a biomarker and a true clinical endpoint corresponds to a prognostic marker, but not to a predictive one. It is the statistically significant difference in treatment effect between the levels of the biomarker (treatment by group interaction), that characterizes a predictive biomarker.

Keywords: interpretation of negative results, non-randomized evidence, multiplicity issues

YI02 CLINICAL TRIALS
SATURDAY, SEPTEMBER 7, 2019 09:00–10:30

YI02.04 BIOINFORMATICS: THE BASICS

Y. Shyr

Vanderbilt University Medical Center, Nashville/United States of America

For physicians, advanced data science methods such as artificial intelligence (AI), machine learning and novel statistical methods are no longer just a headline in the news. Use of advanced data science methods are gaining acceptance in the field of medicine, as researchers push the limits of rapidly progressing technologies to assist in delivering excellence in health care. With the growth in use of advanced data science methods, however, we must bear in mind the limitations of these technologies. AI—specifically, machine learning (ML) of the deep-learning type—is only as good as the training dataset from which the algorithm learns. Deep learning in the clinical setting is most highly developed for image recognition; a training dataset for this purpose consists of a large number of case and control images. The algorithm then uses these images to teach itself how to differentiate, for example, malignant lesions from benign tumors or normal tissue. If the training dataset consists only of unambiguous cases and controls—rather than representing real-world variation and ambiguity—the algorithm will fail to function as desired with real-world patients. Thus, well-considered experimental design remains essential to realize the promise of deep learning. This talk will provide an overview of the state of the art in AI, machine learning, novel statistical methods, and deep learning algorithm for clinical application, including examples from the research literature as well as FDA-approved devices that use advanced data science

methods. We will then address the pitfalls of deep learning, including the need for clear and rigorous standards for regulatory approval of devices and software. We close with thoughts on the future of advanced data science methods in medicine.

YI02 CLINICAL TRIALS
SATURDAY, SEPTEMBER 7, 2019 09:00–10:30

YI02.05 PRINCIPLES TO GET YOUR PAPER PUBLISHED

A. Adjei

Mayo Clinic, Rochester/United States of America

How to get your Manuscript Published Alex A. Adjei, MD;PhD Mayo Clinic, Rochester, MN, USA Scientific publication is the backbone of academic research. Findings by investigators need to be disseminated to the community so that results can influence human health and well-being as well lay groundwork for future research. In spite of the central role of publishing in academic life described above, there are very few formal courses or seminars teaching academics, particularly physician scientists on how to publish their work. The table below outlines reasons for rejection of manuscripts, coming out of a survey of a number of journal editors Using information from this survey as a starting point, we will discuss the "fatal flaws" that lead to outright rejection of manuscripts, and outline strategies on how to write a manuscript of high impact, which is likely to be accepted for publication.

YI03 SCIENTIFIC MENTORING
SUNDAY, SEPTEMBER 8 10:30–12:00

YI03.01 WHY TO APPLY FOR INTERNATIONAL FELLOWSHIP?

C. Mascaux

Strasbourg University Hospital, Strasbourg/France

First of all, if you aim for an academic career, the international fellowship is a requirement in most countries. If you are not choosing an academic career, the international fellowship will be very useful anyway. This fellowship can be clinical, scientific or both, depending on your wish. Be aware of choosing an appropriate destination and team based on what you are looking for. Depending on the country where you trained and the country that you are choosing for your fellowship, you may or may not be fulfill the requirement for clinical practice. You must make sure that your salary will be funded and that your income is sufficient for leaving in the city of your fellowship. A fellowship needs to be planned several months in advance for the administrative preparation. Overall, international fellowship will be a uniquely rich experience. It will open new perspectives in your career. You will learn from the new team and modulate your clinical/scientific interpretations and your decisions. It will diversify your clinical/scientific interests, increase and diversify your knowledge and you expertise. The international fellowship will also allow you to built an international network and collaborations, and increase your visibility. In addition of being a very valuable professional experience, it will be a very rich personal challenge, from which you will enjoy and learn as well, by discovering and experiencing a different context of life, different culture and also perhaps a different language. Both for the professional and the personal side of your life, the international fellowship will open your mind and will be an unforgettable experience

Keywords: international fellowship, experience, requirement

YI03 SCIENTIFIC MENTORING
SUNDAY, SEPTEMBER 8 10:30–12:00

YI03.02 HOW TO APPLY FOR INTERNATIONAL FELLOWSHIP?

M. Tsao

Princess Margaret Cancer Centre, Toronto/Canada

International fellowship to pursue further training is an important part of career development for junior clinicians and investigators. International fellowship will not only increase the clinical and/or research skill of the fellow, it also offers an important opportunity to establish interaction network with senior investigators and peer young investigators across the world. When applying for international fellowship, several aspects should be considered: (1) choosing the field for further training, (2) application procedure, and (3) funding availability. The choice of field for further training will largely determine the future career of the candidate and should be in line with one's scientific or career passion and clinical/research interest. Prior experience with a role model and mentorship during earlier formative years usually has great influence on one's decision to pursue career choice. Fellowship training can be limited to clinical only, research only or combined clinical and research training; the latter for a candidate who wishes to pursue clinician-scientist career. Once a decision to pursue further training is made, the candidate should look for fellowship opportunities. This is often through discussion with local mentors or colleagues with prior international fellowship experience, or via familiarity with potential mentors who have published extensively in the area of candidate's interest or have lectured at international meetings. On-line searches for institutions with established fellowship program may also be useful, but many training programs may not be openly advertised, thus personal approaches and recommendations are often more fruitful. Writing an application letter that demonstrates strong background, qualification, prior track record, commitment and clear post-fellowship career pathway are key elements to win an opportunity for further interview. Availability of secured partial/full funding from local Institution or independent funding agency is a great asset for an application. While one year fellowship that involves only clinical training may be sufficient, training that involves laboratory research will usually require a minimum of 2 years tenure, as the latter usually requires more time to accomplish specific research projects. In such case, preliminary data obtained during first fellowship year may greatly contribute to applications for fellowship offered by international societies (e.g., IASLC, ASCO, AACR) or funding agencies.

Keywords: Training, career development, fellowship fund

YI03 SCIENTIFIC MENTORING
SUNDAY, SEPTEMBER 8 10:30–12:00

YI03.03 SCIENTIFIC MENTORSHIP: WHAT SHOULD YOU EXPECT?

R. Rosell

Germans Trias i Pujol Science Institute, Badalona, Barcelona/Spain

Scientific Mentorship: What Should You Expect? I am honored to speak to young investigators on mentorship. Over several decades I have had the opportunity to serve as mentor of many clinical investigators, both local and worldwide. Throughout the years, most of my mentors have been involved in translational research and laboratory work, which, on many occasions, has resulted in fruitful research, culminating in theses and publications in relevant journals. One of the key points in assuming the responsibility of training is to work very closely, as friends, standing side by side, studying the relevant research project and its progress. There are several emotions among the mentor and young investigators. The mentor feels joy and delights in seeing the young investigators progress, converting in an overall happiness at the project accomplishment. The mentors joy comes once every young investigator achieves the main objective of his/her work in process. Transparency is the fuel of friendship between the mentor and young investigator. The mentor should be fully involved and open, in order to build a strong mentor/investigator relationship. The mentor must show emotional honesty, even if there is the possibility of someone taking advantage of his/her vulnerabilities. Unmasking oneself is the only means to building

successful scientific relationships. The mentor should apply an open policy of collaboration, assuming the young investigators could have an even greater capacity for research, than the mentor himself. Most of the time, this behavior will be a benefit for the investigators. There have been many examples of investigators contributing to important findings in a plethora of different research areas. Cancer biology was recognized as an important cancer field in the late 90's, and many investigators have made exciting contributions in tumors, such as, non-Hodgkin's lymphomas (Calvo et al JNCI 1998), gastric cancer (Wei et al JNCI 2011) and many others, culminating in salient publications in the field of lung cancer (Karachaliou et al JAMA Oncol 2015). The principal contributions will be included in the presentation.

Keywords: young investigators, mentorship

YI03 SCIENTIFIC MENTORING
SUNDAY, SEPTEMBER 8 10:30–12:00

YI03.04 ONCOLOGY FELLOWS' CAREER PLANS AND EXPECTATIONS

M. Ito

Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona/Spain

I will discuss how I planned my fellow career and tips for achieving based on my own experience. My own career is short, at around 10 years, but I would be glad if my presentation could be of some service to fellows in the same position. If you want to achieve something different than your current situation for your own career, then you gain qualifications, earn achievements such as publishing papers, participate in the academic community, or organize projects, but it is difficult to decide on the ultimate goal at an early stage. For young fellows to build a career, the process is more crucial than setting the outcome, therefore it is essential to know oneself, in addition to learning the latest information on thoracic oncology. Read articles, participate in academic conferences and train at other facilities as a means of understanding your own knowledge and competencies, rather than simply as a means of learning about thoracic oncology. Although training at special facility will provide the smallest amount of information about thoracic oncology at one time, I believe it is the most efficient means of learning about oneself. This type of learning enables you to directly and simultaneously understand your disadvantages, advantages and characteristics. I have worked and researched at several hospitals and research institutes both in Japan and overseas. I made use of the scholarship system in the past to conduct clinical training in Spain, which enabled me to gain a wealth of clinical experience that I would not have been able to experience in Japan. I am currently affiliated with a research institute in Barcelona and have been involved in research there since 2017 under world-renowned supervisors. I contribute to joint research between Japan and Spain, and Spain and the US, and this, among other opportunities, has enabled me to learn a great deal at my current facility. This experience has not only strengthened my resolve about the new goals I want to achieve, it has also made me fully aware of areas where I am lacking. For the training at a special facility, getting the grant is crucial. I have received some grant support from several academic associations including IASLC. The financial supports allowed me to gain and achieve ambitious aims. Through the project, I have been inspired and it brought me new ambitions. Although there are more and more opportunities of the grant in these days, winning is getting more competitive. Fortunately, I could receive grant support several times. However, I failed many times to get the support. To get the grant, I will show tips based on my own experience at my presentation. If training at a special facility or getting the grant is difficult, I recommend continuing to participate at international conferences. This is also particularly important for learning the latest information about thoracic oncology. I have participated 13 times in international conferences to date, and have participated in the World Conference on Lung Cancer (WCLC) since the 13th congress held in 2009. I strongly recommend checking all the abstracts before attending the conference, preparing questions and discussing matters with as many people as possible during the conference. WCLC has research in all fields related to thoracic oncology, so it is relatively easy to make new acquaintances and partnership in your own field of research or interest. In this instance also, it is important to make presentations and receive as much input as possible, to clarify areas where you may be lacking and you have advantage, thus using this opportunity as efficiently as you can. Attending congress also gives you chances to get informed the grant opportunity and which facility is attractive for you to make training. In summary, it is not easy to make decisions about your career, and often we are unaware when we are at a turning point. No one knows the correct answer. Building a career involves not only your own intentions, but also your situation and funds. The important thing is to focus on the quality of the process to ensure that you do not waste time, and to always be aware of your own strengths and weaknesses, and using or supplementing these characteristics to discover what you want to achieve and what you can achieve in your career. Training at a special facility and keeping to join academic congress clearly enhance our academic career. It will give you new confidence to find or continue on your mission for thoracic oncology.

YI04 BASICS OF IMMUNOLOGY
SUNDAY, SEPTEMBER 8 13:30–15:00

YI04.02 IMMUNO-ONCOLOGY TRIALS: OTHER ENDPOINTS NEEDED?

M. Reck

Lung Clinic Grosshansdorf, Grosshansdorf/Germany

The implementation of immunotherapies has completely changed and improved management of patients with non-small-cell lung cancer (NSCLC). In contrast to cytotoxic agents and targeted therapies immunotherapies do not directly affect the tumor but lead to an indirect reactivation of T-cell mediated immune reaction. Therefore different endpoints may be required for an appropriate assessment of efficacy of these novel compounds. In various trials it could be demonstrated that in contrast to conventional anti tumor therapies, which show an impact on early overall survival (OS), immunotherapies seem to impact the long term survival rates, leading to a phenomenon, which is characterized as „plateau of long term survival". In contrast other conventional markers of efficacy like response rate (RR) or progression free survival (PFS) do not appear as the best endpoints to reflect the complete efficacy of immunotherapies at least not in biomarker unselected populations. In a number of randomized phase 3 trials in untreated as well as pretreated patients no significant differences in PFS were shown despite the fact that these trials demonstrated a clear survival benefit in favour of the immunotherapies or immunotherapy combinations. In addition exploratory analyses revealed a survival benefit even in patients, who received immunotherapies beyond progression suggesting that indeed response and PFS may be suboptimal endpoints. Reflecting these experiences clearly new statistical approaches are needed to focus on OS as probably the most relevant endpoint and to provide the opportunity to capture the late impact of immunotherapies on OS with the prolongation of long-term survival in an adequate way. Currently the first modifications of conventional statistical models are in development evaluating for example the model of disproportional hazard ratios and others in upcoming trials. Another significant problem is the appearance of „crossing" Kaplan Meier curves, which has frequently been observed in trials with immunotherapy combinations. These curves suggest, that there are different subpopulations with different sensitivities toward the novel treatments represented. Reflecting the lack of valid predictive biomarkers, which are able to separate the different subgroups, innovative statistical models are needed to define and to describe the benefitting populations. Lastly the „explosion" of numerous clinical trials investigating novel immunotherapy combinations will require a modification of our traditional endpoints. Given the number of novel agents and the speed of development it won´t be feasible to conduct individual signal generating phase II trials for each of these agents. New models of platform trials with a new model of statistical assessment are required to provide the opportunity to investigate multiple combinations in one trial and to provide the flexibility to add novel combinations, which just may have been developed to ongoing protocols. In summary immunotherapies have substantially contributed to therapeutic improvements in NSCLC, but they are requesting a change of our conventional consideration of efficacy. Besides all endpoints of objective efficacy it will be of paramount importance that future endpoints also cover patient relevant endpoints like tolerability, improvement of quality of life or duration of symptom control.

YI04 BASICS OF IMMUNOLOGY
SUNDAY, SEPTEMBER 8 13:30–15:00

YI04.03 THE PLACE OF IMMUNOTHERAPY IN NSCLC THERAPEUTIC ALGORYTHM

R. Stahel

University Hospital Zurich, Zurich/Switzerland

Place of immunotherapy in the NSCLC treatment algorithm Therapy with immune checkpoint inhibitors has entered standard of care for patients with metastatic NSCLC. Data from extended phase I studies are available on the long-term effect of single agent immune checkpoint inhibition in later line. These studies demonstrate a 16% 5-year survival for nivolumab and pembrolizumab in pretreated patients (1), the impact of PD-L1 expression on long term outcome (2) and the importance of obtaining an objective response (3). Nivolumab and pembrolizumab, both PD-1 directed antibodies and atezolizumab, a PD-L1 directed antibody all have been approved for second or later line therapy based on comparative studies with docetaxel monotherapy demonstrating superior survival and an improved toxicity profile. However, results of recent studies in first line treatment have led to a rapid adoption of immune checkpoint inhibition upfront. This started with the results of the KEYNOTE-024 study demonstrating survival benefit of single agent pembrolizumab over platin-based combination therapy for patients with advanced NSCLC with a tumor proportion score of 50% or higher (4). With these results, PD-L1 testing has entered clinical routine. A series of clinical trials examined the survival impact of adding immune checkpoint inhibition to standard platin-based chemotherapy. Based on these results pembrolizumab added to platin-based chemotherapy, carboplatin and pemetrexed in non-squamous NSCLC (KEYNOTE,-189), carboplatin-paclitaxel or nab-paclitaxel in squamous NSCLC (KEYNOTE-407) (5,6), or alternatively atezolizumab combined with bevacizumab, carboplatin and paclitaxel (IMpower150) or with carboplatin and nab-paclitaxel (Impower130) for non-squamous NSCLC (7,8) have become standard of care, independent of the expression of PD-L1 in tumor tissues. The results of these t and additional trials in first line metastatic NSCLC have been summarized recently (9). Obviously, important questions remain to be answered. One open question regards the upfront treatment of patients with tumors having a strong PD-L1 expression. Lacking randomized data the debate remains open whether pembrolizumab alone or its combination with platin-based chemotherapy would ultimately be the best option. The KEYNOTE-042 trial compared pembrolizumab with platin-based chemotherapy in patients with tumors with at least 1% PD-L1 expression. The trial was positive for pembrolizumab, however the analysis of patient subgroups according to PD-L1 expression suggests the benefit to be mostly derived from patients with strongly expressing tumors and thus these results might only marginally impact clinical practice. A second open question regards the optimal selection of patients which could be spared from upfront treatment with chemotherapy and could benefit from single agent immune checkpoint or combined PD-+/PD-L1 and CTLA4 inhibition. Two trials examining the role of nivolumab in first line treatment (CHECKMATE-026 and CHECKMATE-227) demonstrated that a high tumor mutation burden is predictive for a better response to immune checkpoint inhibition. The later trial (10) and the analysis subgroups of the MYSTIC trial are in support of the hypothesis of potential superior effects of combining PD-1/PD-L1 inhibition with CTLA4 inhibition for patients with a high tumor mutation burden, measured directly in tumor tissue or indirectly on circulating tumor DNA, however, formal prove from prospective trials is pending. It is important to note that with the exception of IMpower150 and Impower130, all other trials excluded patients with known EGFR and ALK mutations, the main reason being the relative lack of efficacy of second line immune checkpoint inhibition in these patients. The benefit in progression-free survival and overall survival seen in patients with EGFR mutated tumors when treated with the atezolizumab bevacizumab quadruplicate, but not with the atezolizumab triplicate lends support for the use of the quadruplicate regimen for patients with EGFR mutated tumors failing tyrosine kinases. Gettinger, et al. Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study. J Clin Oncol 2018 Jun 10;36(17):1675-1684 Garon E, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol 2019 Jun 2:JCO1900934 Horn, L, et al. 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YI04 BASICS OF IMMUNOLOGY
SUNDAY, SEPTEMBER 8 13:30–15:00

YI04.04 HOW TO SELECT PATIENTS FOR IMMUNOTHERAPY

N. Rizvi

Columbia University Medical Center, New York/United States of America

With the wide application of immune checkpoint blockade in the treatment of cancer, biomarkers may determine the line of therapy immunotherapy may be administered or when to combine with other agents. Patient selection on clinical characteristics and co-morbidities also need to be incorporated into treatment decision making. An overview of patient characteristics and external influencing factors will be provided in this review including more complicated scenarios such as patients with co-existing autoimmune disease or solid tumor transplant populations.

Workshops

WS02 MESOTHELIOMA WORKSHOP (TICKETED SESSION)
SATURDAY, SEPTEMBER 7, 2019 08:00–11:30

WS02.02 PATHOLOGY SECTION I: SYNOPSIS EURACAN/IASLC

A. Nicholson

Royal Brompton and Harefield NHS Foundation Trust, London/United Kingdom

Whilst molecular and immunologic breakthroughs have transformed the management of lung cancers, changes have not been as marked for malignant pleural mesothelioma. Therefore, in 2018, a multidisciplinary group (pathologists, molecular biologists, surgeons, radiologists and oncologists), sponsored by EURACAN/IASLC, met in order to critically review the current classification, in which pathologic diagnosis has hitherto been essentially limited to three histologic subtypes.1 Subsequent recommendations in relation to pathology classification were firstly to include architectural patterns, and stromal and cytologic features that refine prognostication. Second, subject to data accrual, malignant mesothelioma in situ could be an additional category. Third, grading of epithelioid MPMs should be routinely undertaken, 2 Fourth, other prognostically relevant histologic characteristics should be routinely reported. Clinically relevant molecular data such as PD-L1, BAP1, *CDKN2A*) should be incorporated into reports, if undertaken and other molecular data accrued as part of future trials. Resection specimens (i.e. extended pleurectomy/decortication and extrapleural pneumonectomy) should be pathologically staged with smaller specimens being clinically staged. When surgical biopsies are taken, at least 3 separate areas should be sampled from the pleural cavity, if feasible. Image-acquisition protocols/imaging terminology should be standardized to aid research/refine clinical staging. Multidisciplinary tumor boards should include pathologists to ensure appropriate treatment options are considered and all histologic subtypes should be considered potential candidates for chemotherapy and first line clinical trials unless there is a compelling reason. REFERENCES 1. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyons, France.: International Agency for Research on Cancer (IARC); 2015. 2. Rosen LE, Karrison T, Ananthanarayanan V, et al. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. Mod Pathol 2018.

Keywords: classification, multidiciplinary, Mesothelioma

WS02 MESOTHELIOMA WORKSHOP (TICKETED SESSION)
SATURDAY, SEPTEMBER 7, 2019 08:00–11:30

WS02.04 MOLECULAR SECTION

L. Fernandez-Cuesta

International Agency for Research on Cancer (IARC-WHO), Lyon/France

Molecular and immunologic breakthroughs are transforming the management of thoracic cancer, although advances have not been as marked for malignant pleural mesothelioma (MPM) where pathologic diagnosis has been essentially limited to three histologic subtypes. A multidisciplinary group (pathologists, molecular biologists, surgeons, radiologists and oncologists), sponsored by EURACAN/IASLC met in 2018, to critically review the current classification. Multidisciplinary recommendations for pathology classification and application were made, which will allow more informative pathologic reporting and potential risk stratification, to support clinical practice, research investigation and clinical trials. I will present the main points of the discussion around the use of molecular characteristics to inform and improve the current histopathological classification.

WS03 ITONF WORKSHOP: BRIDGING THE GAPS IN THORACIC ONCOLOGY NURSING - A GLOBAL PERSPECTIVE
(SIGN UP REQUIRED)
SATURDAY, SEPTEMBER 7, 2019 11:00–18:00

WS03.08 PANEL - EMERGING THERAPIES - IMMUNOTHERAPY

R. Thomas

Guy's and St Thomas' NHS Trust, London/United Kingdom

This panel session will focus on emerging immunotherapies, the aim is to bring the UK perspective to the panel particularly focusing on the role of the Lung Cancer Clinical Nurse Specialist (CNS) and how to support and counsel patients who are about to commence one of the new therapy combinations. The presentation from the UK will look at the current therapies in immunotherapy and then also look at two case studies which will bring the clinical trial data into real time perspective. In the UK there have been no new immunotherapies launched, however, what the landscape of immunotherapies is changing in the UK for non-small cell lung cancer patients in the form of multi-drug combinations. Most recently we have seen the introduction of Durvalumab as a treatment for locally advanced unresectable non-small cell lung cancer post platinum based chemoradiation (1). This combination is still awaiting formal NICE approval but NHS patients can access this via a Cancer Drugs Fund. The PACIFIC Trial demonstrated that patients who received Durvalumab after platinum based chemoradiation had a significant improvement in their progression free survival when compared to chemoradiation plus a placebo. The median duration of progression free survival was 17.2 months in the Durvalumab arm compared to 5.6 months in the placebo arm. The median time to death or distant metastases was 28.3 months in the Durvalumab arm compared to 16.2 months in the placebo arm (2). In the advanced metastatic setting there has recently been the introduction of the KEYNOTE-189 data which is looking at pembrolizamab + platinum/pemetrexed in patients who did not have any molecular mutations. This trial demonstrated an overall survival with a 51% reduction in the risk of death and superior progression free with a 48% reduction in the risk of progression or death. In March 2019 The IMpower150 trial showed significant improvements in progression-free and overall survival with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) versus the standard-of-care bevacizumab plus carboplatin plus paclitaxel (BCP) in chemotherapy-naive patients with non-squamous metastatic non-small-cell lung cancer who have an ALK rearrangement or who have an EGFR mutation. This combination has now been approved by NICE and will provide patients who progress on a tyrosine kinase inhibitor a multi-drug treatment combination which has been demonstrated in the Impower 150 trial to deliver overall survival of around 19.2 months when compared to bevacizumab/carboplatin and paclitaxel. The UK has demonstrated the importance of the input of the Lung Cancer CNS in supporting patients who are about to commence treatment and also in proactively monitoring patients for potential adverse events (3). However, with the emergence of multidrug treatments how do we as Lung Cancer CNS's assess which adverse events are related to the immunotherapy and which are related to the chemotherapy. Looking at the current clinical trial data from the studies above and then focusing on two real life patient case studies will provide some clear guidance on how to support patients whilst monitoring for any potential adverse events and dealing with these in a timely and accurate manner. The table below sets out just some of the main challenges faced in identifying immunotherapy related adverse events.

We as nurse specialists are now experienced at caring for patients on single agent immunotherapy treatments but one of the many challenges is that many lung cancer patients will have co-morbidities which can cloud the identification of immunotherapy adverse events. For example 40-70% of lung cancer patients will also have a diagnosis of COPD. Pneumonitis can present in a very similar pattern to organising pneumonia and chest infections meaning that accurate and detailed assessments are needed to ensure adverse events are identified and treated accordingly. However, when you also add into the treatment plan platinum doublet chemotherapy with or without radiotherapy the potential for adverse events increases, the panel will look at the PACIFIC data to assess the reporting of adverse events in this patient group. The panel will also then assess the trial data for platimum doublet chemotherapy and immunotherapy in the treatment of metastatic non-small cell lung cancer and whether this patient group with a potentially higher symptom burden reported an increase in the number of adverse events when compared to either single agent immunotherapy or platinum doublet chemotherapy alone. One other important focus of the panel discussion will be to look at what the future treatment landscape for patients may be and how this will impact on progression free survival and living with lung cancer. This will mainly cover recent updates from ASCO and will aim to provide a flavour of what we may see coming into clinical practice in the coming months. References Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation. Technology appraisal guidance [TA578] Published date: 01 May 2019. https://www.nice.org.uk/guidance/TA578 Overall survival with Durvalumab after chemoradiotherapy in Stage III NSCLC. Scott. A; Augusto, V; Davey, D et al. www.nejm.org/doi/full/10.1056/NEJMoa1809697. The National Lung Cancer Audit (2018) www.rcplondon.ac.uk/projects/national-lung-cancer-audit https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30084-0/fulltext Yoest JM (2017) Clinical features, predictive correlates and pathophysiology of immune related adverse events in immune checkpoint inhibitor treatments in cancer: a short review. Immunotargets Therapeutics. 6. P 73-82.

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.01 CHALLENGES OF DATA ENTRY IN IASLC DATABASE

B. Fournier

IUCPQ-Laval University, Quebec/Canada

Session Staging Workshop Part 1: IASLC Database Challenges and Application. Our experience with the registry of the patients at IUCPQ- University Laval Quebec From 2015, IASLC submitted to the Union for International Cancer Control (UICC) & to the American Joint Committee on Cancer (AJCC) recommendations for the 8th Edition for the Staging of Lung Cancer. Those recommendations issued from a retrospective data collection of patients (94,708) diagnosed with lung cancer around the world between 1999 and 2010 were accepted by UICC and AJCC in 2017.1-2-3 Since the Staging and Prognostic Factors Committee of IASLC has entered in the next phase of the project designed to inform the 9th forthcoming TNM edition. Volunteer site participants were invited to submit data on patients diagnosed with lung cancer between January 1, 2011, and December 31, 2019.4 IUCPQ has officially started the collaboration to the Lung Cancer Staging Project in June 2018. So far, we have entered over 1 000 patients in the database. Accesses to Patients' Medical Chart and to the Electronic Data Base (EDB) are the main tools used to participate to this project. Our growing experience at IUCPQ with IASLC database demonstrates that a strategy to access medical charts, a multidisciplinary team work and constant review of the data are key points to ensure the quality of the data collection. This presentation will describe our experience with the registry of the patients in the Electronic Data Capture system. 1 Rami-Porta, R., Bolejack, V., Crowley, J., Ball, D., Kim, J., Lyons, G. et al. (2015). The IASLC Lung Cancer Staging Project Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology Vol. 10 No.990-1003 http://DOI:10.1097/JTO.0000000000000559 2 Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, E.E., et al.(2015). The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology Vol.11 No. 1:39-51. http://dx.doi.org/10.1016/j.jtho.2015.09.000 3 Detterbeck, F.C., Francklin, W.,A., Nicholson, A.G., Girard, N., Arenberg, D.,A., Travis, W.D., et al. (2016). The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancer from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification fir Lung Cancer. Journal of Thoracic Oncology Vol 11 No.5:651-665 http://dx.doi.org/10.1016/j.tho.2016.01.025 4 Giroux, J.,Van Schil, P., Asamura, H., Rami-Porta, R., Chansky, K., Crowley et al. (2018). The IASLC Lung Cancer Staging Project: A Renewed Call to Participation. Journal of Thoracic Oncology Vol.13 No. 6:801-809. https://doi.org/10.1016/j.jtho.2018.02.012

Keywords: Lung Cancer Staging-Registry of patients in the Database

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.02 CHALLENGES IN IMAGING EVALUATION TO ENTER DATA IN THE IASLC DATABASE

H. Prosch

Medical University of Vienna, Vienna/Austria

Soon after the publication of the proposals for the 8thedition of the TNM staging system, the International Association for the Study of Lung Cancer (IASLC) opened a new database for data collection for the next iteration of the lung cancer staging system (1). The database contains more than 450 fields, which address data on patient characteristics, baseline laboratory values, as well as the results of pulmonary function, imaging, and pathological tests. As the database collects the data about lung cancer newly diagnosed between January 1, 2011, and December 31, 2019, the data entered might be predominantly retrospectively collected in some centers. From an imaging perspective, this might lead to a number of problems. First, at least some of the elements required by the database might not be mentioned in the radiological reports. This may necessitate a re-evaluation of the imaging studies by an experienced radiologist, which might not be possible in all centers. Furthermore, the levels of training of the radiologists and reporting across different countries may be variable and thus introduce some degree of imprecision into the quality of the data. As an example, in T staging, particular attention has to be paid to thorough measurements to ensure that the largest diameter in the axial, coronal, or sagittal plane is measured (2). Caution should also be taken not to overdiagnose additional pulmonary nodules as metastases. In N staging, particular attention has to be paid to the lymph node atlas-mining, particularly the well-known pitfall in the correct assignment of lymph nodes at levels 4 and 10 (3-5). Furthermore, the quality of imaging and the availability of more advanced/expensive imaging techniques may also vary from country to country. As an example, the availabilities of PET/CT and/or MRI are not homogenous all over the globe. However, if PET/CT is not performed routinely in operable patients, as many as 20% of unexpected distant metastases might be missed (6). Future staging projects should specifically address these issues in order to further improve the the quality of data necessary to improve the next iteration of the staging system. 1. Giroux DJ, Van Schil P, Asamura H, Rami-Porta R, Chansky K, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: A Renewed Call to Participation. J Thorac Oncol. 2018;13(6):801-9. 2. Travis WD, Asamura H, Bankier AA, Beasley MB, Detterbeck F, Flieder DB, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016. 3. El-Sherief AH, Lau CT, Obuchowski NA, Mehta AC, Rice TW, Blackstone EH. Cross-Disciplinary Analysis of Lymph Node Classification in Lung Cancer on CT Scanning. Chest. 2017;151(4):776-85. 4. El-Sherief AH, Lau CT, Wu CC, Drake RL, Abbott GF, Rice TW. International association for the study of lung cancer (IASLC) lymph node map: radiologic review with CT illustration. Radiographics. 2014;34(6):1680-91. 5. Aviram G, Revel MP. Misclassification of Lymph Nodes in Lung Cancer Staging: Can We Improve? Chest. 2017;151(4):733-4. 6. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative Staging of Lung Cancer with Combined PET-CT. N Engl J Med. 2009;361(1):32-9.

Keywords: Lung cancer, staging, TNM

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.03 HOW TO ADJUST PATHOLOGY EVALUATION ACCORDING TO IASLC DATABASE

P. Joubert

Quebec Heart and Lung Institute, Quebec/Canada

In 2016 the 8th edition of the TNM by the International Association for the Study of Lung Cancer (IASLC) refined the definition of early-stage lung cancer by further subdividing the T1 and T2 descriptors according to 1 cm size cut-offs. In addition, in nonmucinous adenocarcinoma (AC) with a lepidic component only the size of the invasive component defines the T descriptor rather than the total size of the lesion. These modifications not only led to a better prognostication of surgical adenocarcinoma patients, but they also emphasize the importance to accurately assess (grossly and microscopically) and report the histological patterns of adenocarcinoma. In addition, although the number of metastatic lymph nodes was not integrated in the N descriptor, its relevance has been demonstrated and will be addressed in the upcoming edition. The purpose of this presentation is to review the key elements of a pathology report when evaluating a pulmonary carcinoma, and to discuss the challenges encountered in pathology for the development of the upcoming edition of the TNM.

Keywords: Pathology, TNM, Report

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.04 INSTITUTIONAL BENEFITS OF ADHERENCE TO IASLC DATABASE

C. Labbe

IUCPQ, Quebec/Canada

The International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project, through an electronic data capture system, is a global effort to study and improve the current and future lung cancer staging system. In 2016, the 8thedition of the TNM was developed with the participation of 35 centres from 16 countries. In 2018, the Heart and Lung Institute in Quebec City, Canada, started to collect and send data for the upcoming 9thedition of the TNM classification. The purpose of this presentation is to review and discuss the potential institutional benefits of adherence to the IASLC electronic database, namely the comprehension by all participating centers of the role and the importance of the database, the organization of an interdisciplinary group to ensure that the entire clinical pathway of lung cancer patients is evidence-based, the standardisation of radiology and pathology reports, and the improvement in rates of lobe-specific systematic nodal dissection for all lung resections.

Keywords: staging, Lung cancer, TNM

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.05 DEVELOPING THE IASLC LUNG CANCER STAGING DATABASE AND RECOMMENDATIONS FOR THE 9TH EDITION

D. Giroux[1], H. Asamura[2], P. Ugalde[3]

[1]*Cancer Research And Biostatistics (CRAB), Seattle/United States of America,* [2]*Keio University School of Medicine, Tokyo/Japan,* [3]*Institut Universitaire de Cardiologie et Pneumologie de Quebec, Quebec/Canada*

Background Since the turn of the century, the international database of the IASLC Staging Project has served as the foundation for evidence-based recommendations for revisions to the TNM classification system for lung cancer. These recommendations were adopted by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), establishing the IASLC Staging Project as a global resource for lung cancer staging research. The project is currently midway through its third iteration of data collection, which was begun in 2017 and includes lung cancer cases diagnosed from 2011 through 2019, with follow-up for survival through 2021. The preferred mechanism for data collection is direct, online entry into a central database administered by Cancer Research and Biostatistics (CRAB) in Seattle, Washington. Discussion The data fields in the lung cancer database are extensive, having been revised in 20171 by the IASLC Staging and Prognostic Factors Committee (SPFC) to address specific research questions framed by each of its 15 subcommittees, such as the impact of direct extension into specific anatomic sites on survival, the relative effects of location vs size of involved nodes, or the importance of the size of distant metastases relative to the number of lesions and distant sites. The committee will consider the prognostic value of these anatomic parameters independently and in the context of non-anatomic factors such as sex, comorbidity, laboratory values that correlate with survival, or molecular markers. Existing institutional databases and large registries have traditionally been used to supplement the data contributed using the online system; however, these external sources rarely contain sufficient detail to address all of the committee's stated objectives.2 The SPFC is chaired by Hisao Asamura, MD, and has separate subcommittees for T, N, M, ground glass opacities and adenocarcinoma in situ, neuroendocrine tumors, stage groupings, lymph node chart, validation and methodology, prognostic factors, R factor (completeness of resection), radiology and imaging, multiple pulmonary nodules, molecular markers, and data quality, as well as a steering committee that provides oversight. SPFC members are expected to demonstrate leadership and promote participation in the project, as well as develop and evaluate proposals for change. The current SPFC membership reflects the diverse geographic representation in the database used to support the most recent (8th edition) recommendations. As of 5 June 2019, over 3,000 patients from 14 countries have been enrolled directly in the online system. Larger databases designed to be compatible with the project have also been transferred from Japan and the United States. In the newly redesigned IASLC web site (www.iaslc.org), new participants can sign up online to contribute data by choosing the IASLC Staging Project page under the Research & Education heading. Following the publication of the core recommendations for the 9th edition of TNM, the web site may also be used to submit research proposals for secondary use of the data. Secondary use may be restricted according to agreements with individual sites in some cases. All proposals will be reviewed by the steering committee according to published guidelines.3 Conclusion In the context of shifting paradigms and rapid advancements in treatments, diagnostics, and molecular technologies, the SPFC is tasked with evaluating and improving TNM staging on a global scale. To this end, we aim to engage a wide variety of research partners and to increase participation in previously underrepresented regions such as Egypt and India, where the first sites from each of these countries have recently been recruited. The collection of a large and comprehensive database will be pivotal to the SPFC's ability to provide data-informed, universally applicable, and balanced recommendations that will be used world-wide by physicians, researchers, and patients. As we continue to prepare for upcoming analysis of the 9th edition database, the IASLC membership is encouraged to participate through the contribution of data and engagement with the SPFC and its mission. This global effort to improve the TNM staging criteria presents a unique opportunity to collaborate in international public health research. References Giroux DJ, Schil PV, Asamura H, et al. The IASLC Lung Cancer Staging Project: A Renewed Call to Participation. *J Thorac Oncol* 2018;13:801-809. Rami-Porta R, Bolejack V, Giroux D, et al. The IASLC Lung Cancer Staging Project: The New Database to Inform the Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 2014;9:1618-1624. Goldstraw P, Rami-Porta, R, and Crowley J. We Probably Have the Answer: Now What is the Question? *J Thorac Oncol* 2009;4:939-940.

Keywords: Lung cancer, lung cancer databases, lung cancer staging

WS04 STAGING WORKSHOP PART 1: IASLC DATABASE CHALLENGES AND APPLICATION
MONDAY, SEPTEMBER 9 14:00–15:30

WS04.06 CASE DISCUSSION

P. Ugalde[1,2]

[1]*Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec/ Canada,* [2]*Institut Universitaire de Cardiologie et Pneumologie de Quebec, Quebec/Canada*

In this presentation we will present how we access a Patient Medical Record to include a case in the IASLC database. Through a precise strategy we collect patient's data and include in the Electronic Data Base.

WS05 STAGING WORKSHOP PART 2: THE IMPORTANCE OF INVASIVE NODAL STAGING IN THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 9 15:45–17:15

WS05.01 INVASIVE PRE-OPERATIVE STAGING OF LUNG CANCER

S. Call

Hospital Universitari MútuaTerrassa, Terrassa/Spain

Although reliable mediastinal staging is essential for the management of NSCLC, the optimal approach to invasive mediastinal staging remains controversial. According on the current guidelines, preoperative invasive mediastinal staging can be omitted if all the following criteria apply: a) primary tumour located in the outer third of the lung; b) largest diameter of the tumour is ≤3 cm; c) absence of intrathoracic lymph node(s) on CT and PET (1,2). The rationale is that, in this situation, the rate of unsuspected pathologic mediastinal nodal disease is < 10% (3,4). When tumours are classified as clinical (c) N2-3 on PET-CT, the risk of mediastinal nodal involvement is at least 60% (1). In this situation, it is mandatory to pathologically confirm all abnormalities detected by CT or PET starting with an endosonography method (EBUS-FNA, EUS-FNA or their combination) and to reserve mediastinoscopy to validate their negative results (1,2). Regarding those tumours with an intermediate risk of N2-3 disease (and normal mediastinum by CT and PET) the rate of unsuspected N2 disease is: 20%-42%, for tumours classified as cN1, and 6%- 22.2% for tumours classified as cN0 and tumour size greater than 3cm (5-8). For these clinical scenarios, there is a little disagreement between American and European guidelines about the best staging procedure to start with. The American College of Chest Physicians (ACCP) guidelines suggest endosonography methods over surgical procedures (1), and the European Society of Thoracic Surgeons (ESTS) guidelines describe that the choice between mediastinoscopy with biopsies, or with pre-surgical lymphadenectomies or endoscopic staging by EBUS/EUS with FNA depends on local expertise (1,2). Regarding the accuracy of invasive mediastinal staging methods in this type of patients (clinical N0 disease by PET-CT), minimally invasive endoscopic techniques have a poor sensitivity (0.17-0.41) (5,9). On the other hand, due to the fact that performance of mediastinoscopy is investigator dependent, there is an important heterogeneity in the reported sensitivity and negative predictive values:0.32 to 0.97 and 0.8 to 0.99, respectively (2). Transcervical lymphadenectomies (video-assisted mediastinoscopic lymphadenectomy[VAMLA] and transcervical extended mediastinal lymphadenectomy[TEMLA]) are the only pre-surgical staging procedures with the highest sensitivity and negative predictive value reported to date for those patients with normal mediastinum by PET and CT: 0.88-0.96 and 0.94-0.99, respectively (8-10). Focusing oncN1 tumors, endosonography methods have a reported sensitivity ranging from 0.38 to 0.43. (5,6). This sensitivity increased to 0.73 by adding a confirmatory mediastinoscopy to validate negative endosonographies (6). Based on the results from the first prospective multicentre study (ASTER III) to evaluate the performance of surgical mediastinal staging (by mediastinoscopy or by VAMLA) in patients with cN1, the superiority of surgical method was confirmed obtaining a global sensitivity of 0.73 and a negative predictive value of 0.92 (7). Regarding those tumours with high SUVmax, cN0 but size greater than 3cm and specially in adenocarcinomas the rate of unsuspected N2 is: 6%-14.8% (3,4). A recent prospective study to validate the feasibility and accuracy of VAMLA reported a rate of 22.2% of unsuspected N2 disease for cN0 tumour >3cm (19% N2 tumours and 3,2% N3 tumours) (8). Therefore, based on this results, it is recommendable to validate negative results of endosonographies with a surgical procedure in the same line of those patients with tumours classified as cN1. *Conclusions* Currently, surgical methods are mainly indicated to validate negative results of minimally invasive endoscopic techniques for those tumours with high suspicion of mediastinal involvement by PET-CT. Based on the latest evidence, mediastinoscopy and, especially, transcervical lymphadenectomies are the most reliable staging methods for the subgroup of patients with intermediate risk of N2 disease and normal mediastinum by PET and CT. Consequently, future staging algorithms should recommend surgical methods as the preferred technique for this subset of patients. *References* 1. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:787-98 2. 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Keywords: invasive staging, mediastinoscopy, transcervical lymphadenectomies

WS05 STAGING WORKSHOP PART 2: THE IMPORTANCE OF INVASIVE NODAL STAGING IN THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 9 15:45–17:15

WS05.03 HOW TO PERFORM A PROPER SYSTEMATIC NODAL DISSECTION IN LUNG CANCER SURGERY

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In 1960, Cahan first reported lobectomy with regional lymph node dissection, which was called "radical lobectomy."1 Since then, this procedure has been widely accepted, and systematic nodal dissection (SND) is an internationally accepted standard procedure for lymph node dissection in cases of non-small cell lung cancer (NSCLC). The purpose of SND is aimed at removal of all mediastinal lymph node stations regardless of the anatomical location of the primary tumor in the lobe. The significance of SND can be discussed from the clinical aspects of accurate staging and survival benefit. Metastatic lymph nodes obtained via SND can undergo careful and accurate accurate histopathological evaluation, which offers several clinical advantages. However, the therapeutic effect of SND remains unclear.2-5 Technically, SND involves complete excision of all tissues in a particular anatomical compartment along with a few components of surrounding anatomical structures. An ideal technique involves en bloc removal of all tissue that may contain cancer cells, including lymph nodes and surrounding fatty tissue within pre-defined anatomical landmarks. All of lobectomies for NSCLC are performed via posterolateral incision using minimally invasive open surgery (MIOS) approach in our institution. Common to both sides, the fourth or fifth intercostal space provides better access in SND. During the SND, special care is warranted to prevent interruption of

the lymphatic vessels and/or injury to the lymph nodes themselves. Additionally, connective tissue ligation is necessary in a few cases to prevent postoperative chylothorax. Identification of the bilateral recurrent nerves is important because recurrent nerve paralysis can cause serious postoperative complications. Based on AOSOG Z0030 trial, complications of SND include postoperative chylothorax (1.7%), intraoperative bleeding (1.1%), and recurrent laryngeal nerve injury (0.9%).5 Although SND is a standard procedure of lymph node dissection for NSCLC, previous studies have analyzed in detail the lymphatic pathway and the pattern of lymph node involvement based on the primary location by lobe. Asamura et al. 6 reported that right upper lobe tumors and left upper segment tumors tend to metastasize to the superior mediastinum and that these lesions rarely metastasize to the subcarinal nodes without concomitant metastasis to the hilar or superior mediastinal nodes.6 The lobe-specific patterns of nodal metastases are being recognized owing to increasing analyses of the lymph node metastatic pathway.6-9 Based on these results, lobe-specific lymph node dissection is being increasingly performed under certain conditions, for example, based on tumor location, tumor size, cell type, and the percentage of the area of ground glass opacity visualized in the tumor on computed tomography. References 1. Cahan WG. Radical lobectomy. J Thorac Cardiovasc Surg; 1960;39:555-572.2. Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non small cell lung cancer. Ann Surg 1998;227:138-144.3. Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. World J Surg 1998;22:290-294.4. Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer 2002;36:1- 6.5. Wright G, Manser RL, Byrnes G, et al. Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. Thorax 2006;61:597-603.6. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas based on a retrospective study of metastasis and prognosis. J Thorac Cardiovasc Surg 1999; 117:1102-11117. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral non-small cell carcinoma of the lung. Are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125-11348. Okada M, Tsubota N, Yoshimura M, et al. Prognosis of completely resected pN2 non-small cell carcinomas: what is the significant node that affects survival? J Thorac Cardiovasc Surg 1999;118:270-2759. Watanabe S, Suzuki K, Asamura H. Superior and basal segment lung cancers in the lower lobe have different lymph node metastatic pathways and prognosis. Ann Thorac Surg 2008;85:1026-1031.

WS05 STAGING WORKSHOP PART 2: THE IMPORTANCE OF INVASIVE NODAL STAGING IN THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 9 15:45–17:15

WS05.04 PARTICULARITIES OF LYMPHADENECTOMY IN MALIGNANT PLEURAL MESOTHELIOMA

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Malignant Pleural Mesothelioma (MPM) is an aggressive disease with a poor prognosis. Patients treated with multimodality approach have a survival of 20 to 30 months. Survival is worse in patients with nodal disease1. Lymph node involvement is reported in 35 to 50% of patients undergone surgery. The lymph node staging system and the nodal categories (N0–N3) in the mesothelioma TNM staging are based on the lung cancer TNM. There are significant anatomic differences between the lymphatic drainage pathways of the pleura and the lung parenchyma2. The parietal and visceral pleura have two distinct and separate lymphatic drainage probably. The MPM arises from the parietal pleura and the intrapulmonary lymph node may not be the first lymph nodes to be involved, but they may be involved in a later phase. The lymph drainage of the parietal pleura flows initially through intercostal lymphatic channels, anteriorly to the internal thoracic artery nodes or posteriorly to the internal intercostal lymph nodes (Figure 1). Drainage can also be directly into axillary or cervical lymph nodes. Diaphragmatic lymphatic drainage can flow into mediastinal, internal thoracic, or abdominal nodes3. The MPM may involve also the endothoracic fascia, the chest wall, the mediastinal adipose tissue, the pericardium and the diaphragm, making the lymphatic drainage more complex. The intercostal space lymph nodes, the paraspinal lymph nodes, the peri diaphragmatic lymph nodes and the internal mammary chain lymph nodes may be the first lymphatic stations to be involved rather than the intrapulmonary lymph nodes. It was reported that extrapleural and the mediastinal nodes (N2) may in fact be the initial site of nodal metastases in patients with mesothelioma, with N1 nodes becoming secondarily involved only when invasion of lung parenchyma occur4. Data from several single-institutional retrospective series have yielded conflicting evidence as to whether there is indeed a prognostic difference between patients with pathologic N1 (pN1) and pN2 pleural mesothelioma. Those data are based on the lymph node mapped derived from lung cancer staging system. The IALSC TNM collected data from 29 institution and specifically analysed the impact of pathological nodal status on survival5,6. 851 cases were eligible for the pathological N status analysis. According to the analysis for the revision of the N descriptor the survival of pN1 and pN2 was 16.9 and 17.4 months (p=0.28)5. Interestingly 54% had skip metastases based on the lung cancer staging map. Based on this evidence in the 8th TNN edition N1 and N2 were grouped together3 and N3 disease was re classified as N2 disease. Like for other tumours, such as breast or melanoma, few papers tried to identified a sentinel lymph node in MPM with no success7. In the paper of Edwards et al8 there is no mention of the intercostal lymph nodes sampling, reflecting how limited the data on lymph node mapping are and how variable is the sampling technique between surgeons. During the operation an extensive nodal sampling should be performed. The intercostal lymph node at different levels, the mediastinal and intrapulmonary stations, the peri diaphragmatic and the internal mammary lymph nodes should be sampled. Specifically, the peri diaphragmatic lymph node should be categorized in above and below the diaphragm if the diaphragm is removed. All these lymph node stations should be sampled to collect more data on the lymph node drainage and spread of the disease according to the parietal and visceral pleura involvement. In conclusion, there is variability in the lymphatic drainage in mesothelioma. The lymph node map we used for mesothelioma is inadequate and a different lymph node map specific for mesothelioma should be created based on the different lymphatic drainage of the parietal and visceral pleura compared to the lung. There are no guidelines in how to perform lymph node sampling in mesothelioma. A routine lymphadenectomy should be performed at the time of surgery considering extrapleural, mediastinal and intrapulmonary lymph node stations according to the different lymphatic drainage of the parietal and visceral pleura. References Flores RM, Routledge T, Seshan VE, et al. 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Keywords: malignant pleura mesothelioma, lymph node map, Lymphadenectomy

WS05 STAGING WORKSHOP PART 2: THE IMPORTANCE OF INVASIVE NODAL STAGING IN THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 9 15:45–17:15

WS05.05 LYMPHNODE DISSECTION IN THYMIC MALIGNANCIES: IMPLICATIONS OF THE ITMIG/IASLC LYMPH NODE MAP OF THE TNM CLASSIFICATION AND STAGING

Y.T. Kim, I.K. Park

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The significance of lymph node metastases and lymph node dissection (LND) remains unclear and underestimated in thymic malignancies. Given the fact that LND is an important surgical procedure for most of the solid organ malignancies, the role of LND in thymic malignancies should be established. The ITMIG and the IASLC proposed a new lymph node map and separated N stage in the eighth edition of TNM stage classification system for thymic malignancies. They recommended that any suspicious nodes should be routinely removed. For stage I or II thymoma, adjacent nodes as well as anterior mediastinal nodes should be removed, and for stage III thymoma, systematic anterior mediastinal node dissection and systematic sampling of appropriate intrathoracic nodes were recommended. For the thymic carcinoma, a systematic sampling of anterior mediastinal, intrathoracic, supraclavicular, and lower cervical nodes were recommended. However, there is no prospective study to validate such recommendations as these recommendations are based on the old map and old staging system. As a consequence, a revised recommendation based on a new map and a new staging system is necessary. Four aspects should be considered with regards to the appropriate LND during thymectomy. The first aspect is an indication. In what circumstances, the LND should be performed?. The second one is the lymph node stations to be dissected. Proper understanding of lymphatic pathway in thymus would be helpful to select lymph node to dissect. The third aspect is the adequate number of the lymph node to dissect. Often time, the quality of LND is evaluated by the number of the dissected lymph node. The last aspect is the surgical approach. It is sometimes challenging to dissect every nodal station by means of minimally invasive surgery. What are the surrogate markers to predict lymph node metastasis in thymic malignancies? In many studies, histologic type and T stage have been reported as predictors of lymph node metastasis. Lymph node metastasis is more frequent in thymic carcinoma and carcinoid compared with that in thymoma. Also, it is frequent in tumors invading adjacent structures (T2 or T3). Which lymph nodes stations are essential to dissect? Murakami et al. reported that the main lymphatic flow is a cranial direction to the cervical area, and they nicely described that the right paratracheal node group is the largest collecting area. In our group, we found that the right paratracheal lymph node station is the most common area of lymph node metastasis among deep regional node groups. Can we score adequacy of LND in thymic malignancies? Our group previously showed that lymph node dissection more than 10 nodes predict prognosis better. When we divided patients into N0a when LND less than 10 were performed, N0b when LND was performed more than 10, and Nx when no LND was performed, the prognosis of N0a group was inferior to N0b and was similar to Nx group. In our recent paper, we reviewed 131 thymic malignancy patients who underwent LND using 8th TNM staging and ITMIG Lymph node map. Lymph node metastasis was detected in 13 patients (N1 in six and N2 in seven). Six N2 patients (86%) had right paratracheal node metastases. The rates of node metastasis were 1% in T1 as compared to 37.5% in T2 or T3 ($p < 0.001$). The rates of node metastasis were 8% in the M0 as compared to 43% in the M1 ($p = 0.03$). The rate was higher in thymic carcinoma (25%) than in thymoma (5.1%, $p = 0.01$), and the rates also differed between the subtypes of thymoma. There was no node metastasis of the A, AB, or B1 histologic subtypes. Tumor size was also a significant factor which can predict node metastasis. The optimal cutoff value for the node metastasis was 6 cm, and the specificity was 62%. Only 16% of the patients had received a preoperative histologic diagnosis. All patients with node metastasis had cTNM stage II or higher thymic malignancy. The freedom from recurrence rate of the pN1 or pN2 was significantly worse than that of the pN0 (5-year rate 38.5% versus 87.9%, $p < 0.001$). Based on the previously mentioned information, we proposed a revised recommendation for LND in thymic malignancies. For N1, peri-thymic, prevascular, and supradiaphragmatic lymph nodes should be included as a routine en-bloc dissection. Lower cervical lymph nodes and paraaortic nodes should be either sampled or dissected, especially in c-stage II or higher. For right paratracheal N2 nodes, sampling for c-stage I, dissection for c-stage II or higher is recommended. For other N2 nodes, sampling is recommended in c-stage II or higher, or in thymic carcinoma. Almost all of the anterior regional nodes can be dissected during total thymectomy. During MIS, the paratracheal node can be dissected via right side approach. The paraaortic and subaortic nodes can be dissected via left side approach. The cervical lymph node can be dissected by adding cervical approach if it is necessary. However, the routine dissection of the cervical node is not recommended. A bilateral approach may be recommended, especially if the left side is chosen for the resection of the primary tumor. In summary, LND is recommended in locally advanced thymoma and thymic carcinoma. As the frequent metastatic stations are peri-thymic and right paratracheal lymph nodes, LND of these stations are necessary. LND may be possible during minimally invasive surgery, and the bilateral approach may be recommended in tumors with higher than T2, especially in left-sided tumors.

Lymph node group	Recommendations
Anterior regional nodes (N1)	
Peri-thymic nodes	
Prevascular nodes	Routine en-bloc dissection
Supradiaphragmatic nodes	
Low anterior cervical nodes	Sampling in stage I, Dissection in stage ≥ II
Paraaortic nodes	
Deep regional node (N2)	
Right paratracheal nodes	Sampling in stage I, Dissection in stage ≥ II
Other nodes	Sampling in stage ≥ II, thymic carcinoma

***All suspicious nodes should be dissected**

Keywords: Thymic malignancy, lymph node, staging

WS05 STAGING WORKSHOP PART 2: THE IMPORTANCE OF INVASIVE NODAL STAGING IN THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 9 15:45–17:15

WS05.06 RELEVANCE OF LYMPHADENECTOMY IN CARCINOMA OF THE ESOPHAGUS AND OF THE ESOPHAGOGASTRIC JUNCTION

G. Darling

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Historically surgeons thought that removal of lymph nodes was unimportant as esophagectomy was viewed as a palliative operation. As more patients survive their surgery, overall survival has become an important goal. Does lymphadenectomy contributes to improved survival? The optimum lymphadenectomy has two components: required nodal resection for accurate staging and required nodal resection for optimizing survival. Number of resected nodes required for accurate staging In patients who have 8 metastatic nodes, removing more nodes doesn't change prognosis or improve survival. However in early stage disease, resection of a high number of nodes is required to be certain that the patient is truly N0. Using the WECC database, Rice reported that for short (<2.5cm), well differentiated and superficial cancers, >60 resected nodes are required to be certain that the patient is truly N0 [1]. A minimum of >12 resected nodes is required to achieve >90% sensitivity in staging accuracy [2] and Rizk identified that if > 18 nodes are resected the T stage is no longer prognostic [3]. The International Society for Diseases of the Esophagus consensus conference recommended that the minimum number of nodes required for accurate staging is 15 and this remains the current recommendation of the NCCN [4]. Patients with < 15 nodes resected are less likely to have nodal metastases identified and there is a survival benefit when > 15 nodes are resected, suggesting that with < 15 resected nodes, patients are understaged [5,6,7]. Further, with less than 15 nodes examined, N0 vs. N1 becomes the deciding factor in prognosis [8]. Patients who had a transhiatal esophagectomy, or had < 16 nodes resected or were pN1 had similar median survival (13, 14, 12 months respectively) compared to those who have a transthoracic resection (24 months), or were pN0 (38 months) or had> 16 nodes resected (25 months) [9]. Number of resected nodes required to optimize survival Rizk reported that the optimal number of resected nodes varies based on pT stage. For pT1 tumors only 10 nodes are required whereas for pT2 20 nodes but ≥ 30 nodes are required for pT3/4 tumors [10].

However Greenstein reported that survival was improved if > 10 nodes were removed for cT2-3N0 patients but > 18 nodes for cT1N0 [11]. Altorki reported that the number of nodes required to impact survival depended on N status. Survival increases with number of nodes removed but for N1 patients removal of > 17 nodes was required but for N0 patients resection of > 40 nodes was required to improve survival [12]. Using the SEER database, > 30 resected nodes are required to optimize survival [13, 14]. Samson, using the NCDB, compared mortality between patients who met the NCCN guideline of removing ≥ 15 nodes vs those who had < 15 nodes removed. Removal of >15 nodes was associated with lower mortality and the optimum threshold identified was 25 nodes [15]. Peyre also identified that removal of 23 nodes was the optimum threshold for surviva [16]. However, studies by Lagergren report no benefit to increased lymph node removal[17,18]. The minimum number of resected nodes required is 15 however, but the number required to optimize survival is 23-30. Required Nodal stations for resection and the relevance of tumor location and histology The lymphatics of the esophagus run longitudinally in the submucosa as well as draining horizontally into regional lymph nodes or directly into the thoracic duct. Akiyama reported that tumors of the upper third of the esophagus could have lymph node metastases from the upper mediastinum to the upper abdomen. Tumors of the lower third of the esophagus most commonly had lymph node metastases near the celiac and left gastric artery but also in the infracarinal mediastinum. The 8th edition of the AJCC staging manual identified all nodes as regional nodes. Thus all regional lymph nodes should be resected including the upper abdominal nodes and mediastinal nodes. This applies to tumors of all histogies. The effect of induction therapy on lymph node harvest suggests that preoperative chemoradiation may reduce the number of lymph nodes harvested [20,21], however in the CROSS trial there was no difference in lymph node harvest [22]. Summary Lymphadenectomy is important in esophagectomy for cancer with regard to staging accuracy but also contributes to survival. The more nodes examined, the higher the accuracy of N staging. The number needed to ensure accurate N stage for early cancers ranges from 40 to 60 nodes for T1 cancers, while the minimum number for all cancers is 15 nodes. Resection of < 15 nodes understages patients and compromises survival. The more nodes removed, the better the survival. However the optimum threshold appears to be 23-30 nodes. An important consideration is that all nodes are considered regional nodes and should be resected as a key component of esophagectomy for cancer. References 1. Rice. Ann Surg. 2017; 265: 122–129. 2. Dutkowski. Hepatogastroenterology 2002; 49: 176-180. 3. Rizk J Thorac Cardiovasc Surg. 2006;132:1374 –1381. 4. Fumagalli. Dis Esophagus 1996; 9: S30-S38. 5. Barbour. Ann Surg Oncol 2007; 14: 306-316. 6. Gu Cancer 2006; 106: 1017-1025. 7. Bollschweiler J Surg Oncol 2006; 94: 355-363 8. van Sandick J Am Coll Surg 2002; 194: 28-36. 9. Junginger. Eur J Surg Oncol. 2006; 32:749-55. 10. Rizk Ann Surg 2010; 251: 46–50 11. Greenstein. J Am Coll Surg 2008; 206: 239-246 12. Altorki. Ann Surg 2008; 248: 221-226 13. Groth. JTCVS 2010; 139 612-620 14. Schwarz. J Gastrointest Surg 2007; 11: 1384-1393 15. Samson. Ann Thor Surg 2016; 101: 2102-2111 16. Peyre. Ann Surg 2008; 248: 549-556. 17. Lagergren. JAMA Surg 2016; 151: 32-39, 18.Van der Schaaf J Natl Cancer Inst 2015: 107 19. Akiyama. Ann Surg 1981; 194; 438- 446 20. Samson. Ann Thor Surg 2017;103: 406-415 21. Marriette. Ann Surg 2008;247: 3565-371 22. Oppedijk. J Clin Onc 2014;32: 385-391

Keywords: esophagectomy, esophageal cancer, Lymph Node Dissection

Oral Sessions

OA01 OA01 ADVANCED DIAGNOSTIC APPROACHES FOR INTRATHORACIC LYMPH NODES AND PERIPHERAL LUNG TUMORS
SUNDAY, SEPTEMBER 8 10:30–12:00

OA01.01 PREDICTIVE VALUE OF EBUS STRAIN ELASTOGRAPHY IN MEDIASTINAL LYMPH NODE STAGING; THE E-PREDICT MULTICENTER STUDY RESULTS

R. Verhoeven[1], R. Trisolini[2], F. Leoncini[3], M. Bezzi[3], P. Candoli[4], A. Messi[5], M. Krasnik[6], J. Annema[7], C. Korte[8], E. Van Der Heijden[1]

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Background: Systematic assessment of lymph nodal involvement by EBUS-TBNA is indicated for suspected and proven lung cancers. Nodal size and PET characteristics help guide which lymph nodes to sample. Especially smaller lymph nodes remain challenging, since PET is of limited value due to low resolution. Additional ultrasound B-mode features such as lymph node size, margin or node heterogeneity have shown variable predictive outcomes. Ultrasound strain elastography (EBUS-SE) is a promising technique. By monitoring tissue deformation over time using ultrasound imaging, a relative tissue strain can be computed. Lower tissue strain is shown to correlate to malignancy. Using a standardized measurement procedure (RespirationDOI: 10.1159/000494143), we aimed to assess the value of strain elastography for predicting lymph node malignancy in addition to size information. **Method:** This multicenter prospective international trial [NCT02488928] included patient with suspected or proven lung cancer in five hospitals. Measurements were obtained following to a standardized operating procedure using Pentax-Hitachi EBUS systems. Nodal cytopathology combined with follow up imaging (>6 months) or surgery were used as reference standard. If uncertainty in outcome remained, nodes were excluded in final analysis. **Result:** EBUS-SE was performed in 416 patients and 525 lymph nodes (June 2016 – July 2018). Final diagnoses showed 272 benign and 253 malignant nodes. Mean lymph node size was 12.3 mm. B-mode size and mean strain correlated to risk of malignancy with AUC of 78% and 76.8% (95% CI 0.73-0.81). Using a clinical work-up setting with 10mm and 8mm size cut-offs for aspiration, short axis size higher than 8 or 10mm resulted in respective sensitivity of 85% and 72%, specificity of 52% and 71%, PPV of 62% and 70% and NPV of 79% and 73%. Addition of strain elastography (mean<90) to EBUS-short-axis size (<10mm) increased overall sensitivity from 72% to 90% and NPV from 73% to 81%. More nodes were found false positive, specificity decreased from 71% to 42% and PPV went from 70% to 59%. Addition of strain (mean<78) to EBUS-size (<8mm) increased sensitivity from 85% to 94% and NPV from 79% to 85%. Specificity decreased from 52% to 32% and PPV from 63% to 55%. **Conclusion:** EBUS strain elastography is of added value in guiding nodal sampling. Strain and size combined can help identify more malignant nodes, although it will ultimately also lead to more false positive sampling. Strain information may especially be of potential value in nodes of small size, where PET resolution is limited.

Keywords: Elastography, predictive value, EBUS

OA01 ADVANCED DIAGNOSTIC APPROACHES FOR INTRATHORACIC LYMPH NODES AND PERIPHERAL LUNG TUMORS
SUNDAY, SEPTEMBER 8 10:30–12:00

OA01.02 ENDOBRONCHIAL ULTRASOUND STAGING OF OPERABLE NSCLC: TRIPLE NEGATIVE LYMPH NODES MAY NOT REQUIRE ROUTINE BIOPSY

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Background: Current staging guidelines with endobronchial ultrasound (EBUS) still recommend systematic biopsy of at least 3 mediastinal stations prior to surgical resection. Recently, a 4-point ultrasonographic score (Canada Lymph Node Score- CLNS) was developed to determine the probability of nodal metastasis in any given lymph node. A LN with CLNS<2 is considered very low probability for malignancy. We hypothesized that, during EBUS assessment of patients with cN0 non-small cell lung cancer, individual nodal stations that have CLNS<2 do not require routine biopsy because they are likely to represent true pN0 disease.

Method: The CLNS is a prospectively validated score that uses four ultrasonographic features to accurately predict LN malignancy. LNs were evaluated for ultrasonographic features at the time of EBUS and the CLNS was applied. "Triple Negative" LNs were defined as cN0 on CT (LN≤1cm), PET (no hypermetabolic activity) and EBUS (CLNS<2). Specificity, NPV, and false-negative rates were calculated against the gold-standard pathological diagnosis from surgically excised specimens. **Result:** In total, 122 LNs in 58 cN0 patients were assessed. Triple Negative LNs were associated with the following T-stage distribution (T1a=12.07%, T1b=24.14%, T2a=34.38%, T2b=10.34%, T3=17.24%, T4=1.72%). Triple Negative LNs had a specificity, NPV, and false-negative rate of 86.10% (95%CI: 78.40-91.80%), 93.40% (95%CI: 86.90-97.30%), and 6.60%, respectively when using <2 as the CLNS malignancy cut-off. In total, only 5.74%(n=7) Triple Negative nodes were actually proven to be malignant, 6/7 (85.71%) on EBUS-TBNA, and 1/7 (14.29%) only after surgical resection. **Conclusion:** Triple Negative LNs have a high NPV for malignancy. At the time of EBUS in cN0 patients, it may be possible that Triple Negative LNs do not require tissue sampling, thereby saving procedural time, cost, and discomfort. Findings also suggest that Triple Negative LNs with inconclusive biopsy results may not require repeat sampling. A prospective comparative trial is required to confirm these findings.

Keywords: endobronchial ultrasound, ultrasonographic features

OA01.03 PROBABILITY MODEL FOR MALIGNANCY IN HILAR AND MEDIASTINAL LYMPH NODES IN LUNG CANCER BASED ON PET-CT AND EBUS

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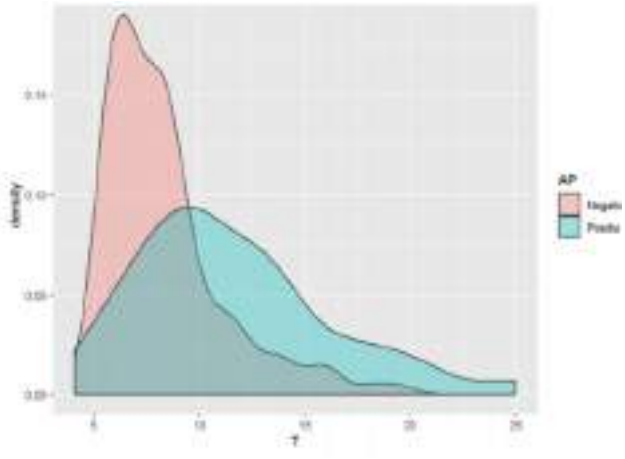
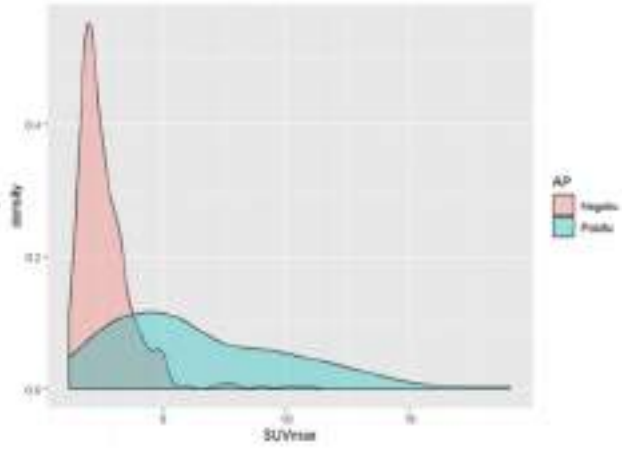
Background: The mediastinal lymph nodes (LN) staging is routinely performed by PET-CT and EBUS- TBNA. Nevertheless, there are no studies that explore the diagnostic capacity of both techniques together. This study aims is to find an algorithm based on combined PET-CT and EBUS image variables together with clinical criteria that provides the most accurate probability of malignancy for each LN explored. **Method:** Retrospective study of mediastinal staging of non-small cell lung cancer, based on PET-CT and EBUS-TBNA. The LN were identified by level (N1, N2 and N3) and by anatomical region (AR) (subcarinal, not subcarinal, and hilar). Standardized Uptake Value (SUV) was determined for each sampled LN (maximum, medium and peak) as well as for pulmonary mass, liver, and blood pool. The ultrasound features collected were: diameter in the short axis (DSA), morphology, border, ecogeneicity and presence of the vascular hilium. For the construction of the predictive algorithm a mixed model of logistic regression of Firth was used. **Result:** 116 consecutive patients were included and a total of 358 LN were evaluated. The set of variables that presented the best discrimination were: age, DSA, SUVmax and AR. The model determines the probability for malignancy for each LN, using the following formula = (-9.26) constant + (-0.21) Age + (4.29) SUVmax + (0.52) DSA + AR. The discrimination power of the model measured by the Area Under the Roc curve was = 0.95.

Distribution density of diameter (mm) and SUVmax of positive and negative lymph nodes





Conclusion: The model including age, DSA, SUVmax and AR provide the probability of malignancy for each LN with the highest accuracy. All other variables can be discarded when combining PET-CT and EBUS image features.

Keywords: EBUS-TBNA, Lung cancer diagnosis, PET-CT

OA01.05 CRYOBIOPSY COMPARED WITH FORCEPS BIOPSY IN PATHOLOGICAL DIAGNOSIS AND BIOMARKER RESEARCH IN LUNG CANCER: A PROSPECTIVE, SINGLE-ARM STUDY

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Background: Cryobiopsy is a novel transbronchial biopsy tool that enables the collection of larger samples than forceps biopsy. We evaluated the usefulness of cryobiopsy compared with forceps biopsy in pathological diagnosis and biomarker research in lung cancer. **Method:** In this prospective single-arm study, 121 patients with or suspected of having lung cancer underwent concurrent transbronchial biopsy using a cryoprobe (ERBECRYO2) and forceps from the same lesion. Sample size and morphological classification were determined for patients whose cryobiopsy and forceps biopsy samples both contained tumor cells (n = 81). Patients diagnosed with non-small-cell lung carcinoma (NSCLC) with adequate samples from the two procedures (n = 65) were analyzed for programmed death ligand 1 (PD-L1) expression score (22C3). Genomic DNA and RNA were extracted from cryobiopsy and forceps biopsy formalin-fixed paraffin-embedded samples (20 NSCLC patients, 20 sections, 10 μm thick each) for whole-exome sequencing and RNA sequencing. **Result:** Cryobiopsy samples were significantly larger than forceps biopsy samples (median 11.1 mm^2[range: 3.3–135.0] vs. 2.0 mm^2[0.7–6.6], $p < 0.01$). The confirmation rate of morphological classification of cryobiopsy samples was significantly higher than that of forceps biopsy samples (86% vs. 79%, $p < 0.01$, adenocarcinoma/squamous-cell carcinoma/small-cell carcinoma/other = 35/19/12/4 and 30/15/11/4, respectively). The success rate for evaluating PD-L1 score using cryobiopsy and forceps biopsy samples was 94% and 95%, respectively. A greater proportion of cryobiopsy samples tended to have PD-L1 > 1% than forceps biopsy samples (51% vs. 42%, $p = 0.06$). Significantly larger amounts of DNA (median 1.60μg vs. 0.58μg, $p = 0.02$) and RNA (median 0.62μg vs. 0.17μg, $p < 0.01$) were extracted from cryobiopsy samples than forceps biopsy samples. The success rate for whole-exome sequencing (90% vs. 15%, $p < 0.01$) and RNA sequencing (75% vs. 10%, $p < 0.01$) was higher for cryobiopsy samples than forceps biopsy samples. The median tumor-mutation burden in cryobiopsy samples was 84 (range 3–2396). **Conclusion:** Cryobiopsy provided larger sample sizes compared with forceps biopsy, and were more useful for morphological classification, PD-L1 evaluation and genetic analysis.

Keywords: cryobiopsy, PD-L1, whole-exome sequencing

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SUNDAY, SEPTEMBER 8 10:30–12:00

OA01.06 CONE BEAM CT IMAGING FOR TRANSBRONCHIAL NAVIGATION IN SMALL PERIPHERAL PULMONARY LESIONS

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Background: Small peripheral lung lesions have historically been identified and followed according to risk of malignancy. Ideally an accurate minimally invasive diagnostic procedure would become the more common first approach. The bronchoscopic approach herein remains of limited widespread use, and reported pooled diagnostic yields remain at approximately 70% even with the help of additional advanced guiding technology. We evaluated if inter-procedural cone beam CT (CBCT) improves yield in two prospective trials: CBCT assisted navigation bronchoscopy with electromagnetic navigation (EMN) guidance (CONTROL-E, NCT03355586) and without EMN using augmented CBCT fluoroscopy alone (CONTROL-A, NCT03274609). **Method:** All patients with an indication for a minimal invasive diagnostic procedure of their peripheral pulmonary lesion as found by our multi-disciplinary tumor board between Dec 2017 and Jan 2019 were included. A total of 84 patients (100 nodules) were included and had a navigation bronchoscopy in the hybrid operating room under general anesthesia. Procedural workflow was as follows: CONTROL-A started off with a CBCT scan. The lesion and pathway were then segmented on a separate workstation. Afterwards, both pathway and nodule were projected 2D on live fluoroscopy for navigation and biopsy guidance. CONTROL-E workflow started with electromagnetic navigation (EMN). Upon reaching the planned target or concluding upon unsuccessful navigation, CBCT imaging was performed for verification (or if applicable; consecutive repositioning guidance). In both workflows, r-EBUS mini probe imaging and ROSE were available for additional guidance and verification. **Result:** The mean lesion size in CONTROL-A (46 patients) was 16.7mm (range 5-43 mm), and 11.5mm (range 4-33 mm) in CONTROL-E (38 patients). A bronchus sign was seen in 62% and 71% of cases, respectively. The CONTROL-E study showed that EMN with r-EBUS had an approximate navigation success rate of 58%. Addition of live 3D-CBCT guidance was performed in all cases, increasing navigation success to 88%. The CONTROL-A study had navigation success of 80% by utilizing only r-EBUS and augmented CBCT-fluoroscopy. However, additional EMN (cross-over) was needed in several cases for navigation guidance, increasing navigation success to 88%. In follow up, both studies showed a diagnostic yield lower than the navigation success: in CONTROL-E 71% and in CONTROL-A, 72% had a biopsy outcome correlating to golden standard follow up. **Conclusion:** Cone beam CT is of significant added value for transbronchial navigation to small peripheral lung lesions, with or without trans-parenchymal access. Diagnostic yield however remains approximately 71%. Additional refining of navigation and biopsy tools is necessary to further increase intuitiveness and accuracy.

Keywords: Early Stage Lung Cancer, navigation bronchoscopy, cone-beam CT

OA01 ADVANCED DIAGNOSTIC APPROACHES FOR INTRATHORACIC LYMPH NODES AND PERIPHERAL LUNG TUMORS
SUNDAY, SEPTEMBER 8 10:30–12:00

OA01.07 ULTRATHIN BRONCHOSCOPY COMBINED WITH VBN AND EBUS FOR THE DIAGNOSIS OF PPLS WITH OR WITHOUT FLUOROSCOPY: A RANDOMIZED TRIAL

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Background: Since the utility of lowdose computed tomography screening for lung cancer, the detection rate of groundglass nodules (GGNs) has increased.Transbronchial biopsy for peripheral pulmonary lesions is generally performed using ultrathin bronchoscopy combined with virtual bronchoscopic navigation (VBN) and endobronchial ultrasound (EBUS). The use of fluoroscopy with this method has not yet been explored. The study was designed as a randomized trial to determine the role of fluoroscopy in this method. **Method:** Patients with peripheral pulmonary lesions suspicious for malignant were enrolled in the study and randomized to two groups, fluoroscopy group and non-fluoroscopy group. Fluoroscopy group was performed with a 3.0 mm external diameter and 1.7 mm internal diameter ultrathin bronchoscope, EBUS, VBN guidance and fluoroscopy. Non-fluoroscopy group was performed with the same ultrathin bronchoscopy combined with EBUS and VBN guidance, but without fluoroscopy. Biopsies Cytological and histological examinations were performed in both groups. **Result:** A total of 126 patients were enrolled and randomized, of whom 120 patients (60, non-fluoroscopy group; 60, fluoroscopy group) were analyzed. The diagnostic yield was 75% (14 benign and 46 malignant lesions) in the non-fluoroscopy group and 83.3% (6 benign and 54 malignant lesions) in the fluoroscopy group (P=0.37). There were no obvious complications including pneumothorax, bleeding, chest pain and pneumonia in both groups. **Conclusion:** There was no difference in the diagnostic yield of the non-fluoroscopy group method compared to the FG method using ultrathin bronchoscopy, navigational technology and EBUS for transbronchial biopsy to diagnose peripheral pulmonary lesions.

Keywords: navigation, Lung cancer, peripheral pulmonary lesion

OA02 A NEW VISION OF TARGETS AND STRATEGIES
SUNDAY, SEPTEMBER 8 10:30–12:00

OA02.01 ALECTINIB IN PREVIOUSLY TREATED RET-REARRANGED ADVANCED NON-SMALL-CELL LUNG CANCER: A PHASE 1/2 TRIAL (ALL-RET)

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Background: *RET* rearrangements occur in 1–2% of non-small cell lung cancers (NSCLCs). Alectinib (300 mg twice daily) has been approved for the treatment of *ALK*-rearranged NSCLC in Japan; it also has a high activity against RET *in vitro*. A global trial (ALEX study) showed the efficacy and safety of alectinib (600 mg twice daily) in *ALK*-rearranged NSCLC patients. We conducted a phase 1/2 study of alectinib to establish the recommended dose (RD) and examined its activity in *RET*-rearranged Japanese NSCLC patients. **Method:** This study was a single-arm, open-label, multi-institutional phase 1/2 trial. *RET*-rearranged NSCLC patients treated with at least one regimen of chemotherapy were recruited. *RET* rearrangements were screened using LC-SCRUM-Japan, a nationwide genomic screening network. In phase 1, alectinib (600 or 450 mg twice daily) was administered, following a 3 + 3 design. The primary endpoint was safety. During phase 2, alectinib at the RD defined in phase 1 was administered. The primary endpoint was the objective response rate in RET inhibitor-naïve patients. **Result:** Between March 8, 2016 and January 29, 2018, 35 patients were enrolled, and 34 patients were administered alectinib. *KIF5B-RET* was the most common fusion gene (22 cases [63%]), and the *CCDC6-RET* fusion was identified in 8 cases. The remaining 5 cases were not distinguishable. In cohort 1 (600 mg twice daily), we observed 5 DLTs (grade 3 rash, increased aspartate aminotransferase, erythema multiforme, thromboembolic event, and increased CPK) in 3 of 6 patients. In accordance with the protocol, we moved to cohort 2 (450 mg twice daily) and observed no DLTs in 3 patients. Additionally, pharmacokinetic analysis indicated that the mean exposure (AUC0–10) of 600 mg twice daily was higher than that previously reported in AF-002JG trial (global phase 1 study). Therefore, we determined 450 mg twice daily as the RD for phase 2. Twenty-five RET inhibitor-naïve patients were treated with the RD, of whom 1 achieved an objective response (4%) and 13 achieved disease control at 8 weeks (52%) as determined by central review. The median progression-free survival was 3.4 months (95% CI 2.0-5.4), and the median overall survival was 19.0 months (5.4-NE). We observed grade 3 neutropenia, pneumonitis, diarrhea, hyponatremia, increased CPK and blood bilirubin (4%) in patients treated with 450 mg alectinib twice daily; no grade 4 adverse events

were observed. **Conclusion:** Alectinib had limited activity in patients with *RET*-rearranged NSCLC. Further investigation of new targeted therapeutics is required to improve outcomes for these patients.

Keywords: Non-Small Cell Lung Cancer, RET fusion gene, alectinib

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OA02.02 PHASE 1 STUDY OF SAFETY, TOLERABILITY, PK AND EFFICACY OF AMG 510, A NOVEL KRAS^{G12C} INHIBITOR, EVALUATED IN NSCLC

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This abstract is under embargo until September 8 09:45 CET

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OA02.03 THE THIRD GENERATION EGFR INHIBITOR (EGFR-TKI) HS-10296 IN ADVANCED NSCLC PATIENTS WITH RESISTANCE TO FIRST GENERATION EGFR-TKI

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Background: HS-10296 is an oral, potent, high selective third generation EGFR tyrosine-kinase inhibitor (EGFR-TKI) for sensitizing mutations, and the EGFR Thr790Met (T790M) resistance mutation which has been demonstrated by phase I study. This phase II, open-label, multicenter single-arm study was designed to confirm the efficacy and safety of HS-10296 in a large population of non-small-cell lung cancer (NSCLC) patients with EGFR T790M mutation, who had progressed after first generation EGFR-TKI treatment. **Method:** Patients aged at least 18 years with centrally confirmed EGFR T790M-positive mutations, locally advanced or metastatic (stage IIIB/IV) NSCLC after first generation EGFR-TKI treatment received HS-10296 110 mg orally once daily until disease progression, or intolerable toxicity, or patient withdrawal. Patients with asymptomatic, stable brain metastases not requiring steroids were allowed to enroll. The primary endpoint was the objective response rate (ORR) by independent central review using Response Evaluation Criteria in Solid Tumors, version 1.1 every 6 weeks. Response endpoints (ORR and disease control rate [DCR]) were assessed in response analysis set. Secondary end points including progression-free survival (PFS), duration of response (DoR), depth of response (DepOR), overall survival (OS) and safety were evaluated in full analysis set. The final data cutoff was on Jan 5, 2019. The study is still ongoing. **Result:** Totally, 244 patients (median age 60.8) entered study in 36 sites in mainland China (189 patients) and Taiwan (55 patients) between May 16, 2018 to Oct 23, 2018. 2 patients were excluded from the evaluable for response analysis set (n=242) due to absence of measurable disease at baseline by independent central review. At data cutoff, 182 (74.6%) patients remained on treatment. The median duration of follow-up was 4.7 months. 160 of 242 patients achieved confirmed partial responses by independent central review. The ORR was 66.1% (95% CI: 59.8-72.1). The DCR was 93.4% (95% CI: 89.5-96.2). The most common adverse reactions ($\geq$ 10%) were blood creatine phosphokinase increased (43 [17.6%]), aspartate aminotransferase increased (29 [11.9%]), pruritus (28 [11.5%]), rash (28 [11.5%]) and alanine aminotransferase increased (26 [10.7%]). The most common all-causality grade 3 and 4 adverse events were blood creatine phosphokinase increased (14 [5.7%]) and hyponatraemia (4 [1.6%]). Serious adverse events were reported in 30 (12.3%) patients, of which 19 (7.8%) were investigator assessed as possibly treatment-related to HS-10296. Three deaths were due to adverse events; one was related to cardiopulmonary failure, other two events occurred after disease progression. There was no interstitial lung disease during study treatment. **Conclusion:** HS-10296 has demonstrated good clinical benefit with minimal toxicity in patients with EGFR T790M-positive NSCLC patients who have progressed after first generation EGFR-TKI treatment. The Phase III study has already launched comparing HS-10296 with gefinitib in advanced NSCLC patients with EGFR sensitizing mutations. (The study was sponsored by Jiangsu Hansoh Pharmaceutical Co., Ltd.; ClinicalTrials.gov number, NCT02981108)

Keywords: The third generation EGFR inhibitor HS-10296, Non-small cell lung cancer (NSCLC), EGFR T790M mutation

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OA02.05 FIRST-IN-HUMAN PHASE 1/2 TRIAL OF ANTI-AXL ANTIBODY–DRUG CONJUGATE (ADC) ENAPOTAMAB VEDOTIN (ENAV) IN ADVANCED NSCLC

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Background: AXL, a transmembrane receptor tyrosine kinase, is aberrantly expressed in various cancers, and associated with poor prognosis and treatment resistance. AXL overexpression is associated with resistance to PD-1 immune checkpoint inhibitors (Hugo *et al*. 2016). EnaV, a novel ADC of anti-AXL human IgG1 and monomethyl auristatin E, demonstrated potent anti-tumor activity in preclinical models, including NSCLC (Boshuizen *et al*. 2018). In a phase 1, dose escalation, multi-cohort trial (NCT02988817) in heavily pretreated patients with relapsed or refractory solid tumors, EnaV 2.2 mg/kg once every 3 weeks (1Q3W; recommended phase

2 dose) showed preliminary anti-tumor activity. Here we present initial results from patients with NSCLC in the phase 2a, expansion phase of this trial. **Method:** We analyzed data from EnaV 2.2 mg/kg 1Q3W, in the cohort of pretreated patients with stage III/IV NSCLC without sensitizing EGFR mutations (EGFR WT) or ALK rearrangements (ALK$^-$) who had failed ≤4 prior lines of therapy, including platinum-based chemotherapy and PD-1/PD-L1 inhibitor (either in combination or sequentially). Endpoints include safety, objective response rate (ORR; RECIST 1.1), and AXL expression in fresh tumor biopsies (immunohistochemistry). **Result:** In the EGFR WT/ALK$^-$ cohort, 26 patients (median age 65.5 years, range 38–74; 57.7% male) with ECOG PS of 0 (11.5%) or 1 (88.5%) have been enrolled. Most patients (23/26) were treated with a checkpoint inhibitor. At a median follow-up of 18 weeks (range: 2–54), the most common (≥20%; any grade) treatment-emergent adverse events (TEAEs) were fatigue, constipation, nausea, decreased appetite, decreased weight, diarrhea, and vomiting. Two patients had a TEAE leading to dose reduction. Grade ≥3 TEAEs occurred in 12 patients, with the most common being gastrointestinal disorders in eight patients (constipation [n=1]; colitis, diarrhea, nausea, vomiting [n=2 each]; abdominal distension [n=1]. The confirmed ORR is 19% (95% CI: 8.5%, 37.9%). The disease control rate (CR+PR+SD) is 50% (13/26). Nine of 12 (75%) evaluable fresh biopsies were positive for AXL tumor cell staining. **Conclusion:** In this high unmet need patient population, with advanced EGFR WT and ALK$^-$ NSCLC who are pretreated with PD-1/PD-L1 inhibitors and platimum-based therapies, EnaV monotherapy demonstrated a manageable safety profile and encouraging preliminary clinical activity. This cohort has expanded to allow up to 60 patients to gain further knowledge of AXL as a potential biomarker for responsiveness to EnaV and to gather additional data on safety and efficacy. Funding: Genmab A/S

Keywords: Enapotamab vedotin, advanced NSCLC, Antibody–drug conjugate

OA02 A NEW VISION OF TARGETS AND STRATEGIES
SUNDAY, SEPTEMBER 8 10:30–12:00

OA02.06 THE SEQUENTIAL THERAPY OF CRIZOTINIB FOLLOWED BY ALECTINIB : REAL WORLD DATA OF 840 PATIENTS WITH NSCLC HARBORING ALK-REARRANGEMENT (WJOG9516L)

S. Watanabe[1], T. Yamanaka[2], K. Ito[3], S. Sakata[4], H. Daga[5], T. Kijima[6], K. Hirano[7], I. Okamoto[8], A. Nakamura[9], T. Kozuki[10], M. Ishihara[11], K. Azuma[12], T. Seto[13], T. Yokoyama[14], Y. Oya[15], H. Kobayashi[16], K. Nishino[17], Y. Hattori[18], K. Nakagawa[19], N. Yamamoto[20]

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Background: Previous clinical trials demonstrated that alectinib (ALEC) had a longer time-to-progression than crizotinib (CRZ) in 1st-line settings. Information on long-term overall survival (OS), however, is still limited with a few studies having reported that the sequential strategy of "CRZ followed by other ALK-inhibitor" can provide extended OS. In Japan, ALEC was approved for a 1st-line setting earlier than in other countries. **Method:** We reviewed the clinical data of ALK-rearranged NSCLC patients who received CRZ or ALEC between May 2012 and Dec 2016. Patients were divided into two groups according to the first-administered ALK inhibitor, the CRZ or ALEC group. In order to evaluate the efficacy of the sequential strategy of "CRZ followed by ALEC", the combined time to treatment failure (TTF) was calculated in the CRZ group as defined by the sum of the "TTF of CRZ" plus the "TTF of ALEC" if patients were treated with ALEC followed by CRZ. In the ALEC group, the "TTF of ALEC" was calculated. The primary endpoint is the comparison between the combined TTF in the CRZ group with the TTF in the ALEC group. **Result:** Of 864 patients enrolled from 61 institutions, 840 patients were analyzed. Median age was 61 (range, 20-94); 56% were female; and 95% had adenocarcinoma. There were 535/305 patients in the CRZ/ALEC group. In the CRZ group, 282 patients received ALEC after CRZ failure. The combined TTF in the CRZ group was significantly longer than TTF in the ALEC group; median, 34.4 vs 27.2 months (mo); hazard ratio (HR), 0.709 [95%CI;0.559- 0.899]; *P*=0.0044. However, there was no significant difference in OS between the patients who received ALEC after CRZ in the CRZ group and the patients in the ALEC group; median, 88.4 months vs. not reached; HR 1.048 [95%CI;0.758-1.451]; *P*=0.7770. In the whole population, the CRZ group had a significantly shorter OS than the ALEC group; median, 53.6 mo vs not reached HR, 1.821 [95%CI;1.372-2.415]; *P*<0.0001. **Conclusion:** The combined TTF in the CRZ group was significantly longer than TTF in the ALEC group, however, OS benefit of sequential therapy of CRZ followed by ALEC was not shown.

Keywords: ALK inhibitor, NSCLC, Real world data

OA02 A NEW VISION OF TARGETS AND STRATEGIES
SUNDAY, SEPTEMBER 8 10:30–12:00

OA02.07 PHASE 3 ALUR STUDY OF ALECTINIB IN PRETREATED ALK+ NSCLC: FINAL EFFICACY, SAFETY AND TARGETED GENOMIC SEQUENCING ANALYSES

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Background: The ALUR (NCT02604342) primary analysis (cut-off January 2017) demonstrated improved efficacy and safety with alectinib versus chemotherapy in patients with *ALK*+ NSCLC previously treated with chemotherapy and crizotinib. These patients can develop crizotinib resistance through *ALK* secondary mutations, but limited data exist regarding alectinib's efficacy in patients with different post-crizotinib genetic profiles. We report final data from ALUR including treatment outcomes according to genetic profile. **Method:** Overall, 119 patients with locally determined *ALK*+ NSCLC were randomised 2:1 to receive alectinib 600mg bid or chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 q3w). The primary endpoint was PFS by investigator. Targeted genomic sequencing (FoundationONE® [tissue; 315 genes] and FoundationACT® [plasma; 62 genes]) was performed retrospectively using tumour tissue (n=33) and baseline plasma (n=59). **Result:** Final efficacy data confirmed those of the primary analysis (table). Grade ≥3 treatment-emergent adverse events were lower with alectinib (37.7%) than with chemotherapy (43.2%); adverse events causing treatment discontinuation were lower with alectinib (5.2% versus 10.8% chemotherapy), despite alectinib's longer treatment duration. *ALK* fusions were confirmed retrospectively in 26/33 (78.8%) tissue and 41/59 (69.5%) plasma (post-crizotinib) samples. ORR in alectinib-treated patients with *ALK* fusions was 72.2% (13/18, tissue) and 63.0% (17/27, plasma) versus 0% for chemotherapy (tissue [0/8], plasma [0/14]). *ALK* secondary mutations were detected in 16/59 (27.1%) patients (plasma, both arms). ORR in the alectinib arm (plasma) was similar in patients with *ALK* fusions with (60.0%, 6/10) or without (64.7%, 11/17) *ALK* secondary mutations, but lower in patients with gene mutations other than *ALK* (23.1%, 3/13). **Conclusion:** Final data from ALUR confirm the primary analysis, demonstrating improved efficacy and safety with alectinib versus chemotherapy in post-crizotinib *ALK*+ NSCLC. The role of reconfirming *ALK* status upon sequential ALK inhibitor treatment requires further investigation, due to the limited data and known technical challenges of plasma testing. Funding: F. Hoffmann-La Roche Ltd.

	Alectinib (n=79)	Chemotherapy (n=40)
Median PFS, months (95% CI; INV) (primary endpoint)	10.9 (8.1–15.5)	1.4 (1.2–1.6)
HR 0.20; 95% CI 0.12–0.33, p<0.001		
CNS ORR (IRC), %	66.7	0
Difference in CNS ORR 66.7%; 95% CI 39.0–86.1, p<0.001		
ORR (INV), %	50.6	2.5
Difference in ORR 48.1%; 95% CI 29.8–63.9, p<0.001		
DCR (INV), %	86.1	25.0
Difference in DCR 61.1%; 95% CI 43.7–75.1, p<0.001		
Median OS, months (95% CI; INV)*	27.8 (18.2–NE)	NE (8.6–NE)
HR 0.91; 95% CI 0.49–1.70, p=0.763		
Risk of 6-month cumulative incidence of CNS progression (95% CI; IRC)§	0.12 (0.07–0.23)	0.47 (0.33–0.67)

*86.5% of patients receiving chemotherapy crossed over to alectinib post progression

§Data cut-off 3 July 2017

CI, confidence interval; CNS, central nervous system; DCR, disease control rate; HR, hazard ratio; INV, investigator; IRC, independent review committee; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival, PFS, progression-free survival

OA03 SYSTEMIC THERAPIES FOR SCLC: NOVEL TARGETS AND PATIENTS' SELECTION
SUNDAY, SEPTEMBER 8 13:30–15:00

OA03.01 A NON-RANDOMIZED, OPEN-LABEL, PROSPECTIVE, MULTICENTER STUDY OF APATINIB AS SECOND-LINE AND LATER-LINE THERAPY IN PATIENTS WITH ES-SCLC

D. Hua[1], Q. Liu[1], J. Xu[2], Y. Xu[3], M. Chen[4], L. Deng[5], J. Wu[6], T. Zhou[7], L. Zhang[8], J. Tan[9], X. Pu[10], Y. Shang[11], J. Hua[12], Y. Li[13], W. Cai[14], Y. Gu[15], X. Peng[16]

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Background: Small-cell lung cancer (SCLC) accounts for approximately 10–15% of the total number of lung cancer cases. In extensive-stage (ES) SCLC, the 5-year survival rate is less than 5%, which was mainly caused by rapid recurrence and resistance to second-line chemotherapy despite the high response to first-line chemotherapy. This study evaluated the efficacy and safety of apatinib, an orally administered small-molecule targeted drug, in second-line and later-line therapy for patients with ES-SCLC (ChiCTR-OPC-17013964. **Method:** From July 28, 2017 to March 24, 2019, 52 patients who failed in first-line and above chemotherapy treatment were enrolled and received apatinib 500 mg per day. The efficacy was evaluated after 4-weeks treatment (1 cycle), and then evaluated once every 2 cycles. The primary endpoint was progression-free survival (PFS), and secondary endpoints were overall survival (OS), overall response rate (ORR) and disease control rate (DCR). The adverse events were also recorded. **Result:** Of 52 enrolled patients, 36 patients were available for efficacy analysis. The median PFS was 6.18 months (95%CI: 3.26-7.99) and the median OS did not achieve. The mPFS of patients received apatinib as second-line treatment was 6.48 months. Patients who received first-line chemotherapy more than 6 months had longer PFS and OS than patients received less than 6months. 31 patients were available for tumor response evaluation. The ORR and DCR were 19.35% and 83.87%, respectively. During the treatment, 96

adverse events were detected. Among them, 3-4 grade adverse reactions were hypertension (8.33%), hand-foot syndrome (5.56%), hypodynamia (5.56%) and proteinuria (2.78%), which all alleviated by reducing dose and symptomatic treatment.

Table 1 Patient baseline characteristics

Baseline characteristics	N = 36	Percentage
Age (< 60 / ≥ 60)	13/ 23	36.11%/ 63.89%
Gender (male/ Female)	30/ 6	83.33%/ 16.67%
ECOG (0/ 1/ 2)	3/ 18/ 15	8.33% / 50.00%/ 41.67%
Primary lesion (Right lung/ Left lung)	25/ 11	69.44%/ 30.56%
Radiotherapy (Yes /No)	30/ 6	83.33%/ 16.67%
First line-PFS (< 6 m / ≥ 6 m)	19/ 17	52.78%/ 47.22%
The number of treatment lines for apatinib		
Second line treatment	18	50.00%
Three-line treatment	15	41.67%
Four-line treatment	3	8.33%

Conclusion: Apatinib was effective for SCLC patients who failed in first-line and above chemotherapy and the adverse events were tolerable.

Keywords: apatinib, Extensive-Stage Small Cell Lung Cancer, Second-line and Later-line Therapy

OA03 SYSTEMIC THERAPIES FOR SCLC: NOVEL TARGETS AND PATIENTS' SELECTION
SUNDAY, SEPTEMBER 8 13:30–15:00

OA03.02 EFFECT OF ANLOTINIB IN ADVANCED SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY RECEIVED CHEMORADIOTHERAPY: A SUBGROUP ANALYSIS IN ALTER 1202 TRIAL

Q. Wang[1], Y. Cheng[2], K. Li[3], J. Shi[4], B. Han[5], L. Wu[6], G. Chen[7], J. He[8], J. Wang[9], H. Qin[10], X.-L. Li[11]

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Background: The ALTER 1202 trial showed significant improvement in progress-free survival and well tolerant with anlotinib in advanced small cell lung cancer (SCLC) patients received at least two lines chemotherapy. Here, we reported the effect of anlotinib in patients previously received chemoradiotherapy. **Method:** The ALTER 1202 was a randomized, double-blind phase 2 trial conducted at 11 centers in China. Patients with advanced SCLC that received at least two previous lines of chemotherapy were enrolled and randomized in a 2:1 ratio to receive either anlotinib or placebo until tumor progression or unacceptable toxicity. The subgroup analysis assessed the effect of anlotinib in patients with previous concurrent, sequential and alternate chemoradiotherapy. The primary outcome was progressive-free survival (PFS). The secondary outcomes were overall survival (OS), objective response rate, disease control rate and safety. Data are reported as per the 30 June 2018, data cutoff date. This trial is registered with ClinicalTrials.gov, number NCT03059797. **Result:** Between March 30, 2017 and June 8, 2018, a total of 120 patients who met all eligibility criteria were randomly assigned to the anlotinib group (82 patients) or placebo group (38 patients). And 46 patients in anlotinib group and 22 patients in placebo group previously received chemoradiotherapy. Among them, the median PFS was 5.49 months (95% confidence interval [CI], 2.83 to 6.47) with anlotinib versus 0.69 months (95% CI, 0.66 to 0.76) with placebo (hazard ratio [HR], 0.14; 95% CI, 0.07 to 0.28; P<0.0001). Meanwhile, anlotinib significantly prolonged OS compared with placebo (9.49 months [95% CI, 7.29 to 12.68] versus 2.56 months [95% CI, 0.49 to 5.22]; HR, 0.46 [95% CI, 0.22 to 0.98]; P=0.0388) in patients previously received chemoradiotherapy. The most common adverse events were hypertension (39.13%), weight loss (39.13%), hypertriglyceridemia (36.96%) and leukopenia (30.43%). While, the most common grade 3 or worse adverse events were hypertension (15.22%), hypertriglyceridemia (10.87%), γ-glutamyl-transferase increased (8.70%). **Conclusion:** Anlotinib improved PFS and OS in advanced SCLC patients previously received chemoradiotherapy and was well tolerated.

Keywords: Anlotinib, chemoradiotherapy, advanced small cell lung cancer

OA03 SYSTEMIC THERAPIES FOR SCLC: NOVEL TARGETS AND PATIENTS' SELECTION
SUNDAY, SEPTEMBER 8 13:30–15:00

OA03.03 INITIAL EFFICACY AND SAFETY RESULTS OF IRINOTECAN LIPOSOME INJECTION (NAL-IRI) IN PATIENTS WITH SMALL CELL LUNG CANCER

L. Paz-Ares Rodríguez[1], D. Spigel[2], Y. Chen[3], M. Jove[4], O. Juan[5], P. Rich[6], T. Hayes[7], V. Gutiérrez Calderón[8], R. Bernabe[9], A. Navarro[10], A. Dowlati[11], B. Zhang[12], Y. Moore[12], T. Wang[12], N. Nazarenko[12], S. Ponce[13], P. Bunn, Jr[14]

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Background: SCLC accounts for ~15% of lung cancers, with 5-year survival <10%. 50-90% of patients with extensive disease respond to initial treatment; many rapidly relapse due to acquired resistance to front-line platinum-based chemotherapy. Limited treatment options are available for second-line patients. nal-IRI is a liposomal formulation of irinotecan (topoisomerase-1 inhibitor), utilizing intraliposomal stabilization technology to enable high drug load and in-vivo stability. **Method:** RESILIENT (NCT03088813) is a two-part Phase 2/3 study assessing the safety, tolerability, and efficacy of monotherapy nal-IRI in SCLC patients who progressed on/after a

front-line platinum regimen: Part 1 includes dose-finding then dose-expansion. Key eligibility criteria included ECOG PS 0-1 and adequate organ function, with prior exposure to immunotherapy allowed. Eligible patients received nal-IRI 70mg/m2 or 85mg/m2 (free-base equivalent) q2w. Primary endpoints were safety and tolerability. Efficacy assessments included objective response rate (ORR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS). **Result:** 30 patients were treated for >12 weeks in Part 1 (male, 43%; median age, 60.4y; platinum-resistant, 40%) with tumor assessments q6w. During dose-finding, 5 patients received nal-IRI 85mg/m2 (deemed not tolerable: dose-limiting toxicity) and 12 patients received nal-IRI 70mg/m2 (deemed tolerable: selected for dose expansion). At data cut-off** (median follow-up, 4.4mo), 25 patients had received nal-IRI 70mg/m2. Diarrhea was the most common gastrointestinal adverse events (AEs) (Gr3, 20%). Hematologic AEs included neutropenia (Gr3, 8%; Gr4, 8%), anemia (Gr3, 8%), febrile neutropenia (Gr3, 4%), thrombocytopenia (Gr3, 4%; Gr4, 4%). Preliminary efficacy identified 11 patients with partial responses (ORR 44%), BOR (PR+SD) of 72%, and 12-week disease control rate (DCR12wks PR+SD) of 48%. PFS and OS are not yet mature. **Conclusion:** Part 1 demonstrated encouraging anti-tumor activity for nal-IRI 70mg/m2 in patients with SCLC (ORR: 44%, BOR: 72%). nal-IRI 70mg/m2 was generally well tolerated. Future research is warranted to assess nal-IRI in second-line SCLC.

Table 1. Baseline Demographic, Patient Disposition, Safety & Tolerability, and Clinical Efficacy for Part 1 of the RESILIENT study

	Dose-Finding / Dose-Exploration Phase	
	Irinotecan Liposome Injection 85mg/m2 (N=5)	**Irinotecan Liposome Injection 70mg/m2 (N=25)**
Baseline Characteristics		
Gender, Male, n (%)	3 (60.0)	10 (40.0)
Age (Years, median)	62.0	59.0
Baseline ECOG		
0	1 (20.0)	3 (12.0)
1	4 (80.0)	22 (88.0)
Time Since Most Recent Progression (Weeks, median)	3.4	3.2
Disease Location, n (%)		
Locally Advanced	0	2 (8.0)
Metastatic	5 (100.0)	23 (92.0)
Disposition, n (%)		
Patient Completed Study	4 (80.0)	12 (48.0)
Patient Currently Ongoing*	–	7 (28.0)
Deaths	2 (40.0)	6 (24.0)
Disease Related	1	3
Adverse Event Not Related to Study Drug	1	1
Cardiac Arrest	1	-
Hepatic Failure	-	1
Adverse Event Related to Study Drug	0	2
Abdominal Sepsis	-	2
Patient Discontinued Treatment	5 (100.0)	18 (72.0)
Safety & Tolerability, n (%)		
Any Treatment-Emergent Adverse Event (TEAE)	5 (100.0)	25 (100.0)
Grade 3 or Higher TEAE (≥ 2 patients)	5 (100.0)	15 (60.0)
Neutropenia	1 (20.0)	4 (16.0)
Anemia	–	2 (8.0)
Thrombocytopenia	–	2 (8.0)
Diarrhea	3 (60.0)	5 (20.0)
Asthenia	–	2 (8.0)
General Physical Health Deterioration	–	2 (8.0)
Pneumonia	2 (40.0)	1 (4.0)
Abdominal Sepsis	–	2 (8.0)
Hypokalemia	1 (20.0)	2 (8.0)
Renal Failure	–	2 (8.0)
Best Overall Response		
Complete Response (CR)	–	–
Partial Response (PR)	2 (40.0)	11 (44.0)
Stable Disease	1 (20.0)	7 (28.0)
Progressive Disease	1 (20.0)	5 (20.0)
Non-evaluable	1 (20.0)	2 (8.0)
Objective Response Rate		
CR + PR	2 (40.0)	11 (44.0)
Non-responder	3 (60.0)	14 (56.0)

** Data Cut-off: May 8, 2019.
* Per RECIST v1.1 or RANO criteria.

Keywords: Irinotecan Liposome Injection, Monotherapy, small cell lung cancer

OA03.05 CHARACTERIZATION OF GENOMIC ALTERATIONS IN CHINESE LCNEC AND SCLC VIA COMPREHENSIVE GENOMIC PROFILING

L. Wu[1], L. Cao[2], L. Chen[3], B. Zhu[4], X. Hu[5], G. Lin[6], Y. Lin[7], S. Zhang[8], W. Peng[1], M. Jiang[1], X. Mao[9], T. Zhang[9], J. Ye[9], L. Zhang[9]

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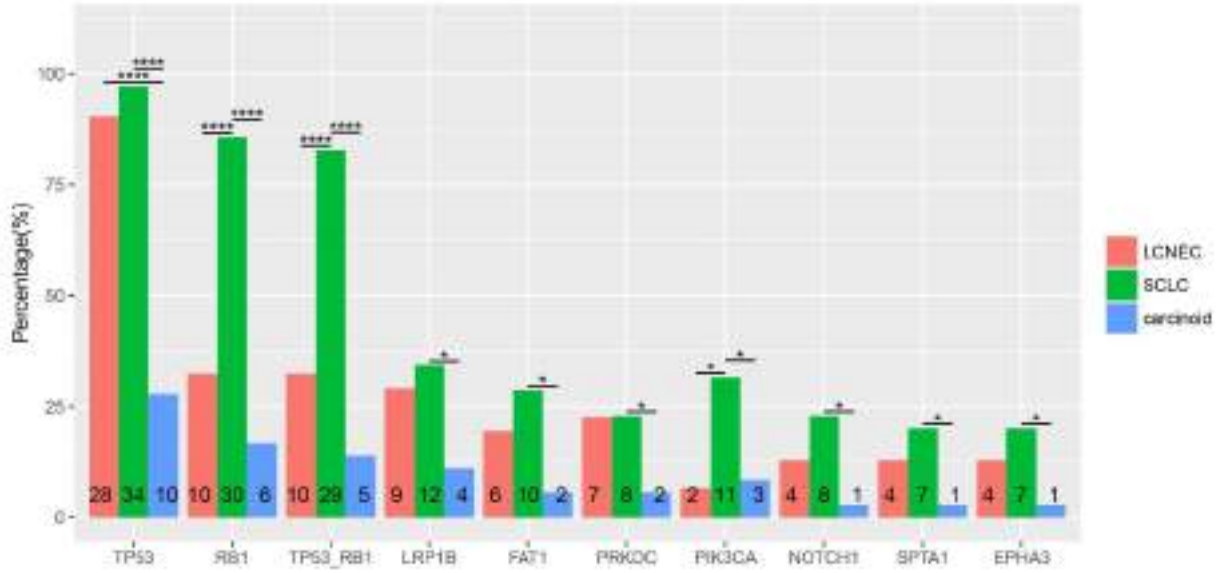
Background: LCNEC and SCLC are aggressive neuroendocrine carcinomas with overlap in clinical, histopathologic, morphologic and genomic features. Differential molecular features between the two subtypes have not been well elucidated, contributing the uncertainty for optimal clinical strategy for each subtype. Here we interrogated the genomic characteristics in LCNEC as compared to SCLC along with their histologically related subtypes: carcinoids and atypical carcinoids via comprehensive genomic profiling. **Method:** FFPE samples from 31 LCNECs, 35 SCLCs, 14 carcinoids and 22 atypical carcinoids were sequenced in a CLIA-certified sequencing laboratory using 520-cancer-related gene panel, with an average sequencing depth of 1385X. **Result:** Comparative mutational analysis revealed that both LCNEC and SCLC sub-cohorts displayed higher rate of TP53 alterations than that of carcinoid (p<0.001, p<0.001). SCLC patients harbored more RB1 and PIK3CA mutations than LCNECs (p<0.001, p=0.014) and carcinoids (p<0.001, p=0.018). In addition, mutation frequencies of *LRP1B*, *FAT1*, *PRKDC*, *PIK3CA*, *NOTCH1*, *SPTA1* and *EPHA3* in SCLC were significantly higher than that in carcinoid. Mutations in *TP53* and *RB1* occurred concurrently in 83% (29/35) SCLC patients, whereas in only 32.3% (10/31) LCNECs. (Fig.1) We further investigated the distribution of mutations across KEGG pathways and found that mutation frequencies in both HIF-1 and Notch signaling pathways were lower in LCNEC than SCLC (p=0.032, p=0.025). Copy number variation (CNV) analysis revealed that LCNEC and SCLC had comparable CNVs which were significantly higher than carcinoid (p<0.001, p<0.001) and atypical carcinoid (p=0.010, p=0.028). TMB analysis also revealed a comparable TMB status of LCNEC (12.7/Mb) and SCLC (11.9/Mb), and relatively lower TMB in both carcinoid (2.4/Mb, p<0.001, p<0.001) and atypical carcinoid (5.6/Mb, p=0.003, p=0.009) than LCNEC and SCLC.



Conclusion: We demonstrated the differential genomic characteristics in the four subtypes of neuroendocrine carcinomas. Compared with SCLC, LCNEC has lower mutation frequencies in *RB1*, *PIK3CA*, as well as HIF-1 and Notch signaling pathways. In addition, LCNEC and SCLC had comparable CNV and TMB status, which significantly higher than that of carcinoids and atypical carcinoid.

Keywords: small-cell lung cancer (SCLC), genomic profiling, Neuroendocrine carcinoma

OA03 SYSTEMIC THERAPIES FOR SCLC: NOVEL TARGETS AND PATIENTS' SELECTION
SUNDAY, SEPTEMBER 8 13:30–15:00

OA03.06 ASCL1, NEUROD1, AND POU2F3 DRIVE DISTINCT SUBTYPES OF SMALL CELL LUNG CANCER WITH UNIQUE THERAPEUTIC VULNERABILITIES

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Background: Background: Accounting for 15% of all lung cancer diagnoses, small cell lung cancer (SCLC) is an aggressive malignancy with dismal clinical outcomes, due in part to failure to define clinical biomarkers predictive of unique, targetable vulnerabilities. Recent data has begun to delineate molecular subsets of SCLC by uncovering inter-tumoral heterogeneity in features such as DNA damage response, EMT, and neuroendocrine (NE) status. However, it remains unclear whether the subsets defined by these features are predictive of response to cancer therapies and could be employed as patient selection criteria. **Method:** Methods: Using RNAseq data from 81 resected SCLC tumor samples and 62 SCLC cell lines, we applied non-negative matrix factorization (NMF) to optimize delineation of transcriptionally defined clusters. Reverse phase protein array (RPPA) and drug response data for cell lines were analyzed post-clustering to compare features between clusters. Clustering analyses were validated *in vivo* using CTC-derived patient xenograft (CDX) models, while single-cell RNAseq (scRNAseq) from these same models was used to assess intratumoral heterogeneity among clusters. **Result:** Results: NMF identifies four biologically distinct clusters among SCLC tumor samples and cell lines, each defined almost solely by differential expression of the transcription factors *ASCL1* (SCLC-A, 36%), *NEUROD1* (SCLC-N, 31%), and

POU2F3 (SCLC-P, 16%), including a cluster defined by the absence of all three (SCLC-Inflamed/Mesenchymal, or SCLC-IM, 17%). SCLC-A are neuroendocrine, epithelial tumors with susceptibility to drug classes including BCL-2 inhibitors. SCLC-N are neuroendocrine, cMYC-high tumors with susceptibilities including Aurora kinase inhibitors that are neither epithelial nor mesenchymal. SCLC-P are non-neuroendocrine, epithelial tumors vulnerable to PARP inhibitors and nucleoside analogs. Lastly, SCLC-IM consists of mesenchymal, non-neuroendocrine tumors with high-expression of immune checkpoints, STING-related genes, and inflammatory markers that may represent those SCLC which are sensitive to immune checkpoint blockade. scRNAseq reveals intratumoral heterogeneity among cluster assignment within tumors that fluctuates coincident with the onset of therapeutic resistance. **Conclusion:** Conclusions: SCLC tumors can be assigned to one of four molecular subtypes on the basis of differential expression of three transcription factors. These subtype assignments reflect profound distinctions in underlying biology and susceptibility to a range of candidate drug classes. While subtype assignment on a single-cell basis within a tumor is largely homogeneous, rare cells from distinct subtypes (or representing multiple subtypes), as well as shifting assignments following treatment indicate the possibility of subtype-switching, or subtype-selection, as mechanisms of therapeutic resistance.

Keywords: small cell lung cancer, predictive biomarkers, tumor heterogeneity

OA03 SYSTEMIC THERAPIES FOR SCLC: NOVEL TARGETS AND PATIENTS' SELECTION
SUNDAY, SEPTEMBER 8 13:30–15:00

OA03.07 IMMUNE-RELATED ADVERSE EVENTS AND CLINICAL OUTCOME TO ANTI PD-1 AXIS INHIBITION IN SCLC: A MULTICENTER RETROSPECTIVE ANALYSIS

B. Ricciuti[1], A.R. Naqash[2], B. Henick[3], D. Rangachari[4], J. Naidoo[5], D. Venkatraman[6], G. Lamberti[6], G. Recondo[1], J. Zhang[7], S. Macherla[2], S. Baig[8], P. Walker[2], K. Sehgal[4], R. Umeton[1], L. Sholl[9], N. Rizvi[3], D. Costa[4], M. Awad[1]

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Background: Immune-checkpoint inhibitors (ICIs) have shown promising activity in only a fraction of patients with small cell lung cancer (SCLC), and factors associated with clinical benefit are not well characterized. The development of immune-related adverse events (irAEs) may correlate with benefit from immune checkpoint inhibitors (ICIs) among patients with cancer. Whether an association exists between irAE development and improved clinical outcomes to ICIs in small cell lung cancer (SCLC) is unknown. **Method:** We retrospectively analyzed data from five participating academic centers: the Dana-Farber Cancer Institute, East Carolina University, Columbia University, Beth Israel Deaconess Medical Center, and Johns Hopkins University. Patients with SCLC who received at least one dose of a programmed death (ligand) PD-(L)1 inhibitor alone or in combination with a cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor were included in this study. To account for the time-dependent nature of irAE onset and clinical benefit from immunotherapy, we identified patients with early irAEs (defined as those occurring within 6 weeks of ICI treatment initiation) and performed a landmark analysis at this time point. **Result:** Among 157 patients treated with ICIs, 65 (41.4%) experienced at least one irAE. Median time to the first irAE onset was 28 days (IQR:15-56). Baseline clinicopathologic characteristics were well balanced between patients who developed irAEs and those who did not. Median tumor mutational burden (TMB) was significantly higher among patients with irAEs compared to those without (14.4 vs 8.4 mutations/megabase [mut/Mb], P <0.01). Patients who developed at least one irAE had a significantly higher objective response rate (26.3% versus 3.3%, P <0.001), and significantly longer median progression-free survival (mPFS, 4.1 vs 1.3 months, HR: 0.30 [0.20-0.43, P <0.001]) and median overall survival (mOS, 14.1 vs 2.9 months, HR: 0.32 [0.21-0.48], P <0.001). The proportion of patients who were progression-free at 6, 9, and 12 weeks was significantly higher in patients who developed early irAEs compared to those who did not develop early irAEs (6 weeks: 89.5% vs 69.5%, P =0.01; 9 weeks: 71.1% vs 40%, P =0.001; 12 weeks: 65.8% vs. 31.6%, P <0.001). The median TMB was also significantly higher in patients who developed early irAEs (14.5 vs 8.7 mut/Mb, P <0.01). **Conclusion:** Patients with SCLC treated with ICIs who developed early irAEs had a higher TMB and enhanced antitumor responses compared to those who did not develop irAEs. Whether a higher TMB is associated with the development of irAEs remains to be determined mechanistically.

Keywords: SCLC, irAEs, Immunotherapy

OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.01 A PHASE III RANDOMIZED STUDY OF NIVOLUMAB/IPILIMUMAB VS NIVOLUMAB FOR PREVIOUSLY TREATED STAGE IV SQUAMOUS CELL LUNG CANCER

L. Bazhenova[1], M. Redman[2], S. Gettinger[3], F.R. Hirsch[4], P. Mack[5], L. Schwartz[6], D. Gandara[7], J. Bradley[8], T. Stinchcombe[9], N. Leighl[10], S. Ramalingam[11], S. Tavernier[12], K. Minichiello[2], K. Kelly[5], V. Papadimitrakopoulou[13], R. Herbst[14]

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Background: Lung-MAP is a master protocol for patients (pts) with stage IV previously treated SqNSCLC. S1400I enrolled pts who were not eligible for a biomarker-matched sub-study. (Lung-MAP Sub-Study S1400I, NCT02785952) **Method:** S1400I is phase III randomized trial for immunotherapy-naïve patients with ECOG 0-1 not selected by PD-L1 expression. Pts were assigned 1:1 to nivolumab and ipilimumab (N+I) vs nivolumab (N). N was given at 3 mg/kg q 2w, I was given at 1 mg/kg q 6w. The primary endpoint was overall survival (OS). Secondary endpoints: investigator-assessed progression-free survival (IA-PFS), response by RECIST 1.1, and toxicity. **Result:** From December 18, 2015 to April 23, 2018, 275 pts enrolled and 252 determined eligible (125 N+I and 127 N). Median follow up for patients still alive was 17.4 months. The study was closed for futility at an interim analysis. Baseline characteristics were similar across arms. mOS was 10.0 m (8.0-12.8) and 11.0 m (8.2-13.5) for N+I and N. HR 0.97 (0.71-1.31), p 0.82. mPFS was 3.8 m (2.3-4.2) and 2.9 m (1.8-3.9) for N+I and N. HR 0.84 (0.64-1.09), p 0.19. The response rate was 18% (12-25) in N+I and 17 % (11, 24) in N. Outcomes were similar across TMB subgroups and PD-L1 expression levels. Most AE were low grade. There were 5 grade 5 AE in N+I arm and 1 in N arm. Grade ≥3 treatment-related AEs occurred in 48(39%) of pts on N+I vs 38(31%) on N. irAE reported in 39% of pts on N+I and 34% of patients on N. Drug-related AEs led to discontinuation in 25% of pts on N+I and 16% of pts on N.

OS and PFS based on TMB and PD-L1				
	N+I Median in months	N Median in months	HR	p
OS PD-L1 ≥5	14.1 (5.8-17.5)	12.0 (8.2-19.8)	1.06 (0.58-1.92)	0.86
OS PD-L1 <5	8.3 (6.0-10.7)	10.3 (6.3-13.5)	1.01 (0.62-1.65)	0.97
OS TMB ≥10	13.1 (9.3-17.0)	11.4 (8.2-16.1)	0.86 (0.56-1.32)	0.48
OS TMB <10	7.6 (5.7-10.2)	10.0 (6.3-15.2)	1.08 (0.68-1.71)	0.74
PFS PD-L1 ≥ 5	3.9 (1.7-7.1)	2.9 (1.8-4.7)	0.65 (0.38-1.08)	0.10
PFS PD-L1 <5	4.4 (2.1-6.0)	1.6 (1.5-3.0)	0.64 (0.41-1.01)	0.06
PFS TMB ≥ 10	4.2 (3.4-5.9)	3.4 (1.8-5.3)	0.75 (0.52-1.10)	0.15
PFS TMB < 10	1.9 (1.5-4.1)	2.7 (1.6-3.3)	0.92 (0.62-1.39)	0.70

Conclusion: S1400I failed to show improvement in outcomes with N+I. Study was closed for futility at interim analysis. Toxicities were not different between two arms. Molecular correlates will be presented at the meeting.

Keywords: Lung cancer, TMB, Immunotherapy

OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.02 CHECKMATE 817: FIRST-LINE NIVOLUMAB + IPILIMUMAB IN PATIENTS WITH ECOG PS 2 AND OTHER SPECIAL POPULATIONS WITH ADVANCED NSCLC

F. Barlesi[1], C. Audigier-Valette[2], E. Felip[3], T.-E. Ciuleanu[4], K. Jao[5], E. Rijavec[6], L. Urban[7], J.-S. Aucoin[8], C. Zannori[9], K. Vermaelen[10], O.A. Frontera[11], N. Ready[12], A. Curioni Fontecedro[13], H. Linardou[14], E. Poddubskaya[15], J. Fischer[16], I. Iordan[17], H. Groen[18], R. Pillai[19], S. Li[20], J. Fiore[20], H. Chang[20], A. Acevedo[20], L. Paz-Ares[21]

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OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.03 A RANDOMIZED PHASE 3 STUDY OF CAMRELIZUMAB PLUS CHEMOTHERAPY AS 1ST LINE THERAPY FOR ADVANCED/METASTATIC NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

C. Zhou[1], G. Chen[2], Y. Huang[3], J. Zhou[4], L. Lin[5], J. Feng[6], Z. Wang[7], Y. Shu[8], J. Shi[9], Y. Hu[10], Q. Wang[11], Y. Cheng[12], J. Chen[13], X. Lin[14], Y. Wang[15], J. Huang[16], J. Cui[17], L. Cao[18], Y. Liu[19], Y. Zhang[20], Y. Pan[18], J. Zhao[21], L. Wang[22], J. Chang[23], Q. Chen[24], X. Ren[25], W. Zhang[26], Y. Fan[27], Z. He[28], J. Fang[29], K. Gu[30], X. Dong[31], F. Jin[32], H. Gao[33], G. An[34], C. Ding[35], X. Jiang[36], J. Xiong[26], X. Zhou[37], S. Hu[38], P. Lu[39], A. Liu[40], S. Guo[41], J. Huang[42], C. Zhu[43], J. Zhao[44], B. Gao[45], Y. Chen[46], C. Hu[47], J. Zhang[48], H. Zhang[48], H. Zhao[49], Y. Zhou[50], Y. Tai[50]

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Background: Platinum-based chemotherapy remains 1st line therapy for advanced non-small cell lung cancer (NSCLC) without oncogenic drivers in China. Camrelizumab (SHR-1210, a potent anti-PD-1 monoclonal antibody) has shown promising activity in multiple malignancies. Here, we report interim analysis results on efficacy and safety of camrelizumab plus carboplatin/pemetrexed as 1st line treatment in Chinese advanced/metastatic non-squamous NSCLC patients with negative oncogenic drivers. **Method:** In this open-label, randomized, multicenter phase 3 study (SHR-1210-303), patients with advanced/metastatic, non-squamous NSCLC with negative EGFR or ALK were stratified by sex and smoking history (≥ 400/year versus < 400/year) and were randomly assigned (1:1) to receive 4 to 6 cycles of carboplatin (AUC=5) plus pemetrexed (500 mg/m2) with or without camrelizumab (200 mg), followed by pemetrexed with or without camrelizumab as maintenance therapy up to disease progression or intolerable toxicity. Treatment was given every 3 weeks. Crossover to camrelizumab monotherapy was permitted for patients in the chemotherapy arm who had confirmed disease progression. The primary endpoint was PFS per blinded independent central review according to RECIST v1.1. Secondary endpoints

included ORR, DCR, DoR and OS. Data of subgroup analysis will be reported. Clinical Trials.gov number: NCT03134872. **Result:** Between May 12, 2017 and Jun 6, 2018, 419 patients were randomized, among whom 205 received camrelizumab plus chemotherapy and 207 received chemotherapy treatment. After a median follow-up of 11.9 months, median PFS was 11.3 months (95% CI 9.5-not reached) in camrelizumab plus chemotherapy arm and 8.3 months (95% CI 6.0-9.7) in chemotherapy arm (HR 0.61 [95% CI 0.46-0.80], p=0.0002). ORR, DCR, DoR and OS with camrelizumab plus chemotherapy were superior to chemotherapy (Table 1). Grade 3/4 adverse events occurred in 66.8% of patients in camrelizumab plus chemotherapy arm and 51.2% of patients in chemotherapy arm. There were 5 treatment-related deaths in camrelizumab plus chemotherapy arm and 4 in chemotherapy arm.

Table 1. Responses per blinded independent central review and overall survival in the total study population

	Camrelizumab plus chemotherapy (n=205)	Chemotherapy alone (n=207)	p-value
Objective response rate	60.0% (53.0-66.8)	39.1% (32.4-46.1)	p<0.0001
Disease control rate	87.3% (82.0-91.6)	74.4% (67.9-80.2)	p=0.0009
Duration of response (months)	17.6 (11.6-NR)	9.9 (8.5-13.8)	p=0.0356
Overall survival (months)	NR (17.1-NR)	20.9 (14.2-NR)	p=0.0272

Data are shown in % (95% CI) or median (95% CI). NR: not reached.

Conclusion: First-line camrelizumab plus chemotherapy shows substantial clinical benefit in patients with advanced/metastatic non-squamous NSCLC with negative EGFR or ALK in terms of PFS, ORR, and OS and acceptable safety profiles. The combination should become novel standard 1st line therapy for this population.

Keywords: Non-Squamous Non-Small Cell Lung Cancer, camrelizumab, phase 3

OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.05 KEYNOTE-021: TMB AND OUTCOMES FOR CARBOPLATIN AND PEMETREXED WITH OR WITHOUT PEMBROLIZUMAB FOR NONSQUAMOUS NSCLC

C. Langer[1], S. Gadgeel[2], H. Borghaei[3], A. Patnaik[4], S. Powell[5], R. Gentzler[6], J. Yang[7], M. Gubens[8], L. Sequist[9], M. Awad[10], R. Cristescu[11], D. Aurora-Garg[11], A. Albright[11], A. Loboda[11], J. Kobie[11], J. Lunceford[11], M. Ayers[11], G. Lubiniecki[11], B. Piperdi[11], M.C. Pietanza[11], V. Papadimitrakopoulou[12]

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This abstract is under embargo until September 8 09:45 CET

OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.06 EVALUATION OF TMB IN KEYNOTE-189: PEMBROLIZUMAB PLUS CHEMOTHERAPY VS PLACEBO PLUS CHEMOTHERAPY FOR NONSQUAMOUS NSCLC

M. Garassino[1], D. Rodriguez-Abreu[2], S. Gadgeel[3], E. Esteban[4], E. Felip[5], G. Speranza[6], M. Reck[7], R. Hui[8], M. Boyer[9], R. Cristescu[10], D. Aurora-Garg[10], A. Albright[10], A. Loboda[10], J. Kobie[10], J. Lunceford[10], M. Ayers[10], G. Lubiniecki[10], B. Piperdi[10], M.C. Pietanza[10], E. Garon[11]

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This abstract is under embargo until September 8 09:45 CET

OA04 IMMUNO COMBINATIONS AND THE ROLE OF TMB
SUNDAY, SEPTEMBER 8 15:15–16:45

OA04.07 MUTATIONS ASSOCIATED WITH SENSITIVITY OR RESISTANCE TO IMMUNOTHERAPY IN MNSCLC: ANALYSIS FROM THE MYSTIC TRIAL

N. Rizvi[1], B.C. Cho[2], N. Reinmuth[3], K.H. Lee[4], A. Luft[5], M. Ahn[6], V. Papadimitrakopoulou[7], J. Heymach[7], U. Scheuring[8], B. Higgs[9], J. Ye[9], M. Kuziora[9], S. Wu[9], F. Liu[9], H. Si[9], S. Peters[10]

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This abstract is under embargo until September 8 09:45 CET

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.01 A PROSPECTIVE STUDY OF SWALLOWING AND VOICE OUTCOMES AFTER TREATMENT FOR SMALL-CELL LUNG CANCER

J. Frowen[1,2], K. Gough[1,2], J. Phipps-Nelson[1,2], R. Hughes[1], S. Siva[1,2], A. Drosdowsky[1], B. Solomon[1,2], N. Kiss[1,3], M. Duffy[1], D. Ball[1,2]

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Background: Dysphagia (difficulty swallowing) and dysphonia (impaired voice) have been identified in patients with lung cancer as being a significant problem. However, research to date has been limited in its measurement and it remains unknown which patients experience dysphagia or dysphonia, and what the impact of these problems are to the patient. The purpose of this study was to identify the prevalence and nature of dysphagia and dysphonia in patients with limited stage SCLC. **Method:** A prospective cohort pilot study was conducted on 12 patients receiving chemoradiotherapy for limited-stage SCLC. Data collection included: videofluoroscopy swallowing studies (VFSS) to investigate swallowing physiology, aspiration risk and oesophageal motility disorders; limitations to oral intake; patient-reported swallowing problems; and patient-reported

voice problems. Data were collected before treatment and again at one, three and six months post-treatment. **Result:** No patient was observed to aspirate, and the pharyngeal swallow was safe and functional in all cases. Three patients exhibited oesophageal motility disorders before treatment, while three more exhibited these disorders at the post-treatment assessments. Oral intake was most compromised one month post-treatment; at this time one patient was tube dependent, two required a single consistency diet and two had a diet requiring special preparation. At all other time-points patients were managing a normal or near-normal diet. Despite an absence of oropharyngeal dysphagia observed on VFSS, three patients reported moderate or severe swallowing difficulties one month post-treatment; these self-reported difficulties were no more than mild at follow-up assessments. Three additional patients reported the onset of moderate or severe swallowing difficulties at three and six months post-treatment. Patients who reported swallowing difficulties at one month post-treatment had all received a mean radiation dose to the oesophagus of ≥15.7Gy and a maximum dose to the oesophagus of ≥42Gy, however these relationships were no longer apparent at three and six months post-treatment. Patient-reported voice difficulties were variable, with the worst scores being reported at one month post-treatment for a subset of patients, who continued to report problems across voice-related physical, functional and emotional domains at three and six months post-treatment. **Conclusion:** This is the first time that detailed swallowing and voice outcomes have been reported in patients with SCLC. Although patient numbers are small, this study identified discordance between observed swallowing function and patient-reported problems, which may have significant clinical implications for the management of patients with SCLC, as well as identify important issues for future research.

Keywords: voice, dysphagia, swallowing

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.02 PATIENT EXPERIENCE, EXPECTATIONS AND KNOWLEDGE: LUNG CANCER IN AUSTRALIA

C. Holliday

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Background: Lung cancer is the fourth most diagnosed cancer in Australia. In 2015, it was the fourth most common cause of death and the most common cause of cancer death. There were over 11,000 new cases of lung cancer in 2013, with more men (approximately 6,600) than women (approximately 4,500) diagnosed. In 2014, more than 8000 people in Australia died from lung cancer, nearly 5000 of whom were men. Patient Experience, Expectations and Knowledge (PEEK) is a research study developed by the International Centre for Community-Driven Research (CCDR). PEEK studies conduct patient experience research using a protocol that will allow for comparisons over time (both quantitative and qualitative components). This study in NSCLC is the largest mixed methodology study in Australia in the past five years. **Method:** In this study, 80 people with NSCLC stages I to IV throughout Australia participated in a structured (qualitative) interview and an online (quantitative) questionnaire. The interview and questionnaire comprehensively covered all aspects of disease experience from symptoms, diagnosis, treatment, communication, information provision, care and support, quality of life, and future treatment and care expectations. Statistical analysis of quantitative data was conducted using R, and content analysis of qualitative data was conducted using conventional analysis to identify major themes. **Result:** The most common symptom experienced before diagnosis was back and/or shoulder pain (n=35, 43.75%), and the most common symptoms leading to diagnosis was breathing difficulties (n=26, 32.50%). The majority (n=58; 72.50%) of participants knew nothing or very little about lung cancer at diagnosis, and the most commonly reported theme relating to discussion about treatment was that patients were presented with only one treatment plan, with little discussion about treatment options (n=36; 45.00%). There were 76.25% (n=61) of this study population that reported receiving support primarily from family and friends. Quality of life was negatively affected in 85.00% (n=68) of the study population, the most common reason being due to the emotional and physical impact on patients and family (n=44; 55.00%). There were 51.25% (n=41) of the study population that reported relationships being strengthened, despite 75.00% (n=60) of the study population reporting feeling burdensome to their family. In relation to future needs, 53.75% (n=43) of participants called for access to treatments to be more affordable and equitable; for information to address stigma and educate the public in relation to causes of lung cancer (n=16, 20.00%); for clinicians to display more compassion/empathy (n=20, 25.00%); and for support more groups and peer support (n=17, 21.25%). **Conclusion:** Based on patient experience and feedback, three recommendations are made to improve patient quality of life and/or ability to manage their own health: Public health campaigns developed to prevent lung cancer should be developed in a way that protects people currently diagnosed from the impact of negative stigma. Information and support services, including support for carers, should be more targeted to specific disease staging and sub-types of disease. Research funding should reflect the mortality and prevalence of lung cancer, and the number of clinical trials available should increase to aid timely decisions about new treatments.

Keywords: patient experience, real-world evidence, Patient-driven research

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.03 DEVELOPMENT OF A FATIGUE AND BREATHLESSNESS GROUP FOR THORACIC ONCOLOGY PATIENTS

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Background: Cancer related fatigue and breathlessness are well-established common symptoms of lung cancer, with 57%-100% of all lung cancer patients experiencing cancer related fatigue and 19%-51% experiencing dyspnoea. Both symptoms can be highly subjective and distressing for the individual, impacting on all domains of their life: physical, social and emotional. Due to this fatigue, dyspnoea and anxiety are a symptom cluster effecting up to 96% lung cancer patients, and is associated with poor performance status and reduced patient reported quality of life (QoL). In order to address this the symptoms of fatigue, breathlessness and anxiety need to be addressed concurrently in order to ensure the best results for the individual and improve QoL. **Method:** A literature review was completed using online journal libraries to determine the incidence and impact of fatigue and breathlessness on lung cancer patients, as well as the most effective symptoms management interventions. Following this, patients attending the thoracic oncology outpatient clinics at Guy's Cancer Centre completed a questionnaire to determine: 1. The incidence fatigue, breathlessness and mood changes 2, Their individual experience of the symptoms 3. If the symptoms are impacting on QoL 4. Would they want to attend a group to address these symptoms 5. The preferred location, time and frequency of the group Outcome measures to address the symptoms were reviewed to ensure that those with the highest validity were selected for use. **Result:** A six session group was developed, using the Breathing, Thinking Functioning model at its core, to ensure that the sessions address all domains of the patients life, as well as the mechanisms of dyspnoea. Sessions also addressed fatigue and sleep hygiene, once again addressing the issues holistically. Each session consists of both an educational element, to address the subject of the week, followed by a practical session to allow for practice of the techniques provided and assist the individuals to gain mastery of these. In order to gain both qualitative and quantitative data, patients complete the FACIT-Fatigue, EORTC QLQ-C30, Dyspnoea 12 and individual goal setting prior to commencing the programme. The individual goals are discussed with the clinician when attending the initial session to ensure that these are addressed during the group. On completion of the session these assessment are repeated in order to determine the impact that the group has had on all symptoms as well as the individuals QoL. **Conclusion:** Fatigue and breathlessness are debilitating side effects of a lung cancer diagnosis, which result in both physical and emotional changes for the patient. In order to address these symptoms holistically they need to be address concurrently, as well as addressing the impact they have on anxiety and depression. By providing a structured group programme to address these symptoms and the impact they have on the individual, it allows patients to master skills to reduce the impact of these symptoms, as well as promote self-management and improve QoL.

Keywords: Fatigue, Breathlessness, QoL

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.05 TRANSFORMING THE PATIENT EXPERIENCE IN LUNG CANCER THROUGH THE USE OF CLINICAL NURSE SPECIALIST VIRTUAL CLINICS–THE LIVERPOOL EXPERIENCE

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This abstract is under embargo until September 8 09:45 CET

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.06 NURSING INTERVENTION ON IMMUNO-RELATED ADVERSE EVENTS IN LUNG CANCER PATIENTS

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Background: New treatment of immunotherapy permits to stimulate the patient's immune responses against cancer. That it supposes a new strategy for melanoma, renal and lung cancers. Although, is different than Chemotherapy's toxicity, the effect on tissues and organs are systemic and can be dealing to unpredictable side-effects that should be detected and treated as soon as possible. Nurses are vital to manage toxicity related to immunotherapy & educate and to provide patient's with best education. Our objetive is to describe lung cancer clinical nurses specialists' role on the management of toxicities related to immunotherapy in lung cancer patients. How is the control and follow–up for those patients **Method:** In 2018, a cross-sectional study was conducted with lung cancer patients receiving immunotherapy at the Lung Functional Unit of Catalan Institute of Oncology, hospital Duran I Reynals in Barcelona-Spain. The variables included were socio-demographic profile, the clinical were; tumour histological, toxicities prevalence and severity and finally variables from the roles and references made by nurses. A descriptive analysis of prevalence was performed with type of toxicities and patient characteristics. **Result:** New patients receiving immunotherapy were 69 and the most common toxicities were; asthenia (82.5%), skin toxicity (35.5%), Pneumonitis (22.5%), colitis (20%), arthralgia (12.5%), endocrine toxicity (12.5%), emesis (10%), vascular (7.5%), gastritis (5%), hepatic (5%), renal (5%) & neurologic (5%). Attending grading severity, it was GI-GII, both were controlled by nurses, GIII and GIV required specialists, hospitalization and other professionals. Nurses visited 95% of the patients previously to initiate their treatments, attended 128 phone calls and in 111 patients they realised the follow-up and control. From total a 50% need emergency services and finally got hospitalization in 30% of them. **Conclusion:** Grades I and II are the most common toxicity. Nurses were in charge for patient education, providing careful information to patients, family members and caregivers, along the whole process. This role is vital to get better and earlier control on the side-effects, higher satisfaction and to facilitate the multidisciplinary team-working dynamic.

Keyword: lung cancer, immunotherapy, nurse care

OA05 INCREASING THE IMPACT OF NURSING AND ALLIED HEALTH PROFESSIONAL INTERVENTIONS IN LUNG CANCER CARE
SUNDAY, SEPTEMBER 8 15:15–16:45

OA05.07 CO-OPERATION BETWEEN THE CITIES OF GLASGOW AND BETHLEHEM AND THE DEVELOPMENT OF A CANCER NURSING DIPLOMA AT BETHLEHEM UNIVERSITY PALESTINE

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Glasgow & Clyde Health Board, Alexandria/United Kingdom

Background: Cancer is a serious public health issue in Palestine. The impact of the conflict between Palestine and Israel has a negative impact on the diagnosis and treatment of cancer patients. In addition, the political situation has hindered the development of effective cancer nursing reflective practice and education for Palestinian nurses. A meeting between Gerry O Hare (oncology CNS Glasgow and Clyde Health Board) and Mariam Awad (Dean of Nursing Bethlehem University) in 2011 led to an exploration of opportunities for cancer nursing educational initiatives between Glasgow, Scotland and Bethlehem Palestine. Support for cancer nurses education was secured from Glasgow Health Board, the office of Lord Provost of Glasgow, Bethlehem University, Medical Aid for Palestine, European Oncology Nursing Society, Palestinian Dept of Health, and supportive UK and Bethlehem nurse academics. This multi-agency commitment and support resulted in the launch of the first Post-Graduate High Diploma in Cancer/Palliative nursing in Palestine by the Nursing Department at Bethlehem University Palestine in 2016. This is an example of motivated nurses from geographical distant countries positively influencing agencies to develop a pioneering cancer/palliative care nurse educational high diploma programme at Bethlehem University, Palestine. This initiative sends a message to cancer nurses globally to encourage them to cross cultural, political and geographical barriers to achieving positive outcomes for cancer nurse education. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** Section not applicable

Keyword: Cancer Palestine Nursing

OA06 OA06 REFINING LUNG CANCER SCREENING
MONDAY, SEPTEMBER 9 11:00–12:30

OA06.01 COMPARISON BETWEEN RADIOMICS-BASED MACHINE LEARNING AND DEEP LEARNING IMAGE CLASSIFICATION FOR SUB-CM LUNG NODULES

I. Janzen[1], S. Seyyedi[1], R. Abraham[1], S. Atkar-Khattra[2], J. Mayo[3], R. Yuan[4], R. Myers[2], S. Lam[2], C. Macaulay[5]

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Background: New clinical challenges have arisen from the recent recognition for an improved mortality of cancers via lung cancer screening using LDCT. A particular challenge for physicians and CADx systems is the classification and prediction of behavior for sub-cm lung nodules that are frequently present in screening CT scans. By predicting and classifying the behavior of these small nodules, we can identify potential cancerous nodules into the earlier stages of malignancy making them more easily treatable. **Method:** We have evaluated a multitude of image processing techniques to assist in CADx systems for these small nodules such as Radiomic feature-based machine learning algorithms (linear discriminant analysis) as well as leveraging pretrained convolution neural networks such as VGG19 and InceptionV3 using deep learning/transfer learning techniques. The linear discriminate Radiomic analysis (LDA) classified a sample of CT imaged nodules (n=514) using quasi-volumetric nodule data (images of the nodules from CT slices above and below the central slice) into three discriminate categories: cancerous (clinically confirmed, n = 140) versus resolved (not present in follow up CT scans, n=107) versus stable (a negligible change in shape, texture, size in multi year follow up CT scans, n=267). Each nodule was segmented from the original CT scan using an inhouse lung CT image segmenation routine. This routine generated 2167 discrete CT nodule images upon which 133 Radiomic shape and texture features were calculated. **Result:** The LDA Radiomic analysis correctly

classified the individual nodual sections with an accuracy of 75.1% (jackknife - leave one out result) using only 18 features predefined traditional image analysis features (4 shape feature(s), 14 texture feature(s)) for cancer vs resolved + stable nodules. Requiring that more than or equal to 50% of sections from a nodule be classified as cancer for the nodule to be classified as cancer individual nodules could be correctly classified with an 80% accuracy. The leveraged pretrained networks (VGG19, and InceptionV3) trained using standard data augmentation and finetuning techniques, trained on this same quasi-volumetric image data as a binary classification task (malignant vs. benign nodules) achieved an average classification accuracy of 71% and 75% respectively through 10-crossfold validation. **Conclusion:** Machine learning using 18 Radiomics features was able to classify 75.1% of the 2167 CT nodule images (up to 5 images/CT slices per nodule) and 80% of the nodules correctly. The best of the Deep Learning networks achieved almost equivalent results. The image classification deep neural network results suggest the implementation of more advanced regularization and initialization deep learning techniques to further refine the decision boundaries for these pretrained networks might be benefitial. We believe the development of visualization neural network software to highlight the defining nodule features during classification would clinically assist in providing context clues for nodule diagnosis. This work has been supported by TFRI project ref:1068

Keywords: deep learning, Radiomics, machine learning

OA06 REFINING LUNG CANCER SCREENING
MONDAY, SEPTEMBER 9 11:00–12:30

OA06.02 THE ROLE OF SIMULATION MODELING IN SHAPING LUNG CANCER SCREENING POLICIES IN THE US AND ELSEWHERE

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This abstract is under embargo until September 9 10:15 CET

OA06 REFINING LUNG CANCER SCREENING
MONDAY, SEPTEMBER 9 11:00–12:30

OA06.03 AN OPEN SOURCE LUNG SCREENING MANAGEMENT SYSTEM

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Background: Starting in 1992, the Early Lung Cancer Screening Project (ELCAP) investigators developed the ELCAP Management System (MS) to ensure high quality care and follow-up of the first 1,000 ELCAP participants. The resulting Lancet publication in 1999 created worldwide interest in screening and an updated web-based ELCAP MS was updated to be web-based and provided free of charge to participating institutions, together with the I-ELCAP protocol. **Method:** The ELCAP MS was designed to be comprehensive and rapidly capture information on each participant to be used by coordinators, navigators, nurses, radiologists, and other medical professionals to ensure appropriate follow-up and care. It provides rapid documentation of telephone or other inquiries, registering, scheduling screening appointments, reporting results, diagnosis of lung cancer, and treatment, and archives all CT images for integrated access of image and patient information. It has been iteratively updated through user feedback, and supports medical reimbursement requirements and continuous quality improvement to minimize harms of lung screening across International ELCAP (I-ELCAP) sites. **Result:** More than 81,000 participants in 80 institutions worldwide have contributed their LDCT findings and images. The MS has provided efficient data collection for rigorous assessment of screening outcomes which has resulted in some 300 publications and abstracts for protocol updating, comparisons, and continuous quality improvement. Having anticipated "open science", the ELCAP MS has been translated into an open source MS that offers a reference standard for data elements (1,500 data fields, 267 required) for robust and efficient management of lung screening programs. This first open source translation has been adopted by the United States Veterans Administration (VA) and integrated into its VistA Electronic Healthcare System for deployment at 10 VA medical centers through a grant for VA Partnership to increase Access to Lung Screening (VA-PALS). The software is being certified by the Open Source Electronic Health Record Alliance (OSEHRA); source code is available on GitHub. Automated quantitative tools have been developed for identification and characterization of nodules, emphysema, major airways, calcification scoring of coronary arteries, aortic valve, thoracic aorta, breast tissue, liver, bone, and image quality. These tools are integrated into the ELCAP MS, and in the future will provide automatically-generated quantitative LDCT reports. **Conclusion:** The ELCAP MS and I-ELCAP protocol have helped define current global standards for lung screening. Its developers have now made the ELCAP MS publicly available through OSEHRA for support of lung screening programs of any scale throughout the world.

Keywords: patient management, open source, lung cancer screening

OA06 REFINING LUNG CANCER SCREENING
MONDAY, SEPTEMBER 9 11:00–12:30

OA06.05 EVALUATION OF A DEEP LEARNING-BASED AUTOMATIC CLASSIFIER FOR THE CLASSIFICATION OF PERIFISSURAL NODULES

D. Han[1], M. Heuvelmans[1,2], M. Rook[1,3], M. Dorrius[1], L. Van Houten[1], N. Waterfield Price[4], L. Pickup[4], P. Novotny[4], J. Declerck[4], M. Oudkerk[5], P.M.A. Van Ooijen[1], F. Gleeson[6], R. Vliegenthart[1]

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Background: Perifissural nodules (PFNs) comprise approximately 20% of screening-detected nodules and are almost certainly benign. Automatic PFN classification could therefore reduce the number of follow-up procedures required for nodule work-up. Prior work has shown some success in AI classification with limited datasets. Here we evaluate the performance of a new deep convolutional neural network (CNN) for PFN classification, trained on a dataset of nodules retrospectively collected from multiple European centers, including validation on an independent reader-study dataset. **Method:** Data (1103 Patients, 1557 unique nodules and 3320 nodule images) were collected from three centers in the UK and the Netherlands. Each nodule was categorized into subtypes, including "PFN", by on-site radiologists. Labels were reviewed centrally, overseen by a single clinician to ensure consistency between sites. A CNN classifier was trained to produce a score that classifies nodules as (typical) PFN or not, using five-fold cross validation. The PFN classifier was developed by "transfer learning" from an existing benign-vs-malignant AI trained on the US National Lung Screening Trial. To compare the CNN with human performance, independent validation was performed on a separate dataset of 158 benign patients (196 nodules/nodule images) from two of the sites. Three readers (two radiologists and a radiology resident) were asked to label each nodule as typical PFN, atypical PFN, or non-PFN. To match the AI training procedure, only the typical-PFN labels were used in the reader study, and compared to atypical/non-PFN classified nodules. Model performance was evaluated by area under the ROC curve (AUC). For the independent validation, Cohen's kappa was used to measure both the model's agreement with reader consensus (at least 2 in agreement) and inter-reader agreement. For Cohen's kappa calculations the CNN score was binarized using a threshold determined from the internal validation data. **Result:** The mean cross-validated AUC on the internal dataset was 92% (95% CI = 90.6–92.9). For the independent dataset, the classifier labelled 61/196 (31%) as typical PFNs, and reader consensus gave 45/196 (23%). Versus reader consensus, the AUC of the CNN on the reader-study dataset was 96% (95% CI 93.3–98.4). Both the classifier–reader agreement [(k=0.74) 90%] and the inter-reader agreement [(k=0.64–0.79) 88%-92%] were substantial. **Conclusion:** The performance of the PFN classifier is similar to that of radiologists and is within the inter-reader variability of radiologists. This demonstrates the potential utility of CNN-based systems for automatic PFN classification.

Keywords: deep learning, Artificial Intelligence, perifissural nodules

OA06.06 INDEPENDENT VALIDATION OF A NOVEL HIGH-RESOLUTION COMPUTED TOMOGRAPHY-BASED RADIOMIC CLASSIFIER FOR INDETERMINATE LUNG NODULES

T. Peikert[1], F. Duan[2], S. Rajagopalan[1], R. Karwoski[1], A. Balar[3], D. Lakhani[3], S. Antic[3], B. Bartholmai[4], J. Tucker[4], P. Massion[3], F. Maldonado[3]

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Background: Optimization of the clinical management of incidentally- and screen-identified lung nodules is urgently needed to limit the number of unnecessary invasive diagnostic interventions, and therefore morbidity, mortality and healthcare costs. We recently developed and internally validated a novel radiomics-based approach for the classification of screen-detected indeterminate nodules, and present herein validation of this algorithm in an independent cohort. **Method:** In a previous study, we developed a multivariate prediction model evaluating independent quantitative variables assessing various radiologic nodule features such as sphericity, flatness, elongation, spiculation, lobulation and curvature. Nodules between 7 and 30 mm of largest diameter were selected from the National Lung Screening Trial (n=726 indeterminate nodules, benign (n = 318) and malignant (n = 408)) were used to derive this model using least absolute shrinkage and selection operator (LASSO) method with bootstrapping method applied for the internal validation. Eight variables capturing vertical location, size, shape, density and surface characteristics were included with an optimism-correct area under the curve (AUC) of 0.94. For this study, an independent dataset of 203 incidentally-identified lung nodules obtained from the indeterminate pulmonary nodule registry at Vanderbilt University was identified. CT datasets were transferred to Mayo Clinic (Rochester, MN) for analysis. Nodules were segmented manually using the ANALYZE software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), and radiomic analysis was performed using the 8-variable radiomic diagnostic algorithm derived from the NLST. The Brock model was also used to calculate probability of malignancy for all NLST and Vanderbilt nodules. **Result:** Brock scores were calculated for 685 NLST nodules (excluded: interval cancers, n=12; missing values needed for Brock score, n=29). The AUC for the Brock score (AUC_{Brock}) for NLST nodules was 0.83 which was inferior to the AUC for the radiomic model ($AUC_{Radiomic}$ =0.94, P<0.001). When the subset of intermediate pre-test probability of lung cancer was considered (Brock score > 10 but <= 60), the AUC_{Brock} was 0.61 (95% CI: 0.54-0.68) whereas the $AUC_{Radiomic}$ was 0.88 (95% CI: 0.84-0.93). A total of 203 incidentally found pulmonary nodules with available clinical information and biopsy or surgery-proven histology identified in the Vanderbilt indeterminate pulmonary nodule registry, and all histology data and corresponding CT images were reviewed. CT images were transferred to Mayo Clinic for analysis. After exclusion of duplicate CT datasets, unanalyzable CT images and not identifiable nodules (n=27 cases), 176 nodules were segmented and analyzed, including 84 benign and 92 malignant nodules. The AUC was 0.89 (95% CI: 0.85-0.94). For comparison, the AUC_{Brock} was 0.88 (95% CI: 0.83-0.94). When the subset of intermediate pre-test probability of lung cancer was considered (Brock score > 10 but <= 60), the AUC_{Brock} was 0.76 (95% CI: 0.63-0.89) whereas the $AUC_{Radiomic}$ was 0.85 (95% CI: 0.74-0.95). **Conclusion:** Our radiomic classifier demonstrates good performance characteristics on an independent retrospective validation dataset. If prospectively validated, integration into clinical decision making algorithm could significantly impact patient care.

Keywords: pulmonary nodule, Screening, Radiomics

OA06 REFINING LUNG CANCER SCREENING
MONDAY, SEPTEMBER 9 11:00–12:30

OA06.07 DISCRIMINATION OF LUNG INVASIVE ADENOCARCINOMA WITH MICROPAPILLARY PATTERN BASED ON CT RADIOMICS

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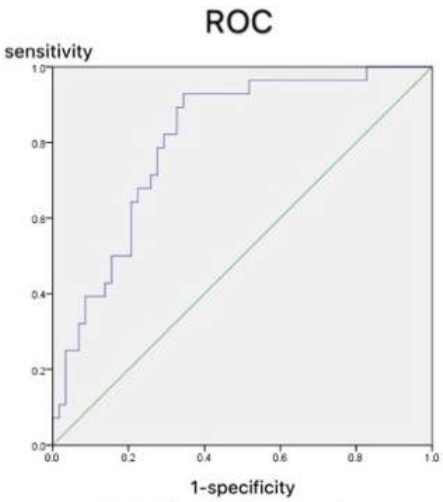
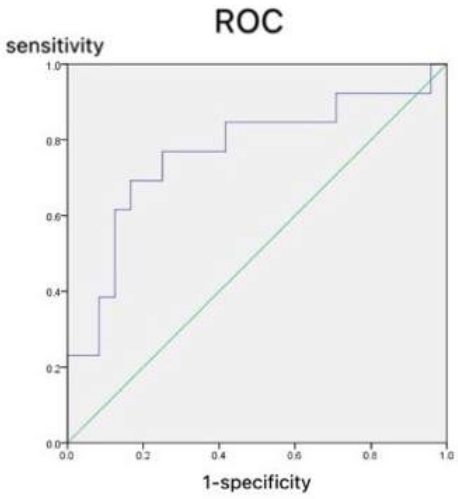
Background: To develop and validate the radiomics nomogram on the discrimination of lung invasive adenocarcinoma (IAC) with micropapillary pattern from non-micropapillary pattern lesion and improve the diagnostic accuracy rate of lung invasive adenocarcinoma with micropapillary pattern before operations and provide guidance for follow-up treatments. **Method:** Forty-one pathologically confirmed lung invasive adenocarcinomas with micropapillary pattern from January 2014 to December 2018 were included. Eighty-two pathologically confirmed lung invasive adenocarcinomas without micropapillary pattern from January 2018 to December 2018 were collected. Select 86 patients (70%) randomly from the 123 patients as the primary cohort, and the other 37 patients (30%) were set as an independent validation cohort. Least absolute shrinkage and selection operator (Lasso) was used for feature selection based on contrast enhancement CT images and then radiomics signature building. ROC analysis and AUC were used to value the ability to identify the lung invasive adenocarcinomas with micropapillary pattern. **Result:** According to GrayLevelCooccurenceMatrix3, Intensity Histogram and Shape, nine hundred and eighty-five radiomics features were extracted by IBEX. And after data pre-processing such as eliminating missing items, strong correlation variables and multicollinear variables, the features were reduced to 40 features. Based on Mann-Whitney U Test, 28 features were figured out from the 40 features. Then Lasso was used to reduce the features to 3 features (10-1clusterprominenc, -333-4clusterprominence, 8-1contrast) as the most meaningful discriminators to build the radiomics signatures (Table 1). According to SPSS21.0 binary logistic regression analysis, ROC analysis and AUC show that the radiomics signature have effective discrimination performance of lung invasive adenocarcinoma with micropapillary pattern from non- micropapillary pattern lesion (AUC=0.766) and it reflects better in the independent validation cohort (AUC=0.807) (Figure 1).

Table 1 Three characteristic prediction parameters in radiomics label

prediction parameter	P value	U value	W value	AUC
10-1clusterprominence	<0.005	765.000	4168.000	0.772
-333-4clusterpromise	<0.005	790.000	4193.000	0.765
8-1contrast	<0.005	919.000	4322.000	0.727



P1. ROC of primary cohort (AUC=0.766)



P2. ROC of validation cohort (AUC=0.807)

Conclusion: The radiomics signature established in this study have effective prediction of lung invasive adenocarcinoma with micropapillary pattern and non- micropapillary pattern lesion.

Keywords: Invasive adenocarcinoma (IAC), Micropapillary pattern, Radiomics

OA07 PRECISION MEDICINE INVOLVES BIOLOGY AND PATIENTS
MONDAY, SEPTEMBER 9 11:00–12:30

OA07.01 OSIMERTINIB PLUS PLATINUM/PEMETREXED IN NEWLY-DIAGNOSED ADVANCED EGFRM-POSITIVE NSCLC; THE PHASE 3 FLAURA2 STUDY

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Background: Osimertinib is a third-generation, CNS-active EGFR-TKI that potently and selectively inhibits both sensitizing EGFR and T790M mutations. Osimertinib is considered the standard of care for patients with newly-diagnosed advanced/metastatic NSCLC harbouring EGFR-activating mutations, based on results of the phase 3 FLAURA trial, which demonstrated a statistically and clinically significant progression-free survival (PFS) benefit for osimertinib over erlotinib or gefitinib. Evidence indicates that adding chemotherapy to gefitinib improves efficacy outcomes versus EGFR TKI monotherapy in newly-diagnosed patients with EGFRm NSCLC (Nakamura et al JCO 2018;36:9005). Adding platinum/pemetrexed to osimertinib could further improve outcomes for newly-diagnosed patients with EGFRm-positive NSCLC. **Method:** The phase 3, open-label, FLAURA2 study aims to assess the efficacy and safety of osimertinib plus cisplatin/carboplatin plus pemetrexed in adults with locally-advanced/metastatic EGFRm-positive (Ex19del and/or L858R) NSCLC who have not received prior therapy for advanced disease. Patients are required to have a WHO performance status (PS) 0-1, life expectancy >12 weeks and not be amenable to curative surgery or radiotherapy. An initial non-randomised run-in phase (n=30) will assess the safety and tolerability of osimertinib 80 mg once daily (QD) with either cisplatin or carboplatin, and pemetrexed, both administered every 3 weeks (Q3W) for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance Q3W until progression or discontinuation. Based on evaluation of safety data from the run-in after ≥12 patients from each group have received ≥3 cycles of study treatment or discontinued therapy, the second phase will randomise approximately 556 patients 1:1 to receive osimertinib 80 mg QD with pemetrexed and cisplatin/carboplatin for 4 cycles followed by osimertinib plus pemetrexed maintenance Q3W or osimertinib alone (80 mg QD), to be continued until progression or discontinuation. Randomisation will be stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and tissue EGFR mutation test at enrolment (cobas® EGFR Mutation Test vs local assessment). A futility analysis of the randomized phase is planned for when approximately 83 PFS events have occurred. The primary endpoint is PFS based on investigator assessment of response using RECIST 1.1 criteria (blinded central assessment is included as a sensitivity analysis). Secondary endpoints include overall survival, objective response rate, duration of response, PFS2, health-related quality of life and safety. Effects on CNS metastases in patients with lesions at baseline will be included as an exploratory endpoint. Enrolment is planned for Q3 2019 for the safety run-in and Q1 2020 for the randomized phase. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Osimertinib, Non-Small Cell Lung Cancer, newly-diagnosed

OA07 PRECISION MEDICINE INVOLVES BIOLOGY AND PATIENTS
MONDAY, SEPTEMBER 9 11:00–12:30

OA07.02 LKB1 MUTATIONS IN METASTATIC NON-SMALL CELL LUNG CANCER (MNSCLC): PROGNOSTIC VALUE IN THE REAL WORLD

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Background: Despite recent advances in treating mNSCLC, many patients fail to respond. Identifying genetic markers may help maximize clinical benefit and avoid unnecessary toxicity. *LKB1/STK11* alterations (*LKB1*m) and co-occurring *KRAS* mutations*/LKB1* loss (*KRAS/LKB1*) have been associated with poor outcomes in patients treated with immunotherapy (IO). Among chemotherapy-treated patients, however, the prognostic value is less understood. This retrospective study examined *LKB1*m, *KRAS/LKB1* and outcomes in patients with mNSCLC receiving IO (as monotherapy or in combination) or chemotherapy in the real-world setting. **Method:** Adult patients with mNSCLC who initiated first line (1L) treatment between Jan 2013 and Jun 2017 and had been profiled with the FoundationOne assay in routine care were enrolled from the Flatiron Health Oncology electronic medical record database. Associations between *LKB1*m, *LKB1/KRAS* and overall survival (OS) or progression-free survival (PFS) were evaluated by line of therapy (1L and second line [2L]) according to histology (non-squamous/squamous and non-squamous only) using multivariate Cox proportional hazards models. All analyses were stratified by IO or chemotherapy. **Result:** 2407 patients (1847 non-squamous) were included; average age was 66.1 years at 1L initiation. 328 (13.6%) patients harbored *LKB1m* and 157 (6.5%) harbored *KRAS/LKB1*. Among IO-treated patients in the 2L setting, *LKB1m* was associated with shorter OS and PFS versus wild type. A similar association was observed in the 1L setting and in the non-squamous only subgroup. In patients receiving chemotherapy, *LKB1m* was associated with worse outcomes only in the 1L setting. All associations were generally more pronounced among *KRAS/LKB1* compared with *LKB1m* patients.

Table. Association between LKB1m and OS or PFS in mNSCLC stratified by IO or chemotherapy and lines of therapy								
Mutation group								
LKB1m								
	All mNSCLC				*Non-Squamous*			
Outcome	*IO*		*Chemotherapy*		*IO*		*Chemotherapy*	
	1L (n = 270)	*2L (n = 670)*	*1L (n =2,137)*	*2L (n = 863)*	*1L (n = 187)*	*2L (n = 498)*	*1L (n = 1,687)*	*2L (n = 683)*
LKB1m, N (%)	40 (14.8)	111 (16.6)	288 (13.5)	83 (9.6)	38 (20.3)	97 (19.5)	257 (15.2)	75 (11.0)
OS								
Median	341	192	340	350	431	201	356	400
(IQR)	(221 – NA)	(72 – 523)	(284 – 405)	(307 – 451)	(221 – NA)	(73 – 613)	(287 – 415)	(307 – 453)
HR	1.43	1.59	1.40	1.07	1.40	1.67	1.43	1.05
(95% CI)	(0.90 – 2.27)	(1.25 – 2.03)	(1.21 – 1.63)	(0.81 – 1.41)	(0.84 – 2.32)	(1.27 – 2.19)	(1.22 – 1.68)	(0.78 – 1.42)
PFS								
Median	122	67	136	122	125	68	136	128
(IQR)	(83 – 295)	(46 – 118)	(119 – 146)	(97 – 147)	(81 – 299)	(46 – 114)	(122 – 149)	(98 – 153)
HR	1.43	1.59	1.40	1.07	1.36	1.55	1.38	1.07
(95% CI)	(0.90 – 2.27)	(1.25 – 2.03)	(1.21 – 1.63)	(0.81 – 1.41)	(0.92 – 2.03)	(1.22 – 1.97)	(1.20 – 1.59)	(0.82 – 1.39)
KRAS/LKB1								
	All mNSCLC				*Non-squamous*			
	IO		*Chemotherapy*		*IO*		*Chemotherapy*	
	1L (n = 270)	*2L (n = 670)*	*1L (n =2,137)*	*2L (n = 863)*	*1L (n = 187)*	*2L (n = 498)*	*1L (n = 1,687)*	*2L (n = 683)*
KRAS/LKB1, N (%)	17 (6.3)	56 (8.4)	140 (6.6)	42 (4.9)	16 (8.6)	52 (10.4)	133 (7.9)	40 (5.9)
OS								
Median	303	209	356	343	341	230	363	350
(IQR)	(222 – NA)	(72 – 666)	(272 – 450)	(254 – 554)	(130 – NA)	(72 – 666)	(284 – 462)	(254 – 554)
HR	1.46	1.63	1.55	1.27	1.44	1.78	1.61	1.28
(95% CI)	(0.74 – 2.86)	(1.16 – 2.29)	(1.26 – 1.90)	(0.87 – 1.84)	(0.68 – 3.05)	(1.22 – 2.59)	(1.29 – 2.00)	(0.86 – 1.90)
PFS								
Median	126	67	136	133	174	68	136	133
(IQR)	(77 – 291)	(46 – 91)	(112 – 160)	(91 – 190)	(72 – 295)	(47 – 91)	(112 – 160)	(91 – 190)
HR	1.34	1.81	1.40	1.08	1.34	1.86	1.44	1.05
(95% CI)	(0.80 – 2.24)	(1.35 – 2.44)	(1.16 – 1.68)	(0.77 – 1.51)	(0.76 – 2.36)	(1.35 – 2.57)	(1.19 – 1.75)	(0.74 – 1.50)
Note: Bold text indicates significant results; reference group for *LKB1m* is *LKB1wt*; reference group for *KRAS/LKB1* is *KRASwt/LKB1wt* Median OS and PFS and IQRs are expressed in days								
Abbreviations: *KRAS* mutation*/LKB1* loss *(KRAS/LKB1),* Hazard ratio (HR), Interquartile range *(IQR),* Confidence interval (CI), Immunotherapy (IO), Overall Survival (OS), Progression-free survival (PFS), Wild type (wt)								

Conclusion: *LKB1m* and *LKB1/KRAS* were associated with numerically worse OS and PFS in the 1L setting, irrespective of treatment, and in IO-treated patients in the 2L setting. Results of this real-world study support previous clinical findings and suggest unique relevance of these mutations in 1L chemotherapy and for 1L and 2L IO.

Keywords: durvalumab, mNSCLC, LKB1

OA07.03 CLINICAL OUTCOME OF NON-SMALL CELL LUNG CANCER WITH EGFR/HER2 EXON 20 INSERTIONS IDENTIFIED IN THE LC-SCRUM-JAPAN

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Background: In-frame insertions in exon 20 (Ex20ins) of *EGFR/HER2* occur in 2-5 % of non-small cell lung cancer (NSCLC). There is no approved targeted therapy for patients with these mutations. Historical control data would be valuable for the development of novel targeted therapies for these rare cancers. **Method:** A nationwide genome screening project in Japan (LC-SCRUM-Japan) has been established for the development of molecular-targeted therapies for lung cancers. In this project, 161 cancer-related genes have been analyzed by a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay. The therapeutic efficacy and survival of the patients with non-squamous (non-sq) NSCLC harboring *EGFR/HER2* Ex20ins were evaluated using a large-scale clinico-genomic database in the LC-SCRUM-Japan. **Result:** A total of 3441 advanced non-sq NSCLC patients were successfully analyzed from 2015 to 2018. *EGFR* Ex20ins were detected in 73 patients (2%; M766_A767insASV/A767_S768insSVD/H773_V774insH/D770_N771insNPH/N771_P772insPH/others=22/17/5/4/4/21) and *HER2* Ex20ins were detected in 128 patients (4%; A775_G776insYVMA/G776delinsVC/P780_Y781insGSP/others=95/16/10/7). The median age of the patients was 62 (range, 33-90) years. Eighty-one patients (40%) were male and 114 (57%) were never smoker. Two-hundred patients (99%) were diagnosed as adenocarcinoma and 1 as adenosquamous-cell carcinoma. Based on our database, the median overall survivals in patients with *EGFR* Ex20ins were 22.4 (95%CI, 15.3-36.8) months, and those with *HER2* Ex20ins were 18.8 (13.6-30.3) months. In the patients with *EGFR/HER2* Ex20ins, the objective response rate (ORR) and median progression-free survivals (mPFS) of 1st-line platinum-containing chemotherapies were 32% and 6.0 (5.7-7.0) months, respectively. The ORR and mPFS of docetaxel with or without ramucirumab were 26% and 5.1 (3.8-5.9) months, respectively. The ORR and mPFS of PD-1 inhibitor were 0% and 2.0 (1.6-2.6) months, respectively. No significant difference in the therapeutic efficacy of these drugs was observed between the patients with *EGFR* Ex20ins and *HER2* Ex20ins. In 19 patients with *EGFR* Ex20ins treated with 1st/2nd generation EGFR-TKIs, the ORR was 5% (a M766_A767insASV-positive tumor responded to afatinib) and the mPFS was 2.1 (1.3-4.2) months. **Conclusion:** The patients with *EGFR/HER2* Ex20ins-positive NSCLC showed poor responses to PD-1 inhibitors and 1st/2nd generation EGFR-TKIs. These historical data are highly informative in evaluating the efficacy of novel targeted therapies for *EGFR/HER2* Ex20ins-positive NSCLC.

Keywords: EGFR/HER2 exon20 insertion mutations, Chemotherapy, immuno-therapy

OA07.05 HIGH-GRADE CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN): AN ANALYSIS OF ECOG-ACRIN LUNG CANCER CLINICAL TRIALS

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Background: High-grade (CTCAE grade ≥3) CIPN implies severe symptoms and limitation of self-care activities of daily living (ADL). To date, studies characterizing the incidence of and factors associated with CIPN have been conducted almost exclusively in breast cancer populations. As such, they generally evaluate only women and lack assessment of platinum-based chemotherapy. We therefore examined the incidence and factors associated with high-grade CIPN among patients treated on ECOG-ACRIN advanced non-small cell lung cancer (NSCLC) clinical trials. **Method:** We included two completed trials in the analysis: E1594 (comparison of 4 chemotherapy regimens: cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, carboplatin-paclitaxel) and E4599 (carboplatin-paclitaxel ± bevacizumab). We identified patients who developed treatment-related grade ≥3 CIPN. Multivariable logistic regression modeling was performed to estimate adjusted odds ratios. For the treatment variable, the reference group ended up combining the cisplatin+paclitaxel and cisplatin+docetaxel arms since their results were not significantly different from one another. Body-mass index (BMI) was categorized by median value (25.2 kg/m^2). **Result:** Among 1,989 total patients, 167 (8.4%) developed grade ≥3 CIPN. Incidence was highest for the carboplatin-paclitaxel regimen (9.9%) and lowest for cisplatin-paclitaxel (4.5%) (P=0.006). Grade ≥3 CIPN was associated with BMI (9.9% for ≥25.2 kg/m^2 vs 6.9% for <25.2 kg/m^2; P=0.02) and sex (6.9% for men vs 10.4% for women; P=0.006). There was a non-significant trend toward association with age (10.4% for ≥70 years versus 7.8% for <70 years; P=0.08). In multivariate analysis, chemotherapy regimen, sex, and BMI remained independently associated with grade ≥3 CIPN. **Conclusion:** Carboplatin-paclitaxel chemotherapy, female sex, and high BMI are associated with the development of high-grade CIPN. Given the clinical severity of this condition and the potential for long-term persistence, consideration of risk-based monitoring and treatment selection may be warranted.

Keywords: Lung cancer, Neuropathy, Chemotherapy

OA07.06 PATIENT KNOWLEDGE AND EXPECTATIONS RELATED TO RETURN OF GENOMIC RESULTS IN THE LUNG-MAP (SWOG 1400) BIOMARKER-DRIVEN CLINICAL TRIAL

J. Roth[1], M. Trivedi[2], S. Gray[3], D. Patrick[4], W. Burke[4], D. Delaney[1], K. Watabayashi[1], P. Litwin[1], P. Shah[1], K. Crew[2], M. Yee[1], M. Redman[1], V. Papadimitrakopoulou[5], K. Kelly[6], D. Gandara[6], D. Hershman[2], S. Ramsey[1]

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This abstract is under embargo until September 9 10:15 CET

OA07 PRECISION MEDICINE INVOLVES BIOLOGY AND PATIENTS
MONDAY, SEPTEMBER 9 11:00–12:30

OA07.07 QUALITY OF LIFE (QOL) ANALYSIS IN LUNG CANCER: A SYSTEMATIC REVIEW OF PHASE III TRIALS PUBLISHED BETWEEN 2012 AND 2018

M.L. Reale[1], E. De Luca[2], P. Lombardi[3], L. Marandino[3], C. Zichi[2], D. Pignataro[1], E. Ghisoni[3], R. Di Stefano[1], A. Mariniello[1], E. Trevisi[1], G. Leone[1], L. Muratori[1], A. La Salvia[1], C. Sonetto[1], P. Bironzo[1], M. Aglietta[3], S. Novello[1], G. Scagliotti[1], F. Perrone[4], M. Di Maio[2]

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This abstract is under embargo until September 9 10:15 CET

OA08 ADVANCED MODELS AND "OMICS" FOR THERAPEUTIC DEVELOPMENT
MONDAY, SEPTEMBER 9 11:00–12:30

OA08.01 ORGANOID CULTURES AS NOVEL PRECLINICAL MODELS OF NON-SMALL CELL LUNG CANCER

M. Tsao[1], R. Shi[2], N. Radulovich[1], C. Ng[1], H. Notsuda[3], M. Cabanero[4], S. Martins-Filho[1], V. Raghavan[1], Q. Li[1], A. Mer[1], N. Liu[1], N.-A. Pham[1], B. Haibe-Kains[1], G. Liu[5], N. Moghal[1]

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Background: There is an unmet need to develop novel clinically relevant models of NSCLC to accelerate identification of drug targets and our understanding of the disease. Organoids, which are cells grown in three-dimensional environments in Matrigel, have emerged as novel preclinical models of cancer. Recently protocols for generating NSCLC organoids have been reported, but the growth, and molecular features of organoids as compared to their matching primary patient tumor or patient-derived xenografts (PDX) remain vague. **Method:** Thirty surgically resected NSCLC patient tumor and 35 PDX tissue of lung adenocarcinoma and squamous cell carcinoma subtypes were processed for organoid establishment. Organoids and matching tumor tissues were characterized by histology and immunohistochemistry, and molecularly profiled by whole exome and RNA-sequencing. Subcutaneous injection of organoids *in vivo* was performed to confirm tumorgenicity. Organoids were subjected to drug testing and drug response was verified in the matched PDX. **Result:** Using a novel culture condition that our laboratory developed, we have collected tumor samples from 16 primary and 13 PDX samples of adenocarcinoma (n=29) and 14 primary and 22 PDX samples of squamous cell carcinoma (n=36). Over 85% (57/65) of our patient and PDX tumor tissues formed organoids that exhibited a wide range of short-term (<3 months) and long-term (>3 months) growth. Specifically, the success rate of establishing short-term and long-term models are 74% (48/65) and 14% (9/65), respectively. The long-term propagable organoids recapitulated the histology of the patient and PDX tumor. They also retained the ability to form xenograft in NOD-SCID mice. The organoids preserved mutation, copy number aberrations and global gene expression profile of the parental tumors. We additionally showed the utility of short-term and long-term organoids for identifying biomarkers of sensitivity to drugs and combinational targeted therapies. **Conclusion:** NSCLC organoids are novel patient-derived ex-vivo tumor models for anti-cancer drug screening and biomarker discovery, thus could be incorporated into novel drug discovery pipelines. Further efforts are ongoing to increase the success rate of establishing long-term organoid lines.

Keywords: *In vitro* model, Patient-derived models, PDX

OA08 ADVANCED MODELS AND "OMICS" FOR THERAPEUTIC DEVELOPMENT
MONDAY, SEPTEMBER 9 11:00–12:30

OA08.02 A MULTIDISCIPLINARY MULTI-OMICS STUDY OF SPATIAL AND TEMPORAL TUMOR EVOLUTION IN THORACIC CANCERS WITH CLINICAL IMPLICATIONS

N. Alcala[1], L. Mangiante[1], A. Poret[1], A. Gabriel[1], J. Derks[2], L. Moonen[2], S. Boyault[3], N. Le Stang[4], A. Ghantous[1], S. Tabone-Eglinger[5], F. Damiola[4], J.-Y. Blay[4], J. Mckay[1], A.M. Dingemans[2], E.-J. Speel[2], C. Caux[6], N. Girard[7], S. Lantuejoul[5], T. Dayton[8], F. Galateau Sallé[4], L. Fernandez-Cuesta[9], M. Foll[1]

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Background: In the context of the MESOMICS and lungNENomics projects[1], we generated comprehensive molecular profiles of Malignant Pleural Mesothelioma (MPM)[2] and pulmonary carcinoids (PCa)[3]. We showed that a continuous molecular model can better explain the prognosis of MPM than the three histologies, with strong differences in the expression of immune checkpoints and pro-angiogenic genes across samples. We also identified a new entity of PCa (supra-carcinoids) with carcinoid-like morphology yet the molecular and clinical features of LCNEC, which challenges the general believe that PCa have no relationship or genetic, epidemiologic, and clinical traits in common with LCNEC and SCLC. These two studies suggest an important role of heterogeneity in the biology of these tumors. **Method:** Much progress has been made in revealing the evolutionary history of individual cancers, in particular using multi-region sequencing. However, most studies focused on a single 'omic technique, and lacked temporal samples. Here we present the results of an innovative approach to study spatial and temporal tumor evolution based on (i) integration of whole-genome and transcriptome sequencing and EPIC 850K methylation arrays on multiple regions from 12 MPM, and (ii) a novel tumor-derived organoid-based strategy for studying the evolution of PCa.

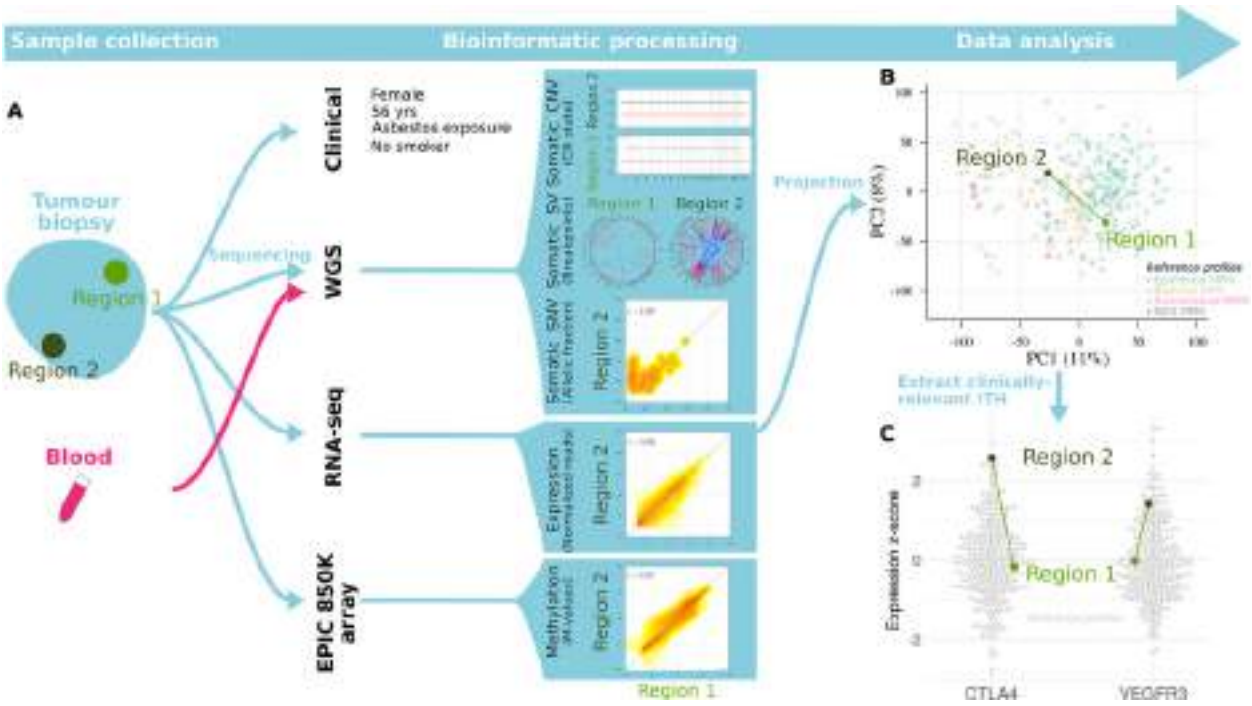

Figure 1. Multi-omic multi-regional profiling of a MPM patient. A) Somatic Copy Number Variants (CNV), somatic Structural Variants (SV), kernel density plots of (top) somatic single nucleotide variants (SNVs) allelic fractions, (middle) expression normalized read counts, and (bottom) methylation array *M*-values. B) Projection of the transcriptomic profile of two tumoral regions into the Principal Component Analysis (PCA) space computed from 284 malignant pleural mesotheliomas[2]C) Expression (*z*-score of normalized read counts) for two clinically relevant genes with substantial inter-regional differences. Biorepositories: French MESOBANK; LungNEN Network

Result: In the data analyses of the 12 MPM we detected significant intra-tumor heterogeneity (ITH) in the expression of immune checkpoints and pro-angiogenic genes (see example in Fig. 1). This might explain the modest and variable response to treatment in clinical trials assessing immunotherapies and antiangiogenic drugs. In the case of PCa, we are currently analysing the organoids genomic data and we will present the preliminary data for the temporal evolution of these diseases. **Conclusion:** We found that our approach can detect clinically and biologically meaningful ITH. All the computational methods we developed for these evolutionary studies are available to the scientific community[4]. [1]RareCancersGenomics.com [2]*Alcala et al., under review in Cancer Res* [3]*Alcala et al., under review in Nat Commun* [4]https://github.com/IARCbioinfo LFC and MF co-supervised this work

Keywords: Genomics, Bioinformatics, Heterogeneity

ORAL SESSIONS

OA08 ADVANCED MODELS AND "OMICS" FOR THERAPEUTIC DEVELOPMENT
MONDAY, SEPTEMBER 9 11:00–12:30

OA08.03 A SINGLE-CELL RESOLUTION MAP OF EMT AND DRUG RESISTANCE STATES FOR EVALUATING NSCLC CLINICAL SPECIMENS

L. Karacosta, B. Anchang, N. Ignatiadis, S. Kimmey, J. Benson, J. Shrager, A. Sung, J. Neal, H. Wakelee, R. Tibshirani, S. Bendall, S. Plevritis

Stanford University, Stanford/United States of America

Background: The role of epithelial-mesenchymal transition (EMT) in NSCLC is well reported and has been shown to prime cells for metastasis. EMT can be adopted or reversed (i.e. mesenchymal-epithelial transition, MET) by cells, revealing plasticity that can also lead to drug resistance. Although it is appreciated that EMT is not a binary process of two extremes but instead a spectrum of intermediate states of EMT phenotypes, these are poorly defined at the single-cell proteomic level in NSCLC clinical specimens. Our overall goal was to dynamically capture and characterize EMT-related drug resistance states in lung cancer cells to construct a single-cell resolution state map of clinical applicability. **Method:** We used mass cytometry (CyTOF) time-course experimentation and novel computational tools to analyze TGFβ and drug treated NSCLC cell lines, as well as NSCLC clinical samples to identify clinically relevant drug resistant EMT and MET states and construct a single-cell resolution proteomic map of phenotypic states. **Result:** Through TGFβ treatment and withdrawal we resolved previously unrealized EMT and MET states in NSCLC cell lines by analyzing the expression of up to 30 surface and intracellular markers. Using a novel computational tool (TRACER) we also provide evidence that EMT and MET trajectories differ and exert differential drug sensitivity profiles. We used the identified EMT and MET states to construct a NSCLC reference EMT-MET state map, on which we projected NSCLC clinical samples to characterize their phenotypic profile in terms of our *in vitro* EMT-MET analysis. Finally, we extended our mass cytometry time-course analysis to NSCLC cells that underwent various drug treatments (e.g. Erlotinib, Docetaxel) and subsequent withdrawal to augment our EMT-MET state map with drug resistance phenotypic traits. We found that NSCLC resistant cells displayed through time overlapping morphological and cell signaling features with EMT and MET and were able to rebound from short-term drug-induced effects. These data are currently being used to evaluate EMT-related drug resistant cell states detected in pleural effusions during and after the course of treatment in different NSCLC patient therapy time-points. **Conclusion:** In summary, we provide a framework that can be extended to phenotypically characterize clinical samples with single-cell resolution in the context of *in vitro* studies showing differential EMT-MET traits related to drug sensitivity. This sets the foundation for developing tools towards evaluating–at a personalized level – disease status and response to treatment in NSCLC patients.

Keywords: NSCLC, Mass Cytometry–Single Cell Analysis, Epithelial-mesenchymal transition (EMT) and drug resistance phenotypic states

OA08.05 NOTCH INHIBITION OVERCOMES RESISTANCE TO TYROSINE KINASE INHIBITORS PROMOTED BY GATE-KEEPER MUTATIONS IN EGFR-DRIVEN LUNG ADENOCARCINOMA

E. Bousquet[1], X. Quantin[2], J.L. Pujol[3], K.-K. Wong[4], J.-C. Soria[5], J. Mazieres[6], L. Paz-Ares[7], A. Maraver[1]

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Background: EGFR mutated lung adenocarcinoma patients treated with gefitinib and osimertinib showed a therapeutic benefit limited by the appearance of secondary mutations, such as *EGFR*^{T790M} and *EGFR*^{C797S}. It has been generally assumed that these secondary mutations render EGFR completely unresponsive to the inhibitors, indicating that the use of single drug to treat efficiently EGFR-driven lung adenocarcinoma might have limited value while a strategy based on combinational drug therapy could be more effective at mitigating the effects of gatekeeper mutations. **Method:** We have combined the use of EGFR-driven genetic engineered mouse models and patient-derived xenografts, adenocarcinoma cell lines and primary samples from EGFR mutated patients. **Result:** We uncover here that gefitinib and osimertinib increase STAT3 phosphorylation (pSTAT3) in *EGFR*^{T790M} and *EGFR*^{C797S} tumoral cells. Interestingly, we also found that concomitant Notch inhibition with gefitinib or osimertinib treatment induces a pSTAT3-dependent strong reduction in the levels of the transcriptional repressor HES1. Importantly, we show that tyrosine kinase inhibitor resistant tumors, with *EGFR*^{T790M} and *EGFR*^{C797S} mutations, are highly responsive to the combined treatment of Notch inhibitors with gefitinib and osimertinib respectively. Finally, in patients with EGFR mutations treated with tyrosine kinase inhibitors, HES1 protein levels increase during relapse and correlate with shorter progression-free survival. **Conclusion:** Our results show that the Notch pathway plays a major role in the relapse of lung adenocarcinoma patients treated with EGFR TKIs, providing a rationale to treat patients that become resistant to EGFR TKI with a combination of the same TKI and Notch inhibitors.

Keywords: EGFR TKI, targeted therapy resistance, NOTCH

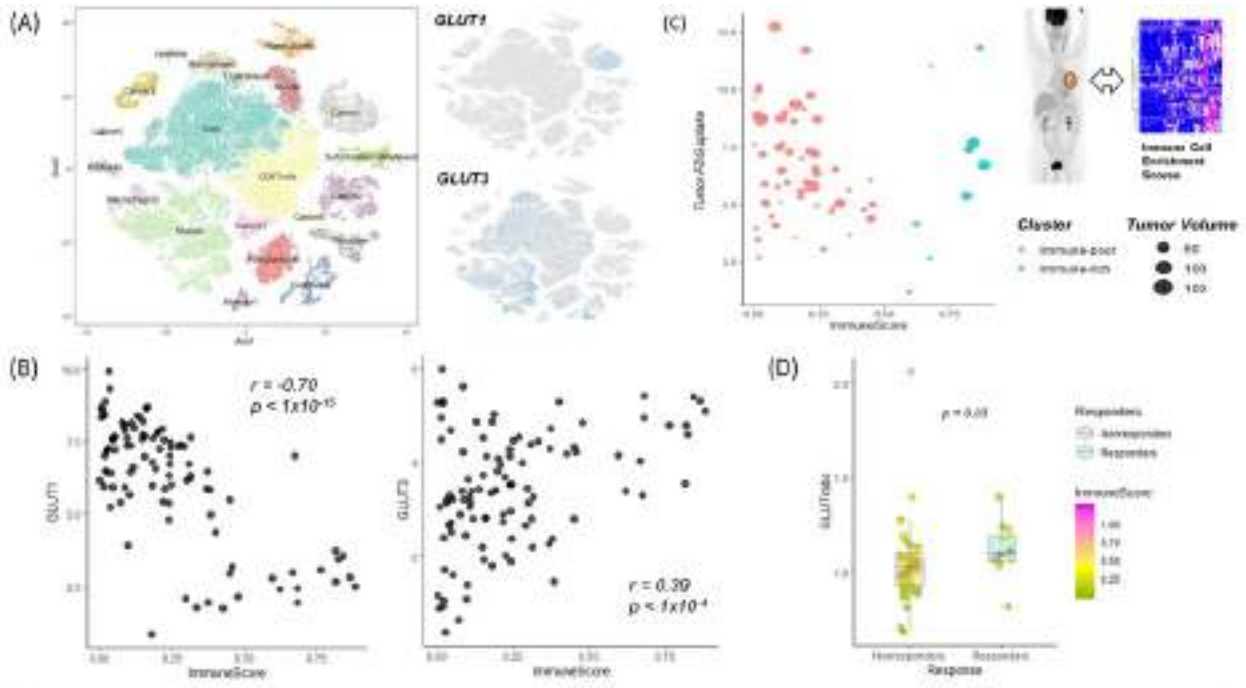
OA08 ADVANCED MODELS AND "OMICS" FOR THERAPEUTIC DEVELOPMENT
MONDAY, SEPTEMBER 9 11:00–12:30

OA08.06 RECIPROCAL CHANGE IN GLUCOSE METABOLISM OF CANCER AND IMMUNE CELLS MEDIATED BY DIFFERENT GLUT PREDICTS IMMUNOTHERAPY RESPONSE

K.J. Na, H. Choi, Y.T. Kim

Seoul National University Hospital, Seoul/Korea, Republic of

Background: Tumor metabolism represented by aerobic glycolysis is dynamically changed in tumor microenvironment (TME) to achieve immune escape. However, *in vivo* properties of glucose metabolism in cancer and immune cells are poorly understood and their clinical implications are still lacking. We scrutinized the association of tumor metabolism and immune properties of TME by comprehensive analyses using tissue RNA-seq, positron emission tomography (PET), and single cell RNA-seq data. **Method:** Lung squamous cell carcinoma (LUSC) samples with both RNA-seq and ^{18}F-deoxyglucose (FDG) PET (n = 63) were collected to examine the association of *in vivo* glucose metabolism, gene expression levels related to glucose metabolism, and immune cell enrichment. An overall enrichment score of TME (ImmuneScore) was estimated from tissue RNA-seq data. The gene expression levels of each cell component of TME were analyzed by single cell RNA-seq from lung cancer patients. The expression patterns of glucose transporters (GLUTs) were evaluated in patients who underwent immunotherapy to investigate whether it can predict immunotherapy response. **Result:** Single cell RNA-seq showed that GLUT1 was mostly expressed in cancer cells while GLUT3 was mostly found in myeloid cells in TME. ImmuneScore showed a negative correlation with GLUT1 ($r=-0.70$, $p<0.01$) and a positive correlation with GLUT3 ($r=0.39$, $p<0.01$) in LUSC samples, and it was validated in TCGA cohort ($r=-0.44$, $p<0.01$ for GLUT1; $r=0.26$, $p<0.01$ for GLUT3). LUSC samples were divided into two distinct groups (immure-rich and immune-poor) by ImmuneScore. In immune-poor cluster, FDG uptake was positively correlated with GLUT1 ($r=0.27$, $p=0.04$), while not correlated with GLUT3. In immune-rich cluster, FDG uptake was positively correlated with GLUT3 ($r=0.78$, $p=0.01$), while not correlated with GLUT1. ImmuneScore was negatively correlated with FDG uptake in immune-poor cluster, while there was positive correlation in immune-rich cluster. We defined GLUT3-GLUT1 ratio (GLUTratio) as a metabolic biomarker representing immune status in TME. High GLUTratio indicates increased metabolic activity in immune cells and decreased metabolic activity in cancer cells in TME. For melanoma patients who underwent anti-PD-1 therapy, GLUTratio was significantly higher in responders than nonresponders ($p=0.03$).



(A) Two-dimensional projection of single cell RNA-seq data of 52,698 single cells from lung cancer patients with associated cell type were presented. Expression pattern of glucose transporters (GLUT1 and GLUT3) demonstrated that GLUT1 mostly expresses in cancer cell clusters and GLUT3 mostly expresses in myeloid cell clusters.
(B) The association between the expression level of glucose transporters (GLUT) and ImmuneScore in lung squamous cell carcinoma patients. ImmuneScore shows negative correlation with GLUT1 and positive correlation with GLUT3.
(C) The association between ImmuneScore and *in vivo* glucose metabolism measured by FDG PET in lung squamous cell carcinoma patients was presented. FDG uptake and ImmuneScore showed negative correlation in immune-poor cluster, while they showed positive correlation in immune-rich cluster.
(D) In melanoma patients who underwent immunotherapy, the GLUTratio (GLUT3/GLUT1) was significantly higher in responder group.

Conclusion: Our findings support a reciprocal change of glucose metabolism between cancer and immune cells within TME mediated by different GLUTs. A new glucose metabolism-based biomarker, GLUTratio, can reflect reciprocal metabolic activity of immune and cancer cells in TME, and be a feasible predictive biomarker for immunotherapy.

Keywords: cancer metabolism, glucose transporter, tumor microenvironment

OA08 ADVANCED MODELS AND "OMICS" FOR THERAPEUTIC DEVELOPMENT
MONDAY, SEPTEMBER 9 11:00–12:30

OA08.07 ABERRANT EPIGENETIC SMAD3 SIGNALING IN TUMOR-ASSOCIATED FIBROBLASTS MODULATES FIBROSIS AND RESPONSE TO NINTEDANIB IN NSCLC

R. Ikemori[1], M. Gabasa[1], M. Vizoso[2], P. Duch[1], S. Moran[2], S. Gea-Sorli[3], P. Bragado[3], T. Jauset[4], M. Esteller[2], L. Soucek[4], E. Monsó[5], V. Peinado[3], C. Fillat[3], F. Hilberg[6], N. Reguart[7], J. Alcaraz[1]

[1]*University of Barcelona, Barcelona/Spain,* [2]*Bellvitge Biomedical Research Institute-IDIBELL, Barcelona/Spain,* [3]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona/Spain,* [4]*Vall d'Hebron Institute of Oncology (VHIO), Barcelona/Spain,* [5]*Hospital Parc Taulí de Sabadell, Sabadell/Spain,* [6]*Boehringer-Ingelheim Inc, Vienna/Austria,* [7]*Hospital Clinic Barcelona, Barcelona/Spain*

Background: Tumor-associated fibroblasts (TAFs) exhibit a fibrotic phenotype in non-small cell lung cancer (NSCLC) that has beeen associated with critical steps of cancer progression. Paradoxically, we reported that the profibrotic TGF-β transcription factor *SMAD3* was epigenetically downregulated through promoter hypermethylation in TAFs from NSCLC patients compared to patient-matched control fibroblasts. In addition, we reported that the antifibrotic drug nintedanib elicited a stronger inhibition of the fibrotic phenotype and its tumor-promoting effects in TAFs from adenocarcinoma (ADC) patients compared to squamous cell carcinoma (SCC) patients upon TGF-β1 stimulation *in vitro*, which was consistent with the selective therapeutic response to nintedanib observed in a clinical trial in ADC (but not SCC) patients. These previous results support the hypothesis that TGF-β1 signaling may be altered in lung TAFs according to their histologic subtype. **Method:** In this study we tested our working hypothesis by determining the expression and activity of SMAD3 and its closely related homologue SMAD2 in patient-derived TAFs and paired control fibroblasts, and by dissecting their potential contribution to the differential therapeutic responses to nintedanib observed in ADC and SCC using *in vitro* and *in vivo* preclinical models. **Result:** *In vitro* studies revealed a marked *SMAD3* epigenetic repression through promoter hypermethylation, a low pSMAD3/pSMAD2 ratio and a limited fibrotic phenotype selectively in SCC-TAFs. In contrast, ADC-TAFs overexpressed a panel of fibrotic markers upon TGF-β1 stimulation concomitantly with a high pSMAD3/pSMAD2 ratio and a limited *SMAD3* promoter methylation. Histologic analysis of a large patient cohort (112 ADC, 96 SCC) confirmed that the extent of fibrosis is larger in ADC than SCC patients. In addition, knocking-down *SMAD3* in ADC-TAFs was sufficient to reduce the antifibrotic and antigrowth effects of nintedanib *in vitro* and in tumor xenografts *in vivo*. On the other hand, long-term exposure of pulmonary fibroblasts to cigarette smoke condensate was sufficient to hypermethylate the *SMAD3* promoter. Since SCC and ADC tumors typically arise in the upper

airways and distal pulmonary sites, respectively, it is conceivable that fibroblasts might be more exposed to the smoking epigenetic effects on *SMAD3* in SCC. **Conclusion:** We report for the first time that tumor fibrosis is higher in ADC than SCC patients, in association with a selective therapeutic response to the antifibrotic drug nintedanib in the former, and identify the subtype-specific extent of *SMAD3* epigenetic repression in TAFs and the subsequent aberrant SMAD3/SMAD2 imbalance as major regulatory mechanisms of tumor fibrosis and response to nintedanib in NSCLC.

Keywords: fibroblast, SMAD3, fibrosis

OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.01 OPT-OUT SMOKING CESSATION PROGRAM IN LUNG CANCER SCREENING PROVIDES EXCELLENT QUIT RATES

R. Myers[1], S. Atkar-Khattra[2], S. Pillainayagam[2], S. Ladhar[2], K. Cho[2], M. Janicker[3], J. Callaghan[4], J. Yee[5], S. Lam[2]

[1]*BC Cancer, Vancouver/Canada,* [2]*British Columbia Cancer Research Center, VANCOUVER/Canada,* [3]*Minister of Health, Ottawa/Canada,* [4]*BC Lung Association, Vancouver/Canada,* [5]*Vancouver General Hospital, vancouver/Canada*

This abstract is under embargo until September 9 10:15 CET

OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.02 SMOKING CESSATION COUNSELING IN A SURGICAL CLINIC IS EFFECTIVE

C. Barone[1], P. Franklin[1], J. Muesse[2], N. Tingquist[2], M. Steliga[2]

[1]*WP Rockefeller Cancer Institute, Little Rock/United States of America,* [2]*University of Arkansas, Little Rock/United States of America*

Background: Many patients in a thoracic surgery oncology clinic are unable to quit despite referral for tobacco related illnesses and the knowledge that smoking is harmful. Continued smoking leads to poorer outcomes in cancer patients. We implemented individualized counseling for all patients in our ambulatory clinic as a standard part of their cancer care using an opt-out framework. All patients were surveyed for use, and cessation support consisted of individual counseling and pharmacotherapy tailored to the individual. **Method:** All patients in the thoracic surgery oncology clinic were surveyed for tobacco use at the intake for each visit. Any patient who was a current tobacco user met with a certified tobacco treatment specialist (CTTS) in the surgery clinic in the exam room before and/or after meeting with the surgeon. This was introduced as a standard part of the patient's treatment plan; patients could opt-out if they chose. Less than 5% of patients who were offered the counseling declined. The cessation counseling was reinforced by the surgeon, and patients were informed about how cessation could improve outcomes. On return visits, the patients met with the CTTS for follow up counseling and feedback. Data was prospectively entered in an IRB approved database for tracking smoking cessation outcomes at our institution. Retrospectively data was harvested for the prior 17 consecutive months. **Result:** Over a consecutive 17 months, a total of 275 patients who were currently smoking were seen in the thoracic surgery oncology clinic by two thoracic surgeons and met with a CTTS for individualized counseling which included a cessation plan and pharmacotherapy tailored to the individual. Follow up information was available on 87% of patients 240/275. Of the 240 patients who were smoking and met with a CTTS for an individualized plan, 2.9% increased their smoking (7/240), 23.3% had no change (56/240), 29.2 decreased (70/240), and 44.6% quit (107/240) on follow up visits. Cessation was validated by a handheld exhaled breath carbon monoxide (CO) detector whenever possible, and often decreased smoking rates were validated with lower CO readings as well. **Conclusion:** Patients in a thoracic surgery oncology are receptive to counseling by a CTTS when provided at the point of care. Despite heavy smoking histories, many of the patients in a thoracic surgery oncology clinic can quit smoking with evidence based support including counseling, pharmacotherapy, and follow up. As cessation improves treatment outcomes in many facets of lung cancer care, cessation support should be integrated in a standard workflow for all patients.

Keywords: smoking cessation, Tobacco, surgery

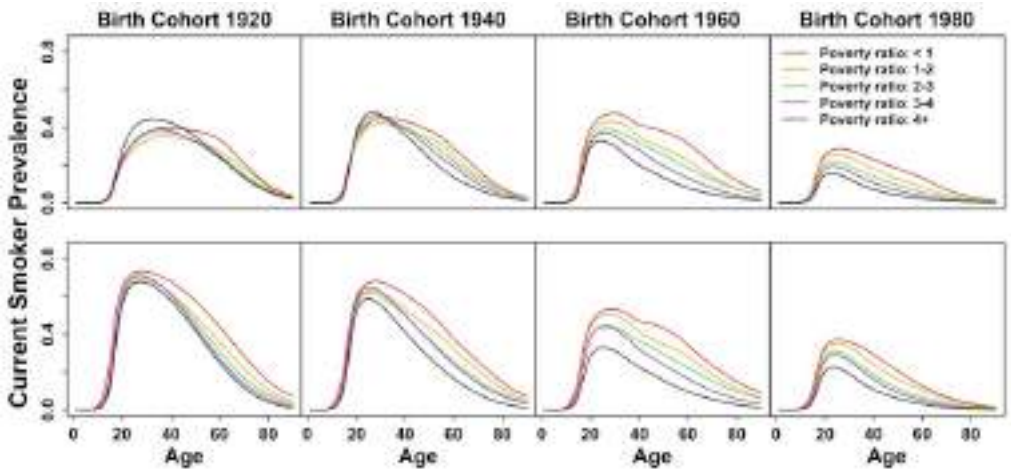
OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.03 PATTERNS OF BIRTH COHORT-SPECIFIC SMOKING HISTORIES BY FAMILY INCOME IN THE USA, 1982-2017

J. Jeon[1], P. Cao[1], D. Luan[1], J. Tam[1], D. Levy[2], N. Fleischer[1], T. Holford[3], R. Meza[1]

[1]*University of Michigan School of Public Health, Ann Arbor/United States of America,* [2]*Georgetown University, Washington/United States of America,* [3]*Yale University, New Haven/United States of America*

Background: Although cigarette smoking has been declining significantly in the US over last several decades, disparities in tobacco use remain across different groups by race/ethnicity, education, socioeconomic status (SES), or regions. Specifically, people in lower family income have higher smoking prevalence, longer smoking durations and lower cessation rates than other income groups. However, little is known about how smoking patterns, including rates of initiation, cessation, and intensity, differ by birth cohort across various income levels. **Method:** Using the National Health Interview Survey (NHIS) family income data, we calculated individual income-to-poverty ratios from 1982-2017. Missing family income data from 1982-1996 was imputed using a sequential regression multivariate imputation method, the NHIS approach to impute missing continuous income from 1997-2017. Age-period-cohort models with constrained natural splines were used to estimate the annual probabilities of smoking initiation, cessation, and intensity by sex and birth-cohort for five income-to-poverty ratio groups (<1, 1-2,2-3,3-4 and 4+ times the poverty threshold). Age- and sex-specific smoking prevalence was also estimated for different income groups and birth cohorts. **Result:** Smoking prevalence and initiation rates are decreasing by birth-cohort in all income-to-poverty ratio groups, while cessation rates are increasing. However, the relative smoking prevalence between low- and high-income groups is markedly increasing by birth-cohort (Figure 1). Smoking initiation probabilities are highest among those living below the poverty threshold, and inversely associated with income level. Conversely, people living below the poverty threshold have the lowest probabilities of quitting, with increasing smoking cessation probabilities in higher income groups. Age-specific smoking cessation probabilities vary considerably by income, especially in recent birth-cohorts for both men and women. Figure 1. Age-specific current smoker prevalence for females (upper panels) and males (lower panels) for five income-to-poverty ratio groups (<1, 1-2,2-3,3-4 and 4+ times the poverty threshold) and selected birth cohorts.



Conclusion: Smoking prevalence has been decreasing in all income groups, however, disparities in smoking pattern between high and low-income populations are increasing with more recent birth-cohorts. Future studies evaluating disparities in smoking should account for differences by birth-cohort. The establishment of effective smoking intervention strategies specifically for low-income groups will be important to reduce tobacco-related health disparities.

Keyword: Smoking disparity, income, SES

OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.05 LUNG CANCER AS A SECOND PRIMARY MALIGNANCY AMONG WOMEN WITH BREAST CANCER: THE ROLE OF HORMONE REPLACEMENT AND SMOKING

J.N. Bodor, S. Fisher, J. Treat, M. Clapper

Fox Chase Cancer Center, Philadelphia/United States of America

This abstract is under embargo until September 9 10:15 CET

OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.06 RESIDENTIAL RADON, SMOKING AND LUNG CANCER RISK. A CASE-CONTROL STUDY IN A RADON PRONE AREA

A. Ruano-Ravina[1], M. Lorenzo-González[1], M. Provencio[2], M. Torres-Durán[3], I. Parente-Lamelas[4], I. Vidal-García[5], J. Barros-Dios[1]

[1]*University of Santiago de Compostela, Santiago de Compostela/Spain,* [2]*Hospital Puerta De Hierro Majadahonda, Madrid/Spain,* [3]*Hospital Álvaro Cunqueiro, Vigo/Spain,* [4]*Ourense Hospital Complex, Ourense/Spain,* [5]*Complejo Hospitalario Universitario de A Coruña, A Coruña/Spain*

This abstract is under embargo until September 9 10:15 CET

OA09 LUNG CANCER: A PREVENTABLE DISEASE?
MONDAY, SEPTEMBER 9 11:00–12:30

OA09.07 IMPLEMENTING AN OPT-OUT APPROACH TO SMOKING CESSATION REFERRALS FOR CANCER PATIENTS IN ONTARIO, CANADA

E. Cameron[1], M. Haque[1], N. Schwartz[1], S. Khan[1], S. Rana[1], R. Truscott[1], W. Evans[2]

[1]*Population Health & Prevention, Cancer Care Ontario, Toronto/Canada,* [2]*McMaster University, Hamilton/Canada*

Background: Smoking is responsible for approximately 30% of all cancer deaths in Canada and more than 85% of lung cancer cases. Continued smoking results in decreased cancer treatment efficacy and safety, increased toxicities, greater risk of cancer recurrence and second primaries, poorer quality of life and decreased survival. Quitting smoking can reduce these adverse effects. In 2013, Cancer Care Ontario (CCO) implemented a smoking cessation program across 14 Regional Cancer Centres (RCCs) in the province of Ontario, Canada, employing a 3As (Ask, Advise, Act) brief intervention model. **Method:** In the first few years of the program, smokers could "opt-in" to smoking cessation services by stating a readiness to quit. However, the provincial rate of smokers accepting support was low. In 2018, CCO adopted an "opt-out" approach, based on emerging evidence and feedback from an expert Advisory Committee. With this approach, healthcare providers (HCPs) automatically refer all smokers to a cessation service, without assessing the patient's readiness to quit. Patients can refuse the referral if they choose. This program change was communicated to the RCCs through a revised program framework, site-specific action plans, and discussion during monthly knowledge exchange meetings with Regional Champions. Communications resources (posters and pocket cards) were created to support HCPs, with suggested scripts. **Result:** The Accepted a Referral (proportion of smokers accepting referral to cessation services) performance metric was used to monitor program implementation. With an opt-in approach, the annual provincial rate of Accepted a Referral improved only slightly over three years (18.1% in 2015/16 to 22.5% in 2017/18). Just prior to launching the opt-out approach in Q3 of 2017/18, the provincial rate of Accepted a Referral was 23.3% (range 9.2% to 37.9% amongst 14 RCCs). One year later, the provincial rate had increased substantially to 31.9% (range 12.9% to 88.7%). Several RCCs showed dramatic increases, while others demonstrated little or no improvement. **Conclusion:** In an effort to help more patients quit smoking and to achieve the best treatment outcomes possible, CCO adopted an opt-out approach to cessation referrals. Overall, there has been a substantial increase in the provincial rate of smokers accepting support, but implementation has varied amongst RCCs. Feedback indicates that while some HCPs

found the approach relatively easy to implement, others have been resistant to change, expressing concern about the ethics of referring patients without assessing willingness to quit. Further research into the reasons behind the variable uptake of the opt-out approach will inform future implementation efforts.

Keywords: smoking cessation

OA10 SOPHISTICATED TNM STAGING SYSTEM FOR LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

OA10.01 IMPACT OF PRE-ORDERED STAGING TESTS ON TIMELINESS OF LUNG CANCER DIAGNOSIS AND STAGING: A QUALITY IMPROVEMENT INITIATIVE

M. Mullin[1], A. Tran[1], C. Noseworthy[2], C. Stone[1], C. Parker[1,3], G. Digby[1,3,4]

[1]*Department of Internal Medicine, Kingston/Canada,* [2]*Cancer Centre of Southeastern Ontario, Kingston/Canada,* [3]*Department of Respirology, Kingston/Canada,* [4]*Department of Oncology, Kingston/Canada*

Background: Timely care for patients undergoing evaluation for suspected lung cancer (LC) is critical to optimize clinical outcomes and minimize patient anxiety. We identified delays in local LC evaluation pathways and sought to improve the timeliness of care provided by the Lung Diagnostic Assessment Program (LDAP), a rapid assessment clinic. We launched a Quality Improvement (QI) initiative consisting of Standardized Triage Pathways (STP) with pre-ordered staging tests for LDAP-referred patients with a high suspicion of LC and seek to evaluate the impact on timeliness of care. **Method:** Data were collected retrospectively for all LDAP-referred patients to establish baseline (January–April 2018) and prospectively for improvement (May–October 2018), including: LDAP referral date, triage pathway, pre-ordered tests (PET, CT/MRI brain) including date of completion, and reasons for not completing pre-ordered testing. Mean data are reported, with significance determine by special cause variation using Statistical Process Control (SPC) XbarS charts; unpaired t-tests assess for differences between independent groups. **Result:** We reviewed 553 consecutive LDAP referrals (185 baseline, 368 post-STP). Compliance with STP and pre-ordered testing for patients with suspicion of LC improved to 100% and 93%, respectively. Post-STP, mean time from referral to PET decreased from 40.5 to 26.0 days, significant by SPC, and was 21.8 days for patients completing pre-ordered testing (p=0.0001). Time from referral to CT/MRI Brain decreased from 35.8 to 19.9 days, significant by SPC, and was 18.5 days for patients completing pre-ordered testing (p=0.0001). While there was a non-significant trend to improvement in time from referral to diagnosis (41.4 to 30.4 days), the improvement was significant for patients completing pre-ordered testing (28.4 days, p =0.0001). Of the 166 (45%) LDAP-referred patients triaged to receive pre-ordered testing, 134 (80.5%) completed pre-ordered tests. Those completing pre-ordered tests experienced more timely care, on average, than those who did not: mean time from referral to PET was 13.9 days faster (p=0.0001), referral to CT/MRI Brain was 15.9 days faster (p=0.0001), and referral to diagnosis was 10.2 days faster (p=0.0004). Main patient barriers to completing pre-ordered testing were preference for physician consultation prior to testing, (10, 31.3%), and barriers regarding travel and cost, (6,18.8%). **Conclusion:** A standardized triage process with pre-ordered staging tests at the time of LDAP referral is associated with improved time from referral to completion of staging tests and diagnosis. Strategies to improve compliance with pre-ordered testing are ongoing, including collaboration with primary care physicians and nurses to support patients and navigate barriers.

Keywords: Quality Improvement, staging

OA10 SOPHISTICATED TNM STAGING SYSTEM FOR LUNG CANCER
MONDAY, SEPTEMBER 9 14:00–15:30

OA10.02 RECOMMENDED CHANGE FOR N DESCRIPTOR PROPOSED BY THE IASLC: A VALIDATION STUDY FROM A SINGLE-CENTER EXPERIENCE

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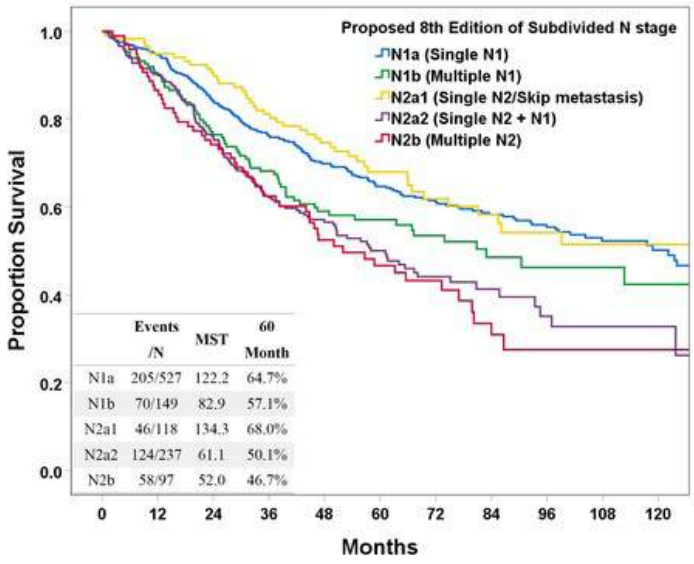
Background: The International Association for the Study of Lung Cancer (IASLC) recently proposed changes for N descriptor based on the location and number of involved lymph node stations. The aim of our study was to evaluate the discriminatory ability and prognostic performance of the proposed N descriptor in a large independent non-small cell lung cancer (NSCLC) cohort. **Method:** IASLC proposals include: a classification of N descriptor by combining the present nodal categories and number of involved lymph node stations into: N0; single-station N1 (N1a); multiple-stations N1 (N1b); single-station N2 without N1 involvement (N2a1); single-station N2 with N1 involvement (N2a2); multiple-stations N2 (N2b) and N3. A total of 1128 patients who underwent major pulmonary resection for pathologic N1 or N2 NSCLC between 2004 and 2014 were analyzed in this study. survival analysis was performed using Cox proportional hazard model to assess the prognostic significance of the N descriptor. **Result:** From 2004 to 2014, 7437 patients were operated on for non-small-cell lung carcinoma (NSCLC). Among those, patients who underwent preoperative treatment for stage IIIA-N2 NSCLC were excluded (N=-698, 9.4%). Patients who were confirmed as pathologic N1 (N=676) or N2 (N=452) after surgery were included in this study. Invasive mediastinal staging (EBUS or mediastinoscopy) was done in 614 patients (54.4%). After surgery, adjuvant treatments were performed in 901 patients (81.7%). The mean total number of dissected lymph node was 25.7 ± 11.0, and the mean number of involved (metastatic) lymph node was 3.0 ± 3.2. The 5-year overall survival rate was 64.7 % in N1a, 57.1% in N1b, 68.0% in N2a1, 50.1% in N2a2, and 46.7% in N2b. Based on our study about the overall survival and recurrence-free survival, N2a1 is not clearly divided into N1a and N1b is not clearly divided with N2a2.

A

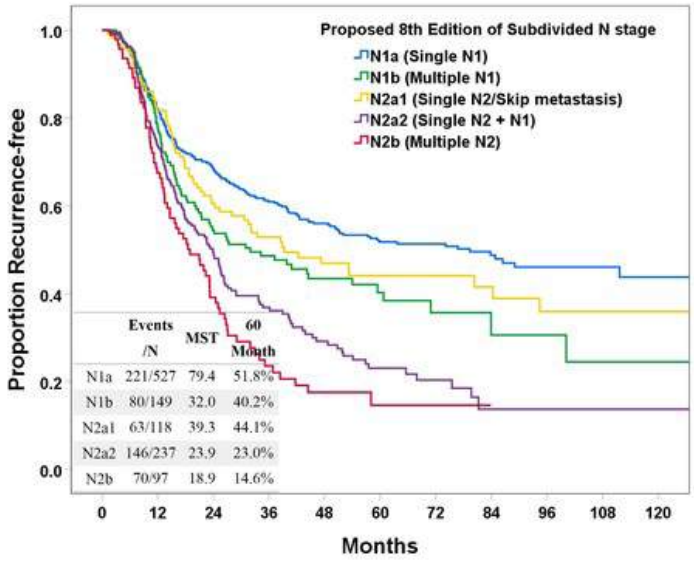


	Events /N	MST	60 Month
N1a	205/527	122.2	64.7%
N1b	70/149	82.9	57.1%
N2a1	46/118	134.3	68.0%
N2a2	124/237	61.1	50.1%
N2b	58/97	52.0	46.7%

N1a vs N1b vs N2a1 vs N2a vs N2b
Overall survival comparisions
adjusted for histology (adeno vs squamous), sex, age, and pathologic T-stage.
(Cox proportional hazards model)

comparision	HR	p-value
N1b vs N1a	1.490	0.004
N2a1 vs N1a	1.011	0.946
N2a2 vs N1a	1.732	<0.001
N2b vs N1a	2.452	<0.001
N2a1 vs N1b	0.679	0.042
N2a2 vs N1b	1.162	0.317
N2b vs N1b	1.646	0.007
N2a2 vs N2a1	1.713	0.002
N2b vs N2a1	2.425	<0.001
N2b vs N2a2	1.416	0.034

B



	Events /N	MST	60 Month
N1a	221/527	79.4	51.8%
N1b	80/149	32.0	40.2%
N2a1	63/118	39.3	44.1%
N2a2	146/237	23.9	23.0%
N2b	70/97	18.9	14.6%

N1a vs N1b vs N2a1 vs N2a vs N2b
Recurrence-free survival comparisions
adjusted for histology (adeno vs squamous), sex, age, and pathologic T-stage.
(Cox proportional hazards model)

comparision	HR	p-value
N1b vs N1a	1.366	0.018
N2a1 vs N1a	1.126	0.415
N2a2 vs N1a	1.701	<0.001
N2b vs N1a	2.283	<0.001
N2a1 vs N1b	0.824	0.252
N2a2 vs N1b	1.245	0.117
N2b vs N1b	1.671	0.002
N2a2 vs N2a1	1.511	0.007
N2b vs N2a1	2.028	<0.001
N2b vs. N2a2	1.343	0.047

Conclusion: Based on the proposed N stage classification by combining the LN station number with the proposed anatomic location in IASLC, all 5 groups were not clearly identified. According to our analysis, it would be better to classify similar prognostic group as 3 or 4 group to divide the group. The new N classifications should be considered for future revisions of TNM staging system for lung cancer.

Keywords: Non-Small Cell Lung Cancer, N descriptor, N stage

OA10.03 MACROSCORE: A PROGNOSTIC MODEL FOR SUPPLEMENTING THE TNM STAGE IN RESECTABLE NON–SMALL CELL LUNG CANCER

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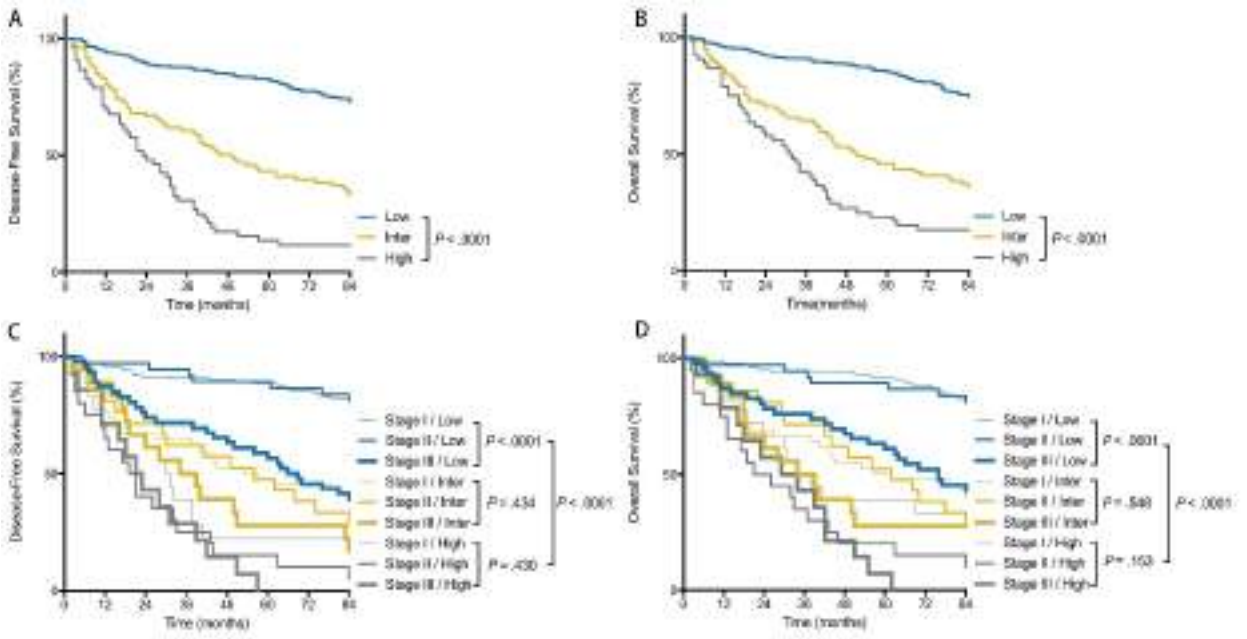
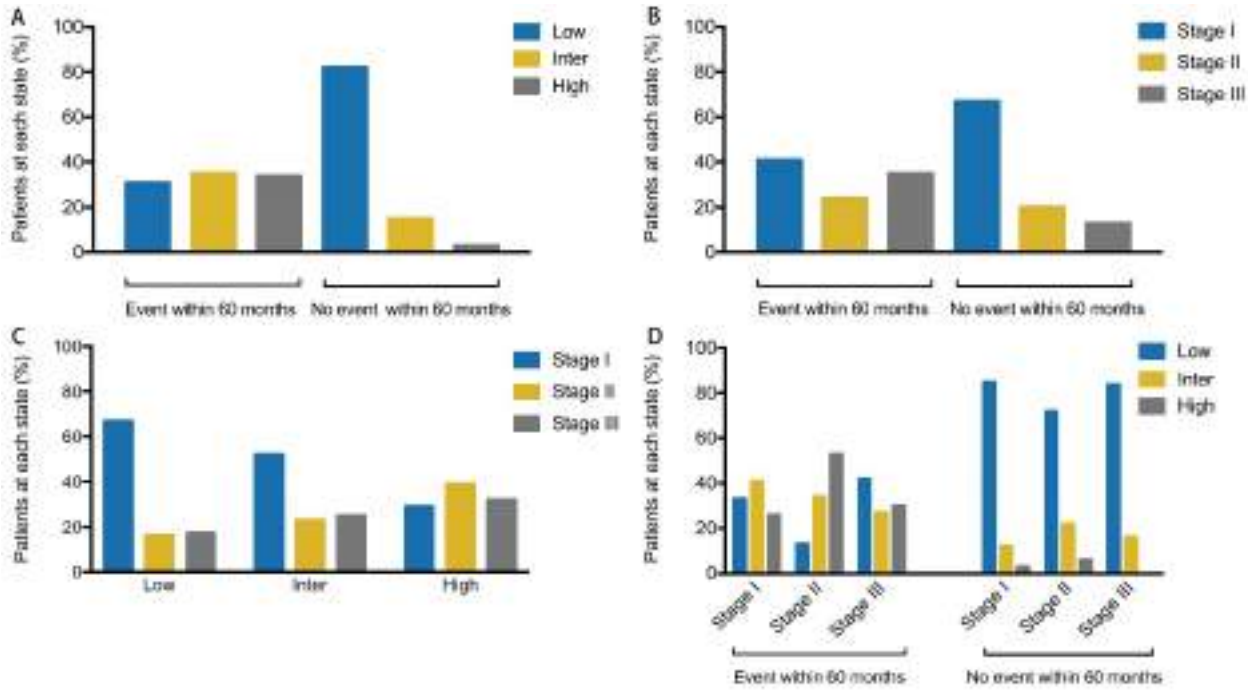
Background: We aim to establish a prognostic model based on the macrophage status to supplement the TNM stage and increase the predictive accuracy for the prognosis of NSCLC patients. **Method:** The macrophage infiltration at the center of the tumor and its invasive margins in stage I to IIIA NSCLC patients (n=368) was evaluated, and a Macroscore model was constructed (Low/Intermediate/High). The relationship between the Macroscore and the clinical outcome was analyzed and validated by 2 additional cohorts. **Result:** The Macroscore was significantly associated with disease-free survival rates and overall survival rates at each TNM stage (all $p < .0001$). The TNM stage could not, however, determine survival rates in patients with the same Macroscore (figure 1). In patients experienced a 5-year event, the Macroscore is usually in high level (26.0%-53.1%). Patients have not experienced a 5-year event usually have a low Macroscore (71.7%-84.8%), regardless of the TNM stage (figure 2). Furthermore, the Macroscore could improve the area under the curve values for the DFS and OS; the values of DFS increased from 0.651 for the TNM system model to 0.822 for the TNM stage plus Macroscore model.





Conclusion: The Macroscore provides an accurate prediction of the clinical outcome in resectable NSCLC tumors, and it complements the prognostic value of the TNM stage.

Keywords: Non-Small Cell Lung Cancer, staging, macrophage

ORAL SESSIONS

OA10.05 WHICH IS BETTER FOR TNM STAGE ASSESSMENT AMONG WHOLE-BODY MRI AND PET/MRI AT 1.5 TESLA AND 3 TESLA AND FDG-PET/CT IN NON-SMALL CELL LUNG CANCER?

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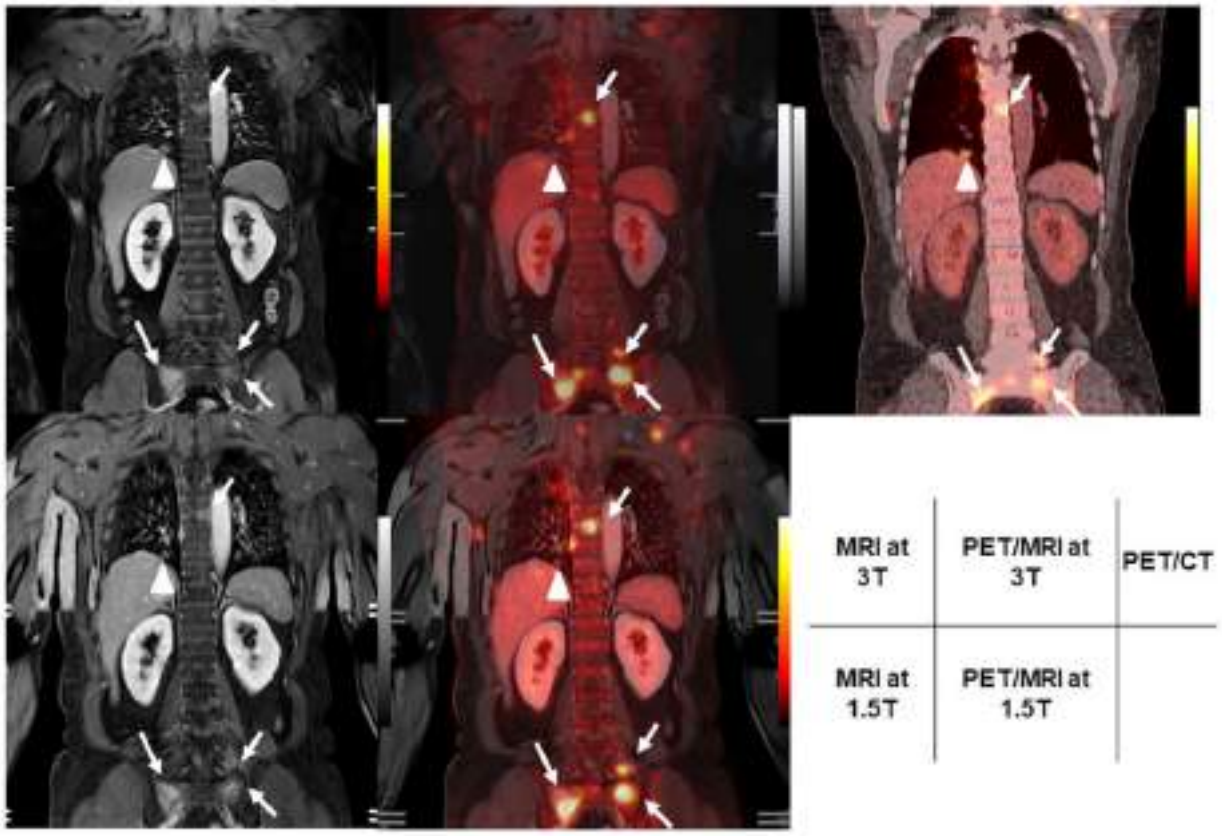
Background: Accurate tumor staging is essential for choosing the appropriate treatment strategy for non-small cell lung cancer (NSCLC) patients. In 1990s, positron emission tomography (PET) or PET combined with CT (PET/CT) using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) were suggested as useful for TNM stag evaluation in NSCLC patients in routine clinical practice. Since 2007, whole-body magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) at 1.5T or 3T systems and PET/MRI have been continuously testing in this setting. Moreover, PET fused with MRI (PET/MRI) with FDG has been suggested as a new tool for TNM stage and postoperative recurrence evaluations since 2015. However, all PET/MRI has been generated by MRI at 3T MR system and not tested that at 1.5T system. No one reported direct comparisons for TNM staging capability among whole-body MRI and PET/MRI at 1.5T and 3T systems and PET/CT in NSCLC patients. We hypothesize that whole-body MRI and PET/MRI at 1.5T and 3T MR systems have better potential for TNM stage assessment than whole-body FDG-PET/CT in NSCLC patients. The purpose of this study was to prospectively and directly compare TNM stage classification capability among whole-body MRI and PET/MRI at 1.5 and 3T MR systems and PET/CT in NSCLC patients. **Method:** 104 consecutive pathologically diagnosed NSCLC patients (62 men, 42 women; mean age 71 years) prospectively underwent whole-body MRI at 1.5T and 3T systems, integrated PET/CT, and surgical, pathological and/ or follow-up examinations. Final diagnoses of T, N and M factors and clinical stage in each patient were determined according to all examination results. Then, each factor and clinical stage were visually assessed on both whole-body MRIs, PET/MRIs and PET/CT with contrast-enhanced brain MRI. Kappa statistics were used to determine agreements for assessment of all factors and clinical stage with final diagnoses, and McNemar's test was used to compare each diagnostic accuracy among all methods. **Result:**



On each factor and clinical stage assessments, agreements between all methods and final diagnosis were substantial or almost perfect ($0.60<\kappa<0.98$). Diagnostic accuracies of N factor and clinical stage on whole-body MRI as well as PET/MRI at both field strengths were significantly higher than those of PET/CT ($p<0.05$). **Conclusion:** Whole-body MRIs and PET/MRIs at 1.5T and 3T systems have significantly better potential for N factor and clinical stage assessments than PET/CT in NSCLC patients.

Keywords: MRI, PET/MRI, staging

OA10.06 TRANSITION PATTERNS BETWEEN N1 AND N2 STATIONS DISCOVERED FROM DATA-DRIVEN LYMPHATIC METASTASIS STUDY IN NON-SMALL CELL LUNG CANCER

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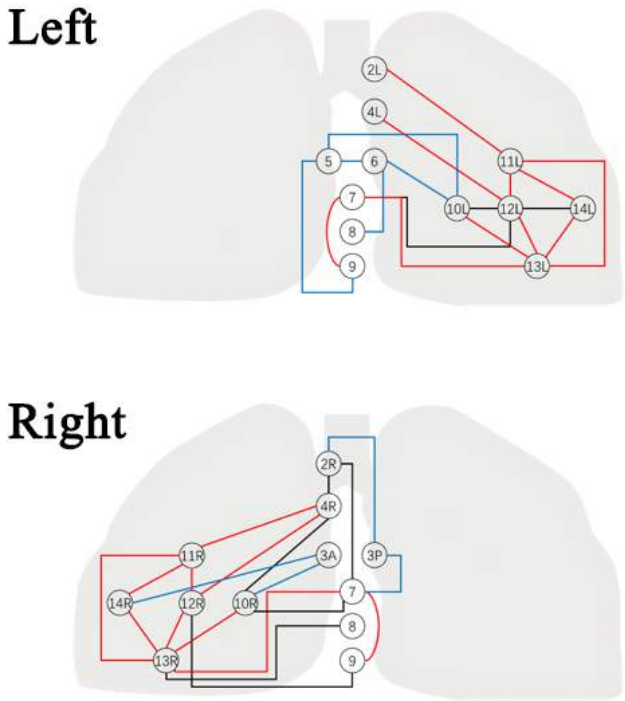
Background: N staging process was essential for evaluation of outcome and indication of following adjuvant therapies in Non-small-cell lung cancer treatment. Various clinical observations on the potential transition patterns of lymph node drainage are reported, however, most of the previous conclusions were made by clinical physicians and focused on specific empirical transition patterns. The fact that there is no definitive and holistic map for lymphatic metastasis transition patterns, and the patients were suffering from either excessive nodes collection along with more damage, or insufficient nodes collection with potential recurrent risks. **Method:** We perform complete lymph node examination of a total of 936 subjects diagnosed with NSCLC lung cancer. Lymph nodes sampling or dissection are performed according to NCCN guidelines. A probabilistic model is developed due to the presence of these missing values. Using the maximum likelihood estimation and proximal gradient algorithm, the summarization of dataset is obtained, which were several explicit metastases and their corresponding probabilities. The metastasis graph is constructed from the summarization result with greedy algorithm and a given threshold. Besides, numerical simulation experiments are conducted to validate the stability of algorithms. **Result:** Lymph node sites are shown as round circles according to their anatomical locations. The inferred transition paths are shown as edges connecting them. Edges colored in red are those consistently found in the left and right lung, and blue for unique nodes at each side thus cannot be compared, and black for different patterns between left and right lungs. Closely connected intra-lobar (N1) nodes: strong connections among intra-lobar nodes (10~14). Over 78% among all the patients have more than 7 edges connecting the 5 intra-lobar nodes. Jumping metastasis from N1 to N2 stations: We found that there exists several jumping metastasis at both sides of the lobes which has not been well-studied yet posing a challenge for the diagnosis and accurate staging (eg. 12 to 4, 13 to7, 11 to 2), revealing potential long-range transition pathways. Correlation among N2 lymph nodes: We discovered the presence of certain metastatic groups, including node 5/6, 5/9, 7/9, 6/8 for left lung, and 2/4,2/7,7/9, 2/3p, 3p/7 for right lung.



Conclusion: So we drew a map precisely to make a better understanding for metastatic pathways and provide a potential tool for the prediction of involved nodes pre/ or intro-operatively,so that an individualized surgical planning strategy could be made.

Keywords: maximum likelihood estimation, transition patterns, NSCLC

OA10.07 CONCORDANCE BETWEEN ROSE AND FINAL DIAGNOSIS IN PATIENTS UNDERGOING EBUS- TBNA FOR NON-SMALL CELL LUNG CANCER STAGING

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Hospital Mutua de Terrassa, Terrassa/Spain

Background: In patients with non-small cell lung cancer (NSCLC) undergoing mediastinal staging through endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) clinical decision making is based in rapid on-site evaluation (ROSE) findings. We aimed to analyze the accuracy of ROSE determining the rate of concordance between ROSE and final diagnosis. **Method:** Prospective study that included patients undergoing EBUS-TBNA for NSCLC staging. Results of ROSE were compared with final diagnosis. **Result:** Sixty-four patients were included and 637 lymph nodes (LN) were sampled: a median of 10 (IQR 8-12) LNs and a median of 5 (IQR: 4-6) nodal stations per patient were sampled. The diagnoses of ROSE were concordant with the final diagnoses in 612 (96.1%) cases and non-concordant in 25 (3.9%). There were 7 (1.2%) LNs in which the diagnosis of ROSE was non-malignant with a final diagnosis of malignancy. On the contrary, there was a single case (0.2%) in which the diagnosis of ROSE was malignant with the final diagnosis being normal LN. Considering final diagnosis as the gold standard, the sensitivity, specificity and overall accuracy of ROSE were 98.6, 97.2 and 98.5% respectively. Table 1:

DIAGNOSIS ROSE FINAL DIAGNOSIS	Non-diagnostic/ Inadequate (82)	Benign/ Normal lymph node (520)	Malignancy (36)
Non-diagnostic/ Inadequate (70)	67	3	0
Benign/ Normal lymph node (526)	14	511	1
Malignancy (42)	1	6	35

Conclusion: The preliminary diagnoses (ROSE) are concordant with the final diagnoses in a high percentage. Consequently, clinical decisions based on the ROSE can be taken with confidence.

Keywords: Concordance, ROSE (rapid on-site evaluation), Endobronchial ultrasound-guided transbronchial needle aspiration

OA11.01 COMPLEX EGFR MUTATIONS IN LUNG ADENOCARCINOMA

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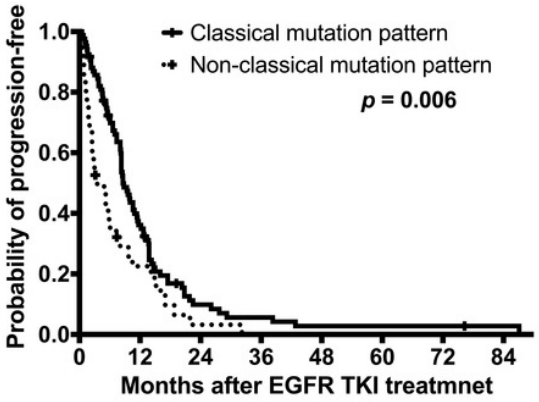
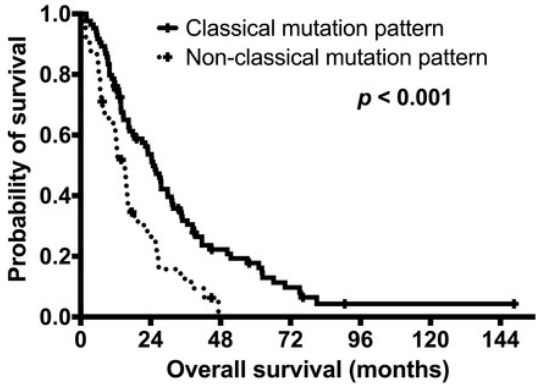
[1]*National Taiwan University Hospital, Taipei/Taiwan,* [2]*Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei/Taiwan*

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) provides a favorable treatment efficacy for *EGFR*-mutant lung cancer patients. Majority of *EGFR* mutations are a single mutation, including deletion in exon 19 (del-19) or L858R in exon 21. There is a subset of patients with complex *EGFR* mutations which contains two or more *EGFR* mutation types. It is unclear the treatment efficacy to different EGFR TKIs and survival prognosis for the complex *EGFR*-mutant patients due to small sample sizes of the prior studies. This study aimed to improve the understanding of the clinical characteristics and the prognosis of EGFR TKI treatment in lung adenocarcinoma patients with complex *EGFR* mutations. **Method:** Between June 2005 to July 2018, patients harboring lung adenocarcinoma with complex *EGFR* mutations who were treated with EGFR TKIs were collected for *EGFR* mutation analysis by direct Sanger sequencing. Patients' clinical characteristics, *EGFR* mutation status, treatment response, progression-free survival (PFS) and overall survival (OS) were analyzed. Patients harboring tumor with de novo T790M mutations were excluded for evaluation of EGFR TKI effectiveness. **Result:** There were 175 patients (6.3%) with complex *EGFR* mutation from 2390 *EGFR*-mutant patients. Of the 175 complex *EGFR*-mutant patients, 122 patients who received EGFR TKIs were enrolled for evaluation of TKI effectiveness. Patients with the classical mutation pattern (del-19 or L858R) had higher treatment response rate (78.6% vs. 47.4%; p = 0.001) and PFS (8.6 months vs. 3.3 months; p = 0.006) than those without the classical mutations patterns (Fig-A). In multivariate analysis, female (p = 0.002), patients with disease relapse status, and the classical mutation patterns (p < 0.001) were associated with prolonged PFS. Compared with gefitinib and erlotinib, afatinib had a longer PFS, especially for patients without the classical mutation patterns. For OS, multivariate analysis revealed that female (p < 0.001), patients harbored classical mutation pattern (p = 0.001) (Fig-B), and patients with disease relapse status had longer OS. There were 51 patients who had re-biopsy tissue samples after acquired resistance to EGFR TKIs, 17 (33.3%) samples harbored T790M. In addition, small cell lung cancer transformation was detected in 3 (2%) patient's re-biopsy tissue samples.

(A)



(B)



Conclusion: Female patients with complex *EGFR*-mutant lung adenocarcinoma and the classical mutation patterns have higher response rate, longer PFS and OS than those without the classical mutation patterns. Afatinib was active in lung adenocarcinoma harboring complex *EGFR* mutations, and may especially benefit patients without the classical mutation patterns due to longer PFS results.

Keywords: Complex EGFR mutation, adenocarcinoma, EGFR TKI

OA11.02 CHANGES OF BRAIN STRUCTURE IN ADVANCED NSCLC PATIENTS RECEIVING EGFR-TKIS: DYNAMIC ANALYSIS BASED ON SERIES MRI IMAGES

C. Luo[1], B. Yang[2], X. Zhou[1], L. Zhou[1], Y. Zhou[1], J. Zhu[1], M. Huang[1], F. Peng[1], Y. Liu[1], Y. Wang[1], Z. Li[3], Y. Lu[1], S. Lui[2], Y. Gong[1]

[1]*Department of Thoracic Oncology and State Key Laboratory of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, sichuan province/China,* [2]*Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province/China,* [3]*Department of Radiation Oncology, West China Hospital, Sichuan University, Chengdu, Sichuan Province/China*

Background: EGFR-TKI was the standard care for metastatic NSCLC patients harboring positive EGFR mutation, which might inhibit EGF signaling pathway and consequently have effect on differentiation, maturation and rehabilitation of neural cells. For the first time, we evaluated the dynamic changes of white matter lesion (WML) and gray matter volume (GMV) among such patients based on series of MRI images. **Method:** We retrospectively identified 778 patients with pathologically diagnosed advanced NSCLC receiving first-generation EGFR-TKIs in our hospital from 2010 to 2017, and 75 patients without brain metastasis and else comorbidity (hypertension, *etc.*) were analyzed. The modified Scheltens visual scale were performed to evaluate the changes of WML based on the series (baseline, 12 months' point and 24 months' point) of MRI images, and CBM (cluster-based morphometry) method based on SPM12 were adopted to identify GMV loss. The statistical methods were performed using SPSS software 22.0. **Result:** During the 24-month EGFR-TKI treatment, the patient's WML visual scores showed a progressive worsen. Comparing to the baseline (6.680±3.636), the scores were significantly changed at the 12 months' point (8.650±3.857; Mean scores increasing 1.973, 95% CI 1.595-2.352, p<0.001) and changed more obviously at the 24 months' point (10.110±3.854; Mean scores increasing 3.427, 95% CI 2.979-3.874, p<0.001), respectively. Also, the significant GMV loss were found in subregions of the right occipital lobe (mean decrease 76.714, 95% CI 40.739-112.690), left occipital lobe (mean decrease 93.476, 95% CI 37.483-149.469) and left basal ganglia (mean decrease 37.571, 95% CI 21.576-53.567), respectively (all p<0.005, the cluster level FDR<0.05). **Conclusion:** Dynamic structural analysis of series brain MRI images showed the significant worsen of the WML and GMV loss in patients with advanced NSCLC receiving EGFR-TKIs chronically. Perspective studies are warranted to verify its impact on the cognitive deficiency and hypomnesis among these patients in future.

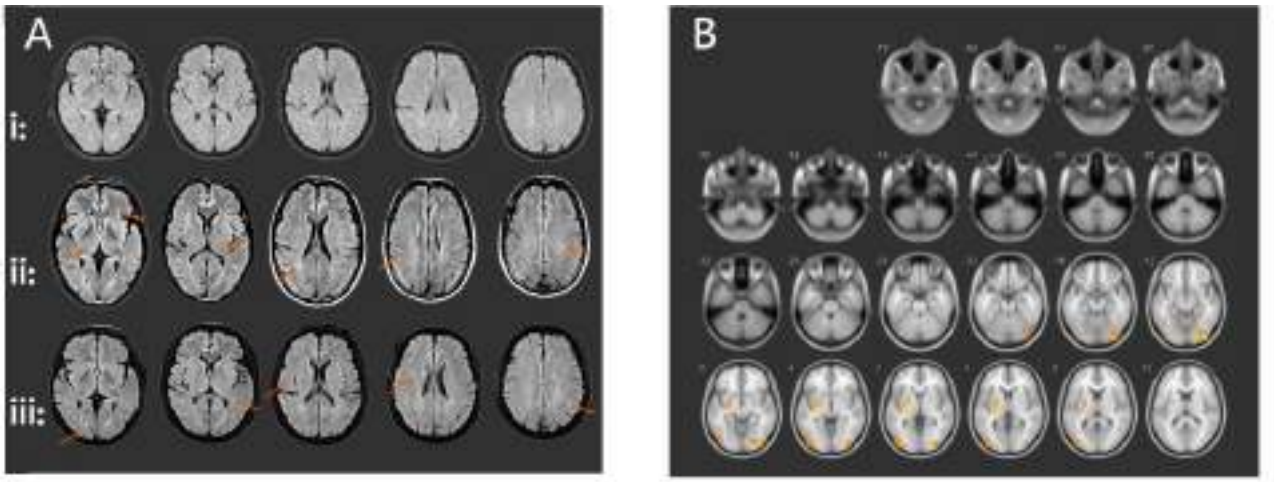


Figure . A. Series MRI images of one representative patient receiving long-term EGFR-TKI. (i. Baseline; ii. 12 months' point; iii. 24 months' point). New white matter lesions were identified in T2 FLAIR images (with yellow arrows). B. Significant loss of gray matter volume (colored areas) was identified by cluster-based morphometry method in the brain subregions among the studied population.

Keywords: NSCLC, EGFR-TKI, Brain MRI

OA11 DECOMPLEXIFYING MOLECULAR TARGETS, IMMUNOTHERAPY AND TREATMENT SETTINGS IN THE REAL WORLD
MONDAY, SEPTEMBER 9 14:00–15:30

OA11.03 SURVIVAL DISPARITIES BETWEEN ACADEMIC AND COMMUNITY CENTERS IN ADVANCED LUNG CANCER IN THE US: CAN WE BRIDGE THE GAP?

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Duke Cancer Institute, Durham/United States of America

Background: Lung cancer causes the most cancer deaths in the US. Our prior study found widening 2-year survival (2YS) disparity between academic and community-based centers (ACs and CCs) prior to 2010, most apparent in adenocarcinoma, suggesting a treatment-related effect. We hypothesized this disparity continued to widen in more recent years. **Method:** Retrospective study of outcomes through 2015 within the National Cancer Database. The primary outcome was 2YS. We used multivariable regression modeling, incorporating diagnosis year, facility type, age, gender, Charlson-Deyo score, and histology to compare AC/CC. A third facility type was identified, Integrated Network Cancer Programs (IC); we did a separate analysis incorporating AC/CC/IC. We formed six cohorts by 1)facility type and 2)time period (2004 through 2008, and 2011 through 2015). Hazard ratios were computed to compare survival between these six cohorts. **Result:** 98,069 patients were included. Treatment in ACs had superior 2YS compared to treatment in CCs, increasing from 16.1% versus 10.3% for those diagnosed in 2004(+5.8%), to 23.7% versus 16.2% for those diagnosed in 2013(+7.5%). Our multivariable model found growth in 2YS disparity of 0.34%-per-year (95% CI 0.18% to 0.50%, p<0.001). This was histology-related: Difference in adenocarcinoma 2YS rose from 7% in 2004 to 9% in 2013(p=0.0023), while squamous carcinoma 2YS difference was 2.7% in 2004 and 0.8% in 2013(p=0.6). 9047 patients were treated at ICs. In the 2004-2008 cohort treatment at ICs had similar outcomes to CCs, however by 2011-2015 ICs had superior histology-related survival, suggesting treatment-related improvements in ICs over CCs (Table 1). **Conclusion:** Survival disparities in metastatic lung cancer between academic and community-based centers in the US continued to widen through 2015. Treatment at integrated centers, a group of facilities with at least one hospital that can include community and academic centers, may help to bridge the divide. Treatment related disparities in other health systems warrant further study globally.

Comparison with 2004 through 2008 Community Center Cohort	Overall	Adenocarcinoma	Squamous
2004-2008 AC	0.80*	0.78*	0.86*
2004-2008 IC	0.93, p=0.0013	0.95, p=0.116	0.94, p=0.29
2011-2015 CC	0.82*	0.82*	0.89*
2011-2015 AC	0.64*	0.62*	0.81*
2011-2015 IC	0.74*	0.72*	0.89,p=0.0218

Table 1: Hazard Ratios for survival in each cohort compared to 2004-2008 Community Center cohort; first overall, then specifically for adenocarcinoma and squamous carcinoma
*significant at 0.001

Keywords: Survival, Disparities, Lung cancer

OA11.05 OPTIMIZING RESOURCES WITH IMMUNOTHERAPY IN DEVELOPING COUNTRIES: EXPERIENCE IN A REFERENCE CENTER IN MEXICO

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Background: Immunotherapy has proven clinical benefit in several tumors as a first line therapy or after standard treatment failure. Pivotal trials with immunotherapy were designed using a weight-based dose. However, recently as part of an effort to standardize the dose of the most common drugs (Nivolumab and Pembrolizumab) the Regulatory Agencies and Pharmaceutics have changed its prescription to fixed doses. In those pivotal studies, the median weight was around 70 to 80 kg. Our hypothesis estimates that a fixed dose increases the use of drug above effective thresholds increasing unnecessary expenses. **Method:** We analyzed a cohort of patients treated with immunotherapy due to lung cancer (NSCLC) diagnosis either during first or second-line of treatment between 2016 and 2018 in the Thoracic Tumors Clinic at National Cancerology Institute in Mexico. We analyzed and estimated the median body in our population. Then, we compared treatment costs between weight-based doses (Nivolumab 3mg/Kg q.2 weeks and Pembrolizumab 2mg/Kg q.3 weeks) versus flat dose treatment (Nivolumab 240mg q.2 weeks and Pembrolizumab 200mg q.3 weeks). **Result:** 792 patients were included with and a median weight of 65 kg (SD ±13.11) was determined. Fixed dose of pembrolizumab administered during one year (17 applications) had an annual cost of $135,218 dlls. while the cost with weight-based dose was $87,913 dlls. with a net difference of $47,305 dlls. In the case of Nivolumab, an annual fixed-dose treatment (26 applications) has a cost of $114,816 dlls, while the weight-based dose has a cost of $93,392 dlls. with a net difference of $21,424 dlls (table1).

PEMBROLIZUMAB (2 mg/Kg) Q3W vs 200mg Q3W						
Comparison	**Total dose per cycle**	**Cost per cycle**	**Excess cost per cycle**	**Dose difference**	**Annual cost treatment (17 cycles)**	**Net difference annual cost per patient**
Weight based dose (Median 65Kg)	130 mg	$5171.4	$2,782.6	70mg	$87,913	$47,305
Fixed-dose	200mg	$7,954	NA	NA	$135,218	NA
NIVOLUMAB (3mg/Kg) Q2W vs 240mg Q2W						
Comparison	Total dose per cycle	Cost per cycle	Excess cost per cycle	Dose difference	Annual cost treatment (26 cycles)	
Weight based dose (Median 65Kg)	195mg	$3,592	$824	45mg	$93,392	$21,424
Fixed-dose	240mg	$4,416	NA	NA	$114,816	NA

Conclusion: General population in developing countries like Mexico are experiencing serious difficulties to get access to immunotherapy due to lack of coverage through Public Health Care System based in costs. According with our study, optimization of resources with weight-base dose could allow us to increase the rate of treated patients. Then, according with our analysis, in the case of Pembrolizumab we calculated coverage of 154 treatments instead of 100 using same budget and favoring the use of weight-based dose. While, in the case of Nivolumab we could increase the number of patients treated from 100 to 126 using weight-based dose. Therefore, our results support that therapies like immunotherapy should be calculated based on body weight as an attempt to increase access and avoid unnecessary expenses in Health Care Systems with limited resources.

Keywords: health care systems, Immunotherapy, pharmacoeconomics

OA11.06 ALTERNATIVE NIVOLUMAB (N) DURATION AND SCHEDULING IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC): REAL-LIFE DATA

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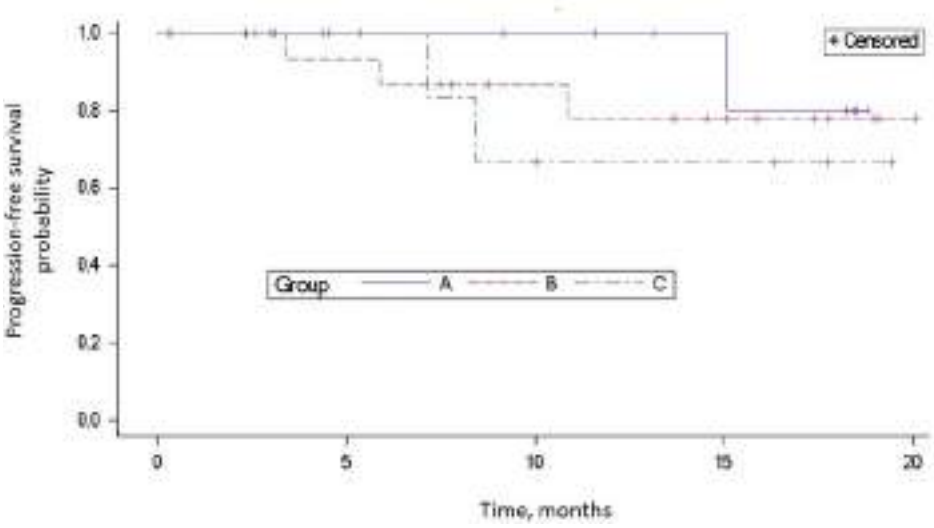
Background: Little is known regarding the optimal scheduling and treatment (Tx) duration of N in aNSCLC. Stopping N after 1 year of Tx negatively affects outcomes. **Method:** 45 consecutive aNSCLC patients (pts) receiving N for ≥2 years (y) were identified in the electronic databases of 4 Israeli cancer centers. These were divided into Groups A (N continued for >2y at a dose 3mg/kg q2w/240mg q2w; n-21), B (N continued for >2y at a dose 3mg/kg q3w-q8w/480mg q4w; n-17), and C (N stopped at 2y for reason other than progressive disease or intolerable toxicity; n-7). PFS (RECIST 1.1) and safety since 2y after N initiation were assessed. **Result:** Baseline, treatment characteristics and outcomes are presented in the Table and the Picture. Allocation to Group B and C was associated with HR for PFS-2.4 (95%CI, 0.3-18.8, p-0.4) and HR for PFS-3.3 (95%CI, 0.3-30.9, p-0.3), respectively. After 2y since N initiation, new N-related toxicity developed in 24%, 18%, and 28% of pts in Groups A, B, and C, respectively (p-NS).

Conclusion: A trend for worse outcomes was observed with alternative N scheduling/N quitting 2y after initiation. So far, continuing N at a standard dose until disease progression/ intolerable toxicity remains the standard treatment option.

Keywords: Nivolumab duration, Nivolumab alternative scheduling, Real-life data

	Age, y (median, range)	Male, %	Smokers, %	Histology: Adeno/Sq/ /Other, %	PD-L1: <1%/1-49%/ /≥50%/NA, %	No of Tx lines prior to N (median, range)	ECOG PS 0/1 at N initiation, %	Response to N: CR+PR/SD/ /Unconventional, %	Time to N re-scheduling/stopping, mo (median, IQR)	Duration of follow-up, mo (median, IQR)	Progression on N, %	Median PFS since 2y after N initiation, mo (95% CI)
Group A, n-21	68 (52-80)	76	95	62/19/19	14/0/5/81	1 (1-3)	81	86/9/5			5	NR (15.1-NR)
Group B, n-17	63 (54-73)	35	100	71/29/0	0/6/12/82	1 (1-4)	71	35/47/18	24.4 [11.7-29.4]	35.6 [28.4-41.8]	23	NR (10.9-NR)
Group C, n-7	68 (51-86)	57	100	57/14/29	0/0/0/100	1 (1-2)	71	72/14/14	24.5 [24.4-24.8]		29	NR (7.2-NR)
p value	NS	0.02*	NS	NS	NS	NS	NS	0.006*	NS	NA	NA	0.54

* Group A vs B



ORAL SESSIONS

OA11 DECOMPLEXIFYING MOLECULAR TARGETS, IMMUNOTHERAPY AND TREATMENT SETTINGS IN THE REAL WORLD
MONDAY, SEPTEMBER 9 14:00–15:30

OA11.07 CHEMOTHERAPY PLUS EGFR-TKI AS FIRST-LINE TREATMENT PROVIDES BETTER SURVIVAL FOR EGFR MUTATION NSCLC PATIENTS: UPDATE DATA FOR NCT02148380

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Background: Previously, we did a prospective study to compare pemetrexed plus carboplatin and gefitinib to either pemetrexed plus carboplatin or gefitinib alone as first-line therapy for lung adenocarcinoma patients harboring sensitive EGFR mutations (NCT02148380). The primary endpoint PFS was met at Oct 1, 2016. However, the OS of combinational group was not mature then [Han B, *et al*. Int J Cancer. 2017;141:1249-1256]. In the present study, we continued the OS follow-up until Sep 28 2018. **Method:** The survival curves for OS were estimated with the Kaplan-Meier method and were compared between combination and gefitinib groups using the log-rank test. 2-years, 3-years survival rates were compared between combination and gefitinib groups using Pearson Chi-Square. **Result:** Baseline characteristics of the intent-to-treat (ITT) population have been reported. At last day of follow-up (Sep 28 2018), 30 (75.0%) patients in the combinational group, 35 (85.4%) patients in the gefitinib group died. 2-year survival rates of combinational and gefitinib groups were 85.0% (34/40), 56.1% (23/41) (P=0.004), respectively. 3-year survival rates of combinational and gefitinib groups were 52.5% (21/40), 24.4% (10/41) (P=0.009), respectively. The median OS was 37.9 months (95%CI: 17.3-58.6) for the combinational group, which was substantially longer than the median OS for first-line gefitinib group (25.8 months [95%CI: 19.2-32.3]). The HR of combinational group versus gefitinib group was 0.56 (95%CI:0.34-0.91, P=0.02). 19del: The median OS was 51.0 months (95%CI: 36.6-65.5) for the combinational group, which was substantially longer than the median OS for first-line gefitinib group (29.8 months [95%CI: 26.7-32.9]). The HR of combinational group versus gefitinib group was 0.61 (95%CI:0.30-1.25, P=0.18). 21L858R: The median OS was 32.3 months (95%CI: 27.8-36.7) for the combinational group, which was substantially longer than the median OS for first-line gefitinib group (22.8 months [95%CI: 13.1-32.5]). The HR of combinational group versus gefitinib group was 0.50 (95%CI:0.25-1.00, P=0.05). Totally, 15 patients had baseline central nervous system (CNS) metastases. The median OS of patients who had baseline CNS metastases was 25.6 months (95%CI: 15.1-36.1); the median OS of patients who had no baseline CNS metastases was 31.7 months (95%CI: 28.2-35.2). The HR of CNS metastases group versus no CNS metastases group was 2.80 (95%CI:1.51-5.18, P=0.001). Among the combinational group, 20% (8/40) percent of patients had baseline CNS metastases. 17.1% (7/41) percent of patients in the gefitinib group had baseline CNS metastases. CNS: The median OS was 27.0 months, (95%CI: 21.8-32.3) for the combinational group, which was substantially longer than the median OS for first-line gefitinib group (15.5 months, 95%CI: 6.8-24.3). The HR of combinational group versus gefitinib group was 0.17 (95%CI:0.04-0.68, P=0.013). No CNS: The median OS was 47.4 months, 95%CI: 27.2-67.7 for the combinational group, which was substantially longer than the median OS for first-line gefitinib group (27.4 months, 95%CI: 23.0-33.7). The HR of combinational group versus gefitinib group was 0.57 (95%CI:0.32-0.99, P=0.044). **Conclusion:** The current study on lung adenocarcinoma patients harboring sensitive EGFR mutations showed that the combined treatment with pemetrexed plus carboplatin with gefitinib provide better survival benefits than gefitinib alone.

Keywords: lung adenocarcinoma, combined treatment, EGFR mutation

OA12 PROFILING THE MULTIDISCIPLINARY MANAGEMENT OF STAGE III NSCLC
MONDAY, SEPTEMBER 9 15:45–17:15

OA12.01 PCI FOR RADICALLY TREATED NON-SMALL CELL LUNG CANCER: A META-ANALYSIS USING UPDATED INDIVIDUAL PATIENT DATA OF RANDOMIZED TRIALS

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Background: In localized non-small cell lung cancer (NSCLC), prophylactic cranial irradiation (PCI) reduced the incidence of brain metastases (BM) (relative risk 0.35), but without a demonstrated effect on overall survival (OS). This may be due to the small sample size in these individual randomized clinical trials (RCTs). Therefore, we aimed to assess the impact of PCI on long term OS for radically treated stage III NSCLC patients compared to observation using updated individual patient data (IPD) from RCTs. **Method:** The main endpoint was OS and secondary endpoints were progression-free survival (PFS), BM-free survival (BMFS) and toxicity. All analyses were performed based on the intention-to-treat principle. The median follow-up was estimated using the inverse Kaplan-Meier method. The log-rank observed minus expected number of events and its variance were used to calculate individual and overall pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) with a fixed effects model. Heterogeneity was studied using the Cochrane test and I^2. Survival curves and 5-year difference between arms were estimated using the Peto method. Interaction between prognostic factors (age, performance status, and histology) and treatment allocation were assessed using Cox proportional hazards models. Toxicities grade $\geq$ 3 were reported descriptively. **Result:** Data on four of the seven eligible trials (SWOG 8300, RTOG 0214, Guangzhou 2005 and NVALT-11) were available for this IPD meta-analysis. In total, 924 patients were analyzed of which 68% was male, median age was 61 years, 94% of the patients had a performance status $\leq$ 1 and 37% had squamous histology. The median follow-up was 8.1 years. All trials provided sufficient IPD for the three endpoints, except for the SWOG 8300 trial (OS only). This trial explained inter-trial heterogeneity. Because of the qualitative interaction with the other trials (p=0.0062) it was separately analyzed (N=254). Compared to observation, OS was significantly lower for PCI in the SWOG 8300 trial (HR 1.38, 95% CI [1.07 to 1.79] p=0.013, 5-year absolute difference -0.9%, 95% CI [-5.9 to 4.1]). However, for the other trials (N=670) no significant OS difference was observed (HR 0.90, 95% CI [0.76 to 1.07] p=0.228, 5-year absolute difference 1.8%, 95% CI [-5.2 to 8.8]). PFS (HR 0.78, 95% CI [0.65 to 0.92] p=0.004, 5-year absolute difference 4.8%, 95% CI [-1.2 to 10.8]) and BMFS (0.38, 95% CI [0.27 to 0.53] p<0.001, 5-year absolute difference 20.7%, 95% CI [12.2 to 29.2]) were significantly higher in the PCI arm. There was no interaction between prognostic factors and treatment allocation for OS. Toxicity data for the PCI arm was available in all trials except the SWOG 8300 trial. The total number of patients with at least one grade $\geq$3 toxicity (for the adverse events pre-specified in the protocol) in the PCI arm was 19/456, including 11/86 in the NVALT-11 trial. Toxicity for the observation arm was only available in the NVALT-11 trial, including 4/88 patients with at least one grade $\geq$3 toxicity. **Conclusion:** Although PFS and BM-free survival were improved for patients who received PCI, no significant PCI benefit for OS was observed.

Keywords: IPD meta-analysis, stage III NSCLC, prophylactic cranial irradiation

ORAL SESSIONS

OA12.02 RANDOMIZED PHASE II STUDY OF CDDP+S-1 VS CDDP+PEM COMBINED WITH THORACIC RT FOR LOCALLY ADVANCED NON-SQ NSCLC: SPECTRA STUDY

T. Seto[1], S. Niho[2], T. Yoshida[3], T. Akimoto[2], K. Sakamaki[4], A. Ono[5], M. Nishio[6], N. Yamamoto[3], T. Hida[7], H. Okamoto[8], T. Kurata[9], Y. Hattori[10], K. Goto[2], T. Yamanaka[4], Y. Ohe[3]

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Background: SPECTRA, a multicenter, randomized phase II study of CDDP+S-1 versus CDDP+pemetrexed (PEM) combined with thoracic radiotherapy (TRT) for locally advanced non-squamous non-small cell lung cancer (NSCLC), previously reported that toxicities were tolerable and manageable in both arms; however, febrile neutropenia was more frequently observed in the CDDP+S-1 arm (9.6%/2%). Completion rate of TRT (60Gy) and chemotherapy (4 cycles) was 92%/98% and 73%/86%, respectively. Response rate was 60%/64% (WCLC 2017, MA17.06). Here, we present primary analysis of 2-year survival data. **Method:** Patients were randomly assigned to receive CDDP+S-1 (CDDP 60mg/m^2, d1, and S-1 80mg/m^2, d1-14, q4w, up to 4 cycles) or CDDP+PEM (CDDP 75mg/m^2, d1, and PEM 500mg/m^2, d1, q3w, up to 4 cycles) combined with TRT 60Gy in 30 fractions. The primary endpoint was 2-year progression-free survival (PFS) rate. The sample size was set at 100 patients. **Result:** Between Jan 2013 and Oct 2016, 102 patients were enrolled in this study from 9 institutions in Japan. All 102 patients were eligible and assessable, of whom 52 were assigned to CDDP+S-1 and 50 to CDDP+PEM. Baseline characteristics were similar (CDDP+S-1/CDDP+PEM): median age (range) 64.5 (39-73)/63.5 (32-74) years; women, n=17 (33%)/n=17 (34%); stage IIIB, n=21 (40%)/n=20 (40%); ECOG PS of 1, n=14 (27%)/n=14 (28%); never smoker, n=12 (23%)/n=12 (24%); and adenocarcinoma, n=47(90%)/n=45(90%); activating EGFR mutation, n=9 (17%)/n=4 (8%); ALK fusion, n=2 (4%)/n=3 (6%). A total of 72 PFS events were observed at the data cut-off (28 November 2018). After a median follow-up of 32.1 months, median PFS was 12.7/13.8 months (HR=1.16, 95% CI, 0.73-1.84, p=0.538), and 2-year PFS rate was 36.5% (95% CI, 23.5-49.6)/32.1% (95%CI, 18.9-45.4). Disease progression was observed in 33 and 36 patients. Distant metastases were the first site of failure in 24 and 31 patients. Local relapse as the first site of failure was observed in 14 and 13 patients. After a median follow-up of 34.6 months, 44 OS events were observed. Median OS was 48.3/59.1 months (HR=1.05, 95%CI, 0.58-1.90, p=0.883), and 2-year OS rate was 69.2% (95%CI, 56.7-81.8)/66.4% (95%CI, 53.0-79.9). 27 patients in each arm received post-study chemotherapy including EGFR-TKIs (n=7/n=5), ALK-TKIs (n=0/n=3), and immune checkpoint inhibitors (n=6/n=10). **Conclusion:** 2-year PFS rate in the CDDP+S-1 arm was better than that in the CDDP+PEM arm. We will select the CDDP+S-1 arm as the investigational arm in a future phase III study. UMIN000009914 (release date: 31/Jan/2013)

Keywords: chemoradiotherapy, NSCLC, non-Sq

OA12 PROFILING THE MULTIDISCIPLINARY MANAGEMENT OF STAGE III NSCLC
MONDAY, SEPTEMBER 9 15:45–17:15

OA12.03 INITIAL REPORTING OF NRG-LU001, RANDOMIZED PHASE II TRIAL OF CONCURRENT CHEMORADIOTHERAPY +/- METFORMIN HCL IN LOCALLY ADVANCED NSCLC

H. Skinner[1], C. Hu[2], T. Tsakiridis[3], R. Santana-Davila[4], B. Lu[5], J. Erasmus[6], A. Doemer[7], G. Videtic[8], J. Coster[9], A. Yang[10], R. Lee[11], M. Werner Wasik[5], P. Schaner[12], S. Mccormack[13], B. Esparaz[14], R. Mcgarry[15], J. Bazan[16], T. Stuve[17], J. Bradley[18]

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Background: Preclinical and retrospective clinical data, have shown that metformin, an inexpensive diabetes drug, has the potential to improve response to chemotherapy and radiation in several solid tumors, including non-small cell lung cancer (NSCLC). These findings led to NRG-LU001, a multi-institutional, international randomized Phase II clinical trial to determine whether metformin can improve outcomes of curative chemoradiation (CRT) in locally advanced NSCLC (LA-NSCLC). **Method:** Unresectable stage IIIA/B NSCLC patients were randomized to either concurrent chemoradiation to 60 Gy with weekly carboplatin-paclitaxel (CP), followed by consolidation CP (Control) or the same regimen combined with metformin (2000 mg/day) (Experimental). The primary endpoint was 1-year progression free survival (PFS). PFS and overall survival (OS) were estimated using the method of Kaplan-Meier. Time to loco-regional progression (TTLRP) or distant metastasis (TTDM) were estimated using the cumulative incidence method. Adverse events (AEs) were graded using CTCAE v4.0. **Result:** 170 patients were randomized between Aug. 2014-Dec. 2016, with planned analysis at 102 events. No significant difference in toxicity was observed between Control and Experimental arms. 1- and 2-year PFS was 60.4% (95% CI: 48.5, 70.4) and 40.1% (95% CI: 29.0, 51.0) in Control vs 51.3% (95% CI: 39.8, 61.7) and 34.5% (95% CI: 24.2, 45.1) in the Experimental arm (multivariable Cox proportional HR=1.20 (95% CI: 0.81, 1.78), p=0.36). On multivariable analysis including treatment arm, performance status, histology and stage, only higher stage (IIIA vs. IIIB) was associated with worse PFS (HR 1.79, 95% CI:1.19, 2.69, p=0.0054). OS at 2 years was 65.4% (95% CI: 53.5, 75.0) for Control vs 64.9% (95% CI: 53.1, 74.5) for the Metformin arm (HR=1.03 (95% CI: 0.64, 1.68)), while deaths due to disease were 90% vs 71%, respectively. No significant differences were found for TTLRP (HR 1.01, 95% CI: 0.57, 1.79, p=0.98) or TTDM (1.38, 95% CI: 0.76, 2.5, p=0.29). 63.4% of patients in the experimental arm received the complete course of metformin, with the most common cause of discontinuation being side effects or complications (13.4%). **Conclusion:** In NRG-LU001, concurrent CRT and metformin presented no noticeable safety concerns. However, this combination failed to improve PFS at the hypothesized effect size. Additionally, no effect on OS or patterns of failure were identified. Blinded central review of imaging based PFS is ongoing. Somewhat unexpectedly, 37% of patients did not complete the prescribed course of metformin. Additionally, deaths due to disease were less in the experimental arm compared to control.
Acknowledgements: This project was supported by National Cancer Institute (NCI) grants: U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG SDMC), UG1CA189867 (NCORP), U24CA180803 (IROC). HS and TT are Co-Principal Investigators in this trial.

Keywords: Lung cancer, clinical trial, chemoradiation

OA12.05 IMAGING-GUIDED TARGET VOLUME REDUCTION IN RADIOTHERAPY OF LUNG CANCER: THE PROSPECTIVE RANDOMIZED MULTINATIONAL PET-PLAN TRIAL

U. Nestle[1], T. Schimek-Jasch[2,3], S. Kremp[4], A. Schaefer[4], A. Kuesters[5], M. Tosch[6], T. Hehr[7], M. Eschmann[7], Y.-P. Bultel[8], P. Hass[9], J. Fleckenstein[4], A. Thieme[10], M. Stockinger[11], M. Miederer[12], G. Holl[13], C. Rischke[2], S. Adebahr[2], E. Gkika[3], J. Koenig[12], A.-L. Grosu[3]

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Background: Advanced medical imaging offers a chance for target volume reduction in modern radiotherapy, which may lead to more effective local treatments with reduced toxicity and offer the protection of draining lymph nodes and large vessels, possibly of importance for the upcoming combination of radiotherapy and immunotherapy. Locally advanced non-small cell lung cancer (NSCLC) with improvable local control and high toxicity is an excellent model to investigate this topic. **Method:** In the prospective randomised controlled PET-Plan trial (NCT00697333), patients with inoperable stage II/III NSCLC and an indication for radiochemotherapy were randomized at a 1:1 ratio. In conventional arm A target volumes were informed by FDG-PET and CT plus elective nodal irradiation and in experimental arm B they were solely informed by FDG-PET. In both arms, quality assured isotoxically dose-escalated IMRT or 3D-CRT (60–74Gy, 2Gy per fraction) was planned and applied to the respective target volumes along with simultaneous platinum-based chemotherapy. The primary objective was time to locoregional progression (LRP) in terms of non-inferiority of experimental arm B. **Result:** 311 patients were recruited, 205 patients included in the intent to treat (ITT) (A: n=99, B: n=106) and 172 patients in the per protocol (PP) analysis (A: n=84, B: n=88). Median FU time in the PP set was 16 months. Non-inferiority of experimental arm B was confirmed for the pre-specified non-inferiority margin. The risk of LRP was lower in the experimental arm B (2y-LRP 0.20 vs. 0.39; HR=0·57; 95% CI: 0·30–1·06; p=0·039) with no difference between study arms concerning survival (2y-OS 0.57 vs. 0.54), out-field recurrence and toxicity. **Conclusion:** In radiochemotherapy for locally advanced NSCLC PET-Imaging based reduction of radiotherapy target volumes is feasible and may improve local control without increasing toxicity. However, in this trial there was no impact on survival. The procedures established in this clinical trial provide a radiotherapy standard for future NSCLC-trials including immunotherapy and may furthermore inspire trials on imaging based target volume reduction for other types of tumours.

Keyword: NSCLC radiotherapy PET-based

OA12 PROFILING THE MULTIDISCIPLINARY MANAGEMENT OF STAGE III NSCLC
MONDAY, SEPTEMBER 9 15:45–17:15

OA12.06 A PROSPECTIVE RANDOMIZED PHASE III STUDY OF PRECISE PORT FOR PATIENTS WITH PIIIA-N2 NSCLC AFTER COMPLETE RESECTION AND ADJUVANT CHEMOTHERAPY

Z. Hui[1], Y. Men[1], C. Hu[2], Z. Zhou[1], J. Liang[1], Q. Feng[1], B. Nan[1], X. Wang[1], D. Chen[1], Z. Xiao[1], J. Lv[1], L. Deng[1], T. Zhang[1], W. Wang[1], S. Gao[1], J. He[1], L. Wang[1]

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Background: For patients with completely resected pIIIA-N2 non-small cell lung cancer (NSCLC), the role of postoperative radiotherapy (PORT) is not well defined. 3D-conformal or simplified intensity modulated radiotherapy (3D-CRT/sIMRT) can precisely deliver high dose to the target volume while decreasing the toxicity of normal tissues, which may improve the treatment outcomes. This phase III randomized clinical trial (NCT00880971) is designed to evaluate the effect of precise PORT on survival and failure pattern in patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy. **Method:** After complete resection and four cycles of platinum based chemotherapy, patients with pIIIA-N2 NSCLC were randomized equally into PORT group or observation group. Using 3D-CRT/sIMRT techniques, PORT of 50 Gy by 25 fractions was given to the ipsilateral hilum, subcarinal region and ipsilateral mediastinum. The primary endpoint was disease free survival (DFS). Secondary endpoints include overall survival (OS), loco-regional recurrence free survival (LRFS), distant metastasis free survival (DMFS) and toxicity. Targeted accrue was 360 patients. With at least 230 DFS events it was designed to detect an improvement in 3-year DFS from 30% to 44% (equivalent to HR=0.69) at 1-sided type 1 error of 0.025 with 80% power. Intent-to-treat populations is used for primary analyses, supplemented with sensitivity analyses using per-protocol population. Log-rank test is used for time-to-event data comparisons. **Result:** Between Jan. 2009 and Dec. 2017, 364 consecutive eligible patients were randomized, including 184 in the PORT group and 180 in the observation group. For this initial reporting of planned final analysis, as Jan 31, 2019, 230 DFS events were reported and the median follow up time was 53.3 months. The clinical features were comparable between the two groups. The 3-year DFS rates in PORT and observation were 42.7% vs. 34.5% (mDFS: 26.5 vs 22.7 months, HR=0.85, 95% CI: 0.65-1.10, 1-sided p=0.10), with OS of 81.5% vs. 85.4% (mOS: not reached vs 90.9 months, HR=1.01, 95% CI: 0.68-1.51, 2-sided p=0.94), LRFS of 69.8% vs. 62.4% (HR=0.71, 95% CI: 0.51-0.97, 2-sided p=0.03), and DMFS of 44.8% vs. 43.5% (HR=0.93, 95% CI 0.71-1.22, 2-sided p=0.60), respectively. For 310 per-protocol patients (140 with PORT and 170 without PORT), PORT marginally improve the DFS (44.8% vs 32.6%, HR=0.76, 95% CI: 0.57-1.00, 2-sided p=0.05), but not OS (85.7% vs 85.0%, HR=0.83, 95% CI: 0.53-1.30, p=0.41). Relapses of any type were observed in 110 (59.8%) and 116 patients (64.4%) in the PORT and observation groups, respectively. Forty-seven over 50 deaths (94.0%) in the PORT group and 42 over 47 deaths (89.4%) in the observation group died of cancer progression, respectively. No radiotherapy-related grade 5 AE was observed. **Conclusion:** For pIIIA-N2 NSCLC patients after complete resection and adjuvant chemotherapy, precise PORT has not been shown to significantly improve DFS or OS , though it can significantly improve LRFS.

Keywords: IIIA-N2, postoperative radiotherapy, Non–small-cell lung cancer

OA12.07 RADICALITY OF LYMPHADENECTOMY IN LUNG CANCER ACCORDING TO SURGICAL APPROACH. RESULTS FROM THE SPANISH GROUP OF VIDEO-ASSISTED THORACIC SURGERY

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Background: The minor standard of systematic nodal dissection (SND) in lung cancer surgery, which is the minimum recommended by the Union for International Cancer Control, requires the resection/sampling of, at least, 3 mediastinal (including subcarinal station) and 3 hilar/intrapulmonary lymph nodes (LN). The objective of this study is to analyze differences in intraoperative LN assessment in patients with surgically treated non-small cell lung cancer (NSCLC) according to surgical approach (open vs VATS), from the results of the Spanish Group of Video-Assisted Thoracic Surgery (GEVATS) database. **Method:** Prospective multicenter cohort study of anatomic pulmonary resections (n=3533) performed from 20/12/16 to 20/03/18. Exclusions criteria were: indications different from NSCLC, previous lung cancer, synchronous tumors and induction therapy. Patients who did not meet the criteria for SND but had no nodal involvement were coded as pathologic (p)Nx (instead of pN0). Corresponding tests for homogeneity were performed. Multiple logistic regression analysis was used to determine the odds ratio (OR) and 95% confidence interval (95%CI). Stata/SE vs 13 statistical package was used for data analysis. Significance was considered when p<0.05. **Result:** 2532 patients were analyzed (1801 men [71.1%]; median age: 67 years). SND was performed in 65%, with a median of LN resected/sampled of 7 (IQR 4-12) and a rate of pN2 of 9.5%. Table1 summarizes results from bivariate analysis.Independent risk factors for thoracotomy at multivariate analysis (OR; 95%CI) were: squamous cell carcinoma vs adenocarcinoma (1.3; 1.04-1.68), staging mediastinoscopy (2.8; 1.83-4.22), LN resected (1.02; 1.00-1.04), SND (1.4; 1.07-1.8), tumour >3cm (1.8; 1.5-2.2), central tumour (2.5; 2.0-3.1); pN1 (1.5; 1.1-2.1) and pN2 (1.6; 1.1-2.3). A significantly higher proportion of nodal upstaging was observed in thoracotomy group: from cN0 to pN1/pN2, and from cN1 to pN2 (table1).

Conclusion: The intensity of lymphadenectomy in GEVATS was superior in the thoracotomy approach. Therefore, intraoperative lymph node evaluation performed at VATS should improve to have better prognostic information and indicate adjuvant therapy.

Keywords: surgical approach, intraoperative lymphadenectomy

BIVARIATE ANALYSIS

VARIABLES	THORACOTOMY; n (%)	VATS; n (%)	p**
Number of patients (n)	1097 (43,3%)	1435 (56.7%)	
Systematic nodal dissection	757 (69%)	890 (62%)	<0.001
Number of LN	8 (5-13)*	6 (4-11)*	<0.0001
pN:			
• pN0	491 (45.1%)	742 (51.8%)	0.001
• pN1	211 (19.4%)	106 (7.4%)	<0.0001
• pN2	129 (11.8%)	110 (7.6%)	<0.001
• pNx	258 (23.7%)	475 (33.1%)	<0.0001
Tumor size			
- T≤3cm			
- pN1	70 (13.9%)	52 (5%)	<0,0001
- pN2	49 (9.7%)	64 (6.2%)	< 0.015
- T>3cm			
• pN1	140 (24.1%)	54 (13.7)	<0.001
• pN2	79 (13.6%)	45 (11.4%)	0.374
Central tumour:			
• pN1	164 (27.3%)	41 (11.8%)	<0.0001
• pN2	72 (12%)	37 (10.6%)	0.6
Peripheral tumour:			
- pN1	47 (9.6%)	65 (6%)	0.01
- pN2	57 (11.7%)	73 (6.7%)	0.001
Number of LN in:			
- pN :			
• pN0	10 (7-14)	10 (7-14)	0.748
• pN1	11 (6-17)	7 (5-11)	<0.001
• pN2	10 (6-17)	8 (5-13)	0.092
• pNx	4 (3-5)	4 (3-5)	0.521
- Tumor size			
• T≤3cm	7 (4-12)	6 (4-10)	0.002
• T>3cm	9 (6-14)	7 (5-11)	0.002

STAGE MIGRATION

cN	pN	THORACOTOMY; pN/cN (%)	VATS; pN/cN (%)	p**
cN0	pN0	418 / 894 (46.7%)	647 / 1233 (52.5%)	0.01
	pN1	165 / 894 (18.4%)	86 / 1233 (6.9%)	<0.0001
	pN2	91 / 894 (10.2%)	87 / 1233 (7%)	0.013
	pNx	220 / 894 (24.6%)	413 / 1233 (33.5%)	<0.0001
cN1	pN0	26 / 89 (29.2%)	34 / 80 (42.5%)	0.101
	pN1	30 /89 (33.7%)	17 / 80 (21.2%)	0.102
	pN2	22 / 89 (24.7%)	8 / 80 (10%)	0.021
	pNx	11 / 89 (12.4%)	21 / 80 (26.2%)	0.035
cN2	pN0	22 / 48 (45.8%)	13 / 33 (39.4%)	0.729
	pN1	8 / 48 (16.7%)	0	0.036
	pN2	12 / 48 (25%)	12 / 33 (36.4%)	0.394
	pNx	6 / 48 (12.5%)	8 / 33 (24.2%)	0.283
cNx	pN0	24 / 57 (42.1%)	48 / 84 (57.1%)	0.114
	pN1	8 / 57 (14%)	2 / 84 (2.4%)	0.021
	pN2	4 / 57 (7%)	2 / 84 (2.4%)	0.361

n: number of patients; **VATS**: video-assisted thoracic surgery; **LN**: lymph nodes.* Median (IQR 25-75%)
** p value by Chi-square or Mann-Whitney U tests, or comparison test of proportions for independent samples through z statistic, as appropriate.

OA13.01 SPECS2 LUNG CANCER CONSORTIUM PROSPECTIVE MULTICENTER VALIDATION OF PROGNOSTIC SIGNATURE FOR EARLY STAGE SQUAMOUS LUNG CANCER

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Background: Squamous Lung Cancer (SC) which constitutes 30% of all non-small cell lung cancers (NSCLC) has few targeted therapy options for advanced disease. Surgery for early SC is the best treatment strategy; however, even patients who undergo surgery for stage IA or IB disease are still at a substantial risk for recurrence and death. Adjuvant therapy is not currently indicated for stage I SC smaller than 4 cm. Prior reports suggest gene expression-based signatures that may predict recurrence in patients with stage I SC, but none has been validated or is in clinical use. The SPECS2 Lung Cancer Consortium was assembled to compare and attempt to validate previously published prognostic signature(s) according to the guidelines proposed by Subramanian and Simon (J Natl Cancer Inst 2010; 7:327). **Method:** The multi-institutional team assembled 249 frozen SC samples representing six participating institutions (cohort 1). These samples were fully annotated in a redcap database hosted by the independent statistical core. Cohort 2 was assembled utilizing 234 frozen SC samples from a prospective multi-institutional NCTN lung biobanking protocol (NCT00899782). RNA was extracted and profiled with U133A microarrays (Affymetrix) in independent core facilities. The data was transferred directly to the SPECS2 Lung statistical core in collaboration with the Alliance Statistical core and the performance of 6 most promising candidate signatures was evaluated relative to a base model that included only age, gender and AJCC stage (editions 6, 7, 8). **Result:** Analysis of Cohort 1 demonstrated that only one signature (Raponi et al, Cancer Res 2006; 66:7466) significantly enhanced prognosis relative to the base model, independent of AJCC edition. This was also observed in Cohort 2, where Uno's C index associated with AJCC 8th edition stage, sex and age (0.561; 0.468-0.654) was significantly ($p < 0.05$) increased when the prognostic signature was added to the model (0.683; 0.611-0.755). **Conclusion:** The SPECS2 Lung Cancer Consortium was successful in validating a previously published prognostic molecular signature for early stage SC using rigorous experimental design. To our knowledge, this is the first unbiased validation of a lung cancer prognostic signature using multi-institutional prospective specimens. These results support a clinical trial designed to evaluate the potential role of adjuvant therapy in completely resected early stage SC.

Keyword: Prognostic Biomarkers; Early stage Squamous lung cancer; Multi-institutional prospective validation

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TUESDAY, SEPTEMBER 10 11:30–13:00

OA13.02 VIDEO-ASSISTED THORACOSCOPIC SURGERY VS. THORACOTOMY FOR NON-SMALL CELL LUNG CANCER: SURVIVAL OUTCOME OF A RANDOMIZED TRIAL

D. Situ[1], H. Long[1], Q. Tan[2], Q. Luo[3], Z. Wang[4], G. Jiang[5], T.-H. Rong[6]

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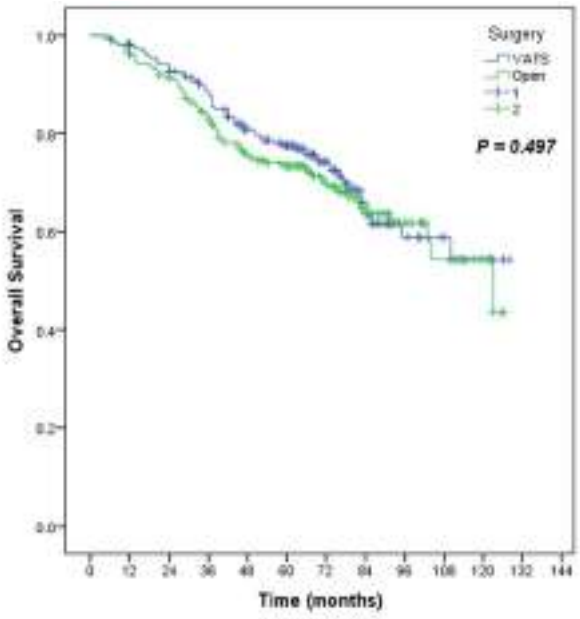
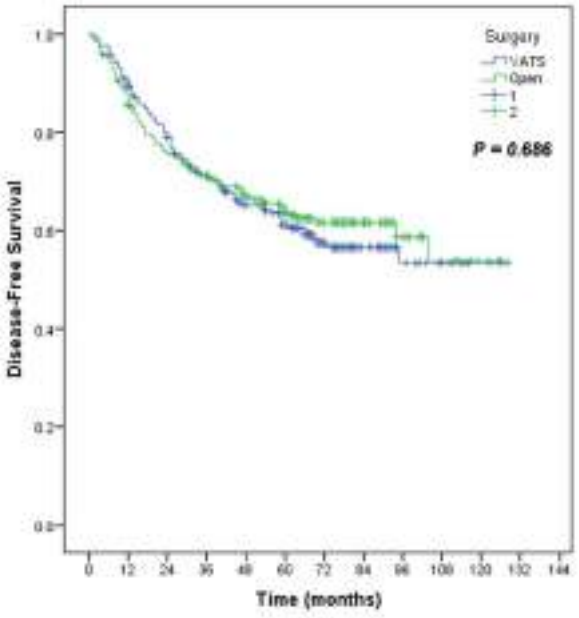
Background: Video-assisted thoracoscopic surgery (VATS) has been widely used in the treatment of early-stage non–small cell lung cancer (NSCLC). However, there has not been a robust randomized control trial (RCT) to confirm the non-inferiority of VATS to open lobectomy in term of oncologic efficacy. Therefore, a large multicenter RCT in China was designed and initiated to verify the role of VATS. **Method:** A phase 3 RCT was undertaken at five thoracic surgery tertiary centers in China. Patients aged 18-75 years old who were diagnosed of clinically early-stage NSCLCs were randomized in a 1:1 ratio into VATS and thoracotomy groups. Radical lobectomy plus hilar and mediastinal lymph node dissection was the standard surgical intervention. The primary end-point of study was 5-year overall survival (OS). The secondary end-points including 5-year disease-free survival (DFS) and cancer relapse rates would also be reported here. Analysis was by intention to treat. This study is registered with the ClinicalTrials.gov, number NCT01102517. **Result:** A total of 508 patients were recruited between January 2008 and March 2014. The final follow-up for 5-year survival analysis was completed in March 2019. And 432 patients were eligible for analysis (222 cases in VATS group and 210 cases in thoracotomy group). The cancer relapse (recurrence and metastasis) rates were 39.2% in VATS group and 36.7% in thoracotomy group respectively (P=0.621). Patients who received VATS lobectomies had a similar 5-year DFS to those who underwent open surgery (58% versus 62%, P=0.686). Finally, the 5-year OS rates were of no significant difference between VATS and thoracotomy groups (74% versus 71%, P=0.497).





Conclusion: The non-inferiority of VATS to thoracotomy lobectomy was confirmed in our RCT in terms of oncologic efficacy for clinically early-stage NSCLCs.

Keywords: Thoracoscopic Surgery, Non-Small Cell Lung Cancer, Survival

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OA13.03 PREDICTING POSTOPERATIVE RECURRENCE IN COMPLETELY RESECTED EGFR-MUTANT NON-SMALL CELL LUNG CANCER: VALUE OF IHC MARKERS

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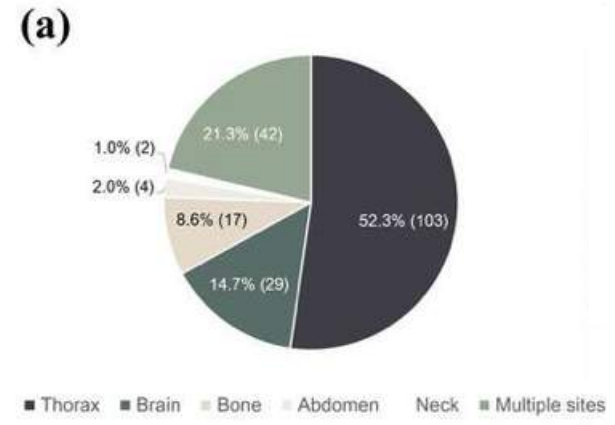
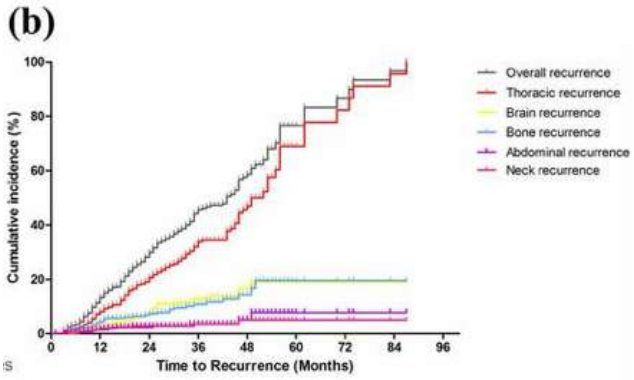
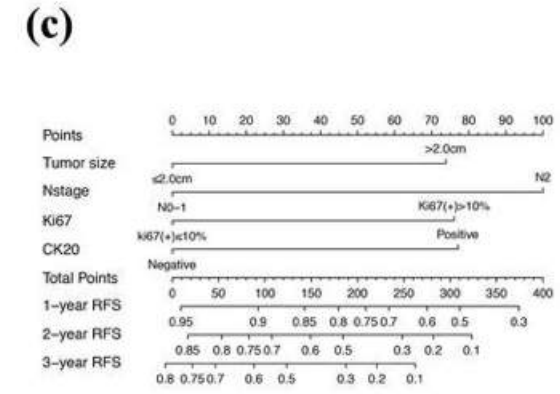
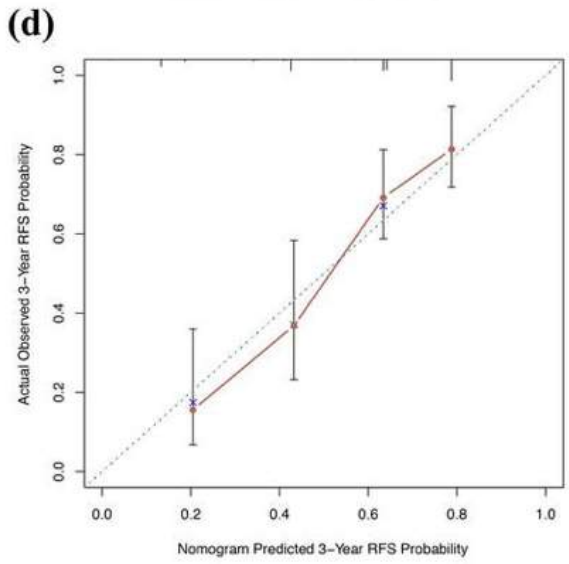
Background: EGFR mutations are detected in up to 50% of non-small cell lung cancer (NSCLC) and recent studies indicate that EGFR-mutant NSCLC is a heterogeneous disease with varying co-mutations, diverse histologic subtypes and distinct expression of oncoproteins. However, the risk factors and clinical patterns of postoperative recurrence among patients with completely resected EGFR-mutant NSCLC have not been fully understood. Moreover, the prognostic values of routinely used immunohistochemical (IHC) markers in NSCLC are seldom reported. **Method:** Consecutive patients with curative resected NSCLC and confirmed EGFR mutations at Fudan University Shanghai Cancer Center from January 2007 to December 2017, were retrospectively enrolled. The initial recurrence sites were recorded and categorized into five groups: thoracic recurrence, brain recurrence, neck recurrence, abdominal recurrence, and bone recurrence. The indicators of overall and site-specific recurrence were identified using the Cox regression model, where a panel of routinely used IHC markers (including Her2, Ki67, TTF-1, CK20, CK7, CK5/6, p53, RRM1, NapsinA, p40, syn, Bcl-2, CDX2, ERCC1 and p63) were incorporated. A nomogram was developed based on variables selected in multivariate analysis. The bootstrapping method (1000 repetitions) was applied to internally validate the nomogram **Result:** After a median follow-up of 32 (range, 5-122) months, disease recurrence was observed in 197(37.1%) out of the 531 patients, with a median recurrence-free survival (RFS) of 19 (95% CI, 16.63-21.37) months. Most patients (n=136; 69.0%) had thoracic recurrence, followed by brain recurrence (n=41; 20.8%), bone recurrence (n=41; 20.8%), abdominal recurrence (n=14; 7.1%), and neck recurrence (n=13; 6.6%). Sex, tumor size, Ki67, and N stage were independent indicators of thoracic recurrence. Tumor size, N stage, CK20, and Syn were independent indicators of brain recurrence. N stage and Ki67 were independent indicators of bone recurrence. N stage was the independent indicator of abdominal recurrence and neck recurrence. Tumor size, Ki67, CK20, and N stage were independently associated with overall recurrence, and thus a nomogram predicting the 1-, 2-, and 3-year RFS probability was developed based on these four factors. The concordance index (C-index) was 0.723 (95% confidence interval, 0.675 to 0.771) and the calibration curves displayed good agreement between the predicted RFS and the actual observation.









ORAL SESSIONS

Conclusion: Independent prognostic indicators based on clinic-pathological parameters and routinely used IHC markers were identified to predict overall and site-specific recurrence, which may help to identify optimal candidates for adjuvant therapies and design individualized surveillance strategies among patients with completely resected EGFR-positive NSCLC

Keywords: Non-Small Cell Lung Cancer, EGFR mutation, postoperative recurrence

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TUESDAY, SEPTEMBER 10 11:30–13:00

OA13.05 NADIM STUDY: UPDATED CLINICAL RESEARCH AND OUTCOMES

M. Provencio[1], E. Nadal[2], A. Insa[3], R. Garcia Campelo[4], J. Casal[5], M. Domine[6], M. Majem[7], D. Rodriguez-Abreu[8], A. Martinez-Marti[9], J. De Castro Carpeno[10], M. Cobo[11], G. López-Vivanco[12], E. Del Barco[13], R. Bernabe[14], N. Viñolas[15], I. Barneto[16], S. Viteri[17], P. Martin Martorell[3], M. Jove[18], V. Calvo De Juan[1], B. Massuti[19]

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This abstract is under embargo until September 10 10:45 CET

OA13 IDEAL APPROACH TO LUNG RESECTION AND NOVEL PERIOPERATIVE THERAPY
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OA13.06 SURGICAL OUTCOMES FOLLOWING NEOADJUVANT NIVOLUMAB OR NIVOLUMAB PLUS IPILIMUMAB IN NON-SMALL CELL LUNG CANCER–NEOSTAR STUDY

B. Sepesi, T. Cascone, W. William, H. Lin, C. Leung, A. Weissferdt, G. Walsh, D. Rice, J. Roth, R. Mehran, W. Hofstetter, M. Antonoff, F. Fossella, F. Mott, X. Le, F. Skoulidis, J. Zhang, L. Byers, V. Lam, B. Glisson, J. Kurie, G. Blumenschein, A. Tsao, C. Lu, M. Altan, Y. Elamin, D. Gibbons, V. Papadimitrakopoulou, J. Lee, J. Heymach, A. Vaporciyan, S. Swisher

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Background: Surgical outcomes following neoadjuvant immune checkpoint inhibitors (ICIs) are limited. We report 90-day perioperative results of the NEOSTAR phase II trial of neoadjuvant nivolumab or nivolumab/ipilimumab in resectable non-small cell lung cancers (NSCLCs). **Method:** 44 pts with stage I-IIIA NSCLC (AJCC 7th) were randomized to nivolumab (3 mg/kg IV, days 1, 15, 29, n=23) or nivolumab/ipilimumab (1 mg/kg IV, day 1, n=21) with resection planned between 3-6 weeks after last dose. Surgical approach and extent of resection were at surgeons' discretion. **Result:** 39 (89%) patients underwent R0 resection, of those 2 (5%) were resected off trial after additional induction chemotherapy (1 nivolumab, 1 nivolumab/ipilimumab). Among 37 patients, 21 underwent surgery following nivolumab and 16 following nivolumab/ipilimumab. Median age 66 (43-83) years, 24 (65%) male, 33 (89%) white, 22 (59%) adenocarcinoma, 22 (59%) stage I, 9 (24%) stage II, 6 (16%) stage IIIA. 5 (11%) were not resected, 1 (1/23, 4%) after nivolumab (stage II), 4 (4/21, 19%) after nivolumab/ipilimumab (1 stage I, 1 stage II, 2 stage IIIA). Reasons for unresectability were change in surgeon's judgement (n=2), toxicity (n=1), progression (n=1), and declining pneumonectomy (n=1). Median time to surgery was 31 days (range 21-87). 8 (22%) operations were delayed beyond 42 days, 5 after nivolumab/ipilimumab (5/16, 31%) and 3 after nivolumab (3/21, 14%). 33 (89%) underwent lobectomy, 2 (5%) pneumonectomy, 1 (3%) segmentectomy and 1 (3%) wedge resection. 27 (73%) had thoracotomy, 7 (19%) thoracoscopy, 3 (8%) robotic approach. 2 (5%) were electively converted from thoracoscopy to thoracotomy. Median operative time was 147 minutes (71-315), median blood loss was 100cc (50-1000), and median length of stay was 4 days (1-18). Perioperatively, pulmonary complications occurred in 8 (22%) patients: 8 (22%) prolonged air leak, 2 (5%) pneumonitis/pneumonias, 1 (3%) empyema, and 1 (3%) bronchopleural fistula (BPF). 1 (3%) died from complications of BPF and steroid therapy for pneumonitis. 4 (11%) developed atrial fibrillation, 1 (3%) diarrhea, 1 (3%) ileus, and 1 (3%) transient ischemic attack. Surgeons subjectively judged 15/37 (40%) of operations to be more complex than usual with 7/37 (19%) lasting > 4 hours. **Conclusion:** Following three cycles of neoadjuvant ICIs 89% of patients underwent complete R0 resection, including two patients who received additional induction chemotherapy off trial. Five marginally operable patients who didn't proceed to resection, and one perioperative mortality highlight the importance of cautious patient selection for neoadjuvant ICIs in the management of operable NSCLC.

Keywords: surgery, Lung cancer, neoadjuvant immunotherapy

OA13 IDEAL APPROACH TO LUNG RESECTION AND NOVEL PERIOPERATIVE THERAPY
TUESDAY, SEPTEMBER 10 11:30–13:00

OA13.07 NEOADJUVANT ATEZOLIZUMAB IN RESECTABLE NSCLC PATIENTS: IMMUNOPHENOTYPING RESULTS FROM THE INTERIM ANALYSIS OF THE MULTICENTER TRIAL LCMC3

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Background: The immune mechanisms dictating response and resistance to PD-(L)1 blockade are not well understood in early stage non-small cell lung cancer (NSCLC). Understanding these mechanisms will be key to improve outcomes and identify the next generation of predictive biomarkers of response to these therapies. Here, we present updated immunophenotyping at time of interim analysis of LCMC3, a multicenter trial of neoadjuvant atezolizumab in resectable NSCLC (NCT02927301). **Method:** Patients received 2 cycles of atezolizumab before resection. Tumor, LN biopsies and PB were obtained pre-atezolizumab and at surgery. Paired PB, screening and surgical LN were analyzed using IMMUNOME flow

cytometry. Plasma-based cytokine arrays were performed on a subset of patients. Immunophenotypic analyses were correlated with treatment effect, major pathologic response (MPR, primary endpoint) and preoperative treatment-related adverse events (preop-TRAE). **Result:** We report on 55 patients with paired PB samples (analyzed within 72h after collection) and completed surgery. We observed preop-TRAE in 32/55 patients (18 grade 1, 13 grade 2, 1 grade 3). CD1c+ and CD141+ myeloid cells (MC) were lower at baseline in patients developing preop-TRAEs, while monocytic M-MDSCs were higher in those patients. Senescent T cells decreased in patients with preop-TRAE and increased in patients with non-preop-TRAE. After treatment, the absolute cell counts of late activated CD4+and CD8+T cells decreased in patients achieving MPR. LN IMMUNOME data, cytokine data and 12-month follow-up (DFS, OS) will be reported.

Conclusion: Preliminary immunophenotyping data from the interim analysis showed significantly lower baseline immunosuppressive cell subsets in patients with preop-TRAE and decreased late activated CD4+and CD8+T cells from PB in patients with MPR.These results, together with additional LN IMMUNOME and cytokine analyses, may improve our understanding of immunophenotypic features associated with outcome, and changes induced by neoadjuvant atezolizumab in early stage NSCLC patients.

Keywords: NSCLC, neoadjuvant anti-PD-L1 treatment, immunophenotyping

Table 1

Preop TRAE vs. non-Preop TRAE Patients at Baseline				
Representative Immune Cell Subset(s) in PB	Surface Markers	Median (min, max) cells/µl blood		Nominal p-value **
		Preop TRAE (n=32)	Non-Preop TRAE (n=23)	
CD141+ myeloid cells	CD141+ LIN- HLA DR+ CD33+ CD16+ CD11b+ CD15+	66.52 (0, 576)	95.77 (0, 380)	0.0162
CD1c+ myeloid cells	CD1c+ LIN- HLA DR+ CD33- CD16- CD11b- CD15+	45.14 (0, 507)	101 (0, 271)	0.0029
Monocytic M-MDSCs	CD33+ HLA DR- CD124- CD14+ CD11b+ CD66b- CD16- CD33+ CD15+	13.58 (0, 163)	4.73 (0, 30.96)	0.0253
Change in Preop TRAE vs. Non-Preop TRAE Patients after Treatment				
Representative Immune Cell Subset(s) in PB	Surface Markers	Median change (min, max)*		Nominal p-value
		Preop TRAE (n=32)	Non-preop TRAE (n=23)	
Senescent T cells	CD28- CD16- CD56- AND CD8+	-35.38 (-2445, 1930)	120 (-2193, 2175)	0.0265
Change in MPR vs. Non-MPR Patients after Treatment				
Representative Immune Cell Subset(s) in PB	Surface Markers	Median change (min, max)*		Nominal p-value
		MPR (n=9)	non-MPR (n=46)	
Late activated CD8+ T cells	CD107a/b- CD274- CD14- CD13- CD63- CD49a+ CD4- CD3+ CD8+	-16.44 (-192, 111)	1.62 (-255, 385)	0.0273
Late activated CD4+ T cells	CD107a/b- CD274- CD14- CD13- CD63- CD49a+ CD4+ CD3+ CD8-	-69.31 (-1420, 27.54)	2.61 (-1153, 1405)	0.0169
DC inducing Th1 response	CD141+ LIN- HLA DR+ CD33+ CD16+ CD11b- CD15-	27.78 (0, 152)	0 (-266, 947)	0.0490
CD141+ myeloid cells	CD141+ LIN- HLA DR+ CD33+ CD16- CD11b+ CD15+	319 (-49.57, 1550)	49.86 (-686, 851)	0.0122

Abbreviations:
DC- dendritic cell; TRAE – treatment-related adverse event; Th -T helper cell; M-MDSC- Monocytic myeloid-derived suppressor cell; MPR- major pathologic response; NK – natural killer cells; *cells/µl at surgery – cells/µl at screening; ** unadjusted for multiple comparisons

OA14 UPDATE OF PHASE 3 TRIALS AND THE ROLE OF HPD
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OA14.01 KEYNOTE-024 3-YEAR SURVIVAL UPDATE: PEMBROLIZUMAB VS PLATINUM-BASED CHEMOTHERAPY FOR ADVANCED NON–SMALL-CELL LUNG CANCER

M. Reck[1], D. Rodríguez-Abreu[2], A.G. Robinson[3], R. Hui[4], T. Csőszi[5], A. Fülöp[6], M. Gottfried[7], N. Peled[8], A. Tafreshi[9], S. Cuffe[10], M. O'Brien[11], S. Rao[12], K. Hotta[13], T. Garay[14], E. Jensen[14], V. Ebiana[14], J.R. Brahmer[15]

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TUESDAY, SEPTEMBER 10 11:30–13:00

OA14.02 IMPOWER131: FINAL OS RESULTS OF CARBOPLATIN + NAB-PACLITAXEL ± ATEZOLIZUMAB IN ADVANCED SQUAMOUS NSCLC

R. Jotte[1], F. Cappuzzo[2], I. Vynnychenko[3], D. Stroyakovskiy[4], D. Rodriguez Abreu[5], M. Hussein[6], R. Soo[7], H. Conter[8], T. Kozuki[9], K. Huang[10], V. Graupner[11], S. Sun[10], T. Hoang[10], H. Jessop[11], M. Mccleland[10], M. Ballinger[10], A. Sandler[10], M. Socinski[12]

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OA14 UPDATE OF PHASE 3 TRIALS AND THE ROLE OF HPD
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OA14.03 CLINICAL RATIONALE AND PRECLINICAL EVIDENCE FOR CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY CLINICAL TRIAL IN KRAS-MUTANT LUNG CANCER

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OA14.04 FIVE-YEAR OUTCOMES FROM THE RANDOMIZED, PHASE 3 TRIALS CHECKMATE 017/057: NIVOLUMAB VS DOCETAXEL IN PREVIOUSLY TREATED NSCLC

S. Gettinger[1], H. Borghaei[2], J. Brahmer[3], L. Chow[4], M. Burgio[5], J. De Castro Carpeno[6], A. Pluzanski[7], O. Arrieta[8], O. Aren Frontera[9], R. Chiari[10], C. Butts[11], J. Wojcik-Tomaszewska[12], B. Coudert[13], M. Garassino[14], N. Ready[15], E. Felip[16], M. Alonso Garcia[17], D. Waterhouse[18], M. Domine[19], F. Barlesi[20], S. Antonia[21], M. Wohlleber[22], D. Gerber[23], G. Czyzewicz[24], D. Spigel[25], L. Crino[5], W. Eberhardt[26], A. Li[27], S. Marimuthu[27], E. Vokes[28]

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OA14 UPDATE OF PHASE 3 TRIALS AND THE ROLE OF HPD
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OA14.06 HYPERPROGRESSIVE DISEASE IN ADVANCED NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

G. Lo Russo[1], D. Signorelli[1], C. Proto[1], G. Galli[1], A. Prelaj[1], R. Ferrara[1], M. Sommariva[1], M. Moro[1], V. Cancila[2], M. Ganzinelli[1], S. Brich[1], S. Sangaletti[1], G. Pruneri[1], C. Tripodo[2], M.P. Colombo[3], L. Rivoltini[1], A. Balsari[1], G. Sozzi[1], M. Boeri[1], M. Garassino[1]

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Background: Hyperprogressive disease (HPD) is a paradoxical boost in tumour growth described in a subset of cancer patients treated with immune checkpoint inhibitors (ICIs). **Method:** We retrospectively collected data about all consecutive patients with advanced Non-Small Cell Lung Cancer (aNSCLC) treated with ICIs at our Institution between 04/2013 and 12/2018. Patients were classified according to our previously published clinical/radiological criteria for HPD (Lo Russo G, *Clin Canc Res 2018*). (Table). All ICIs administered for ≥1 cycle were admitted. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analyses were performed with Cox hazard model.

Table HPD definition on the basis of 3 concomitant out of the five possible criteria

HPD CLINICAL & RADIOLOGICAL CRITERIA
Time-to-treatment failure < 2 months
Increase of ≥ 50% in the sum of target lesions major diameters between baseline and first radiological evaluation
Appearance of at least two new lesions in an organ already involved between baseline and first radiological evaluation
Spread of the disease to a new organ between baseline and first radiological evaluation
Clinical deterioration with decrease in ECOG performance status ≥ 2 during the first 2 months of treatment

Result: We reviewed 301 cases and 257 were evaluable for response. We identified four categories: responders (R, 57 cases, 22.2%), patients with stable disease as best response (SD, 69 cases, 26.8%), patients with progressive disease as best response (P, 78 cases, 30.4%) and patients with HPD (53 cases, 20.6%). Clinical/pathological variables were uniformly distributed among groups, except for a higher rate of patients with *Eastern Cooperative Oncology Group Performance Status* (ECOG-PS) >1 in HPD group (p = 0.0141). After a median follow-up of 23.49 months (IQR 10.72–44.21 months), median Progression-Free Survival (mPFS) and median Overall Survival (mOS) were 14,2 vs 6,5 vs 2,3 vs 1,5 months (p < 0.0001) and 32,5 vs 17,8 vs 7,8 vs 4,1months (p < 0.0001) in R, SD, P and HPD group, respectively. The multivariate analyses, between P and HPD groups, adjusted for ICIs line, number of metastatic sites and ECOG-PS according to PFS (HR 2.448, 95% CI 2.137-2.899, p<0.0001) and OS (HR 2.481, 95%CI 2.092-2.950, p < 0.0001) confirmed the worse outcome of HPD group. **Conclusion:** Our updated analysis confirmed patients with HPD as a distinct category that performs significantly worse than other groups, including P patients. The incidence of HPD in our cohort is relevant. The ICIs' detrimental effect has to be taken into account and further investigated.

Keyword: Hyperprogressive Disease, Non–small Cell Lung Cancer, Immune Checkpoint Inhibitors

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OA14.07 CLINICAL AND GENETIC CHARACTERIZATION OF HYPERPROGRESSION BASED ON VOLUMETRY IN ADVANCED NSCLC TREATED WITH IMMUNOTHERAPY

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Background: Hyperprogressive disease (HPD), characterized by accelerated tumor progression, has been proposed as a new pattern of progression following immune checkpoint inhibitor (ICI) treatment. The aim of this study was to describe the characteristics of HPD and investigate its predictive markers. **Method:** Clinical and radiological findings of 335 advanced non-small cell lung cancer (NSCLC) patients treated with ICI monotherapy were retrospectively analyzed. Radiological data were quantitatively and longitudinally analyzed for tumor size and volume by comparing baseline and follow-up computerized tomography results. The findings were matched to individual genomic profiles generated by deep sequencing of 380 genes. **Result:** Among 135 patients with progressive disease (PD), as assessed by RECIST, 48 (14·3% of total and 35·6% among PD) and 44 (13·1% of total and 32·6% among PD) were found to have HPD by volumetric (HPD_V) and one-dimensional (HPD_R) analysis, respectively. HPD_V patients were associated with significantly inferior overall survival (OS) compared with non-HPD_V PD patients (median OS (months), 4·7 [95% confidence interval (CI), 3·5–11·9)] vs. 7·9 [95% CI, 6·0–13·5], p=0·004); OS did not differ between HPD_R and non-HPD_R patients. HPD_V status was an independent OS factor. Derived neutrophil-to-lymphocyte ratio (dNLR) greater than 4 and lactate dehydrogenase (LDH) greater than the upper normal limit were significantly associated with HPD_V. Moreover, we identified coinciding *KRAS* and *STK11* mutations in the HPD_V cohort (3/16), while none were found in the non-HPD_V cohort (0/28). **Conclusion:** Defining HPD treated with ICI based on volumetric measurement is more precise than that based on one-dimensional analysis. Pre-ICI dNLR, LDH, and concurrence of *STK11* and *KRAS* mutations could, thus, be used as potential biomarkers for HPD prediction.

Keywords: hyperprogression, volumetry, Immunotherapy

OA15 OA15 TARGETED AGENTS AND IMMUNOTHERAPY FOR SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 10 14:30–16:00

OA15.01 COMBINATION OLAPARIB AND TEMOZOLOMIDE IN RELAPSED SMALL CELL LUNG CANCER: UPDATED RESULTS FROM PHASE 1/2 CLINICAL TRIAL

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Background: DNA damage repair inhibition is an emerging strategy for treating small cell lung cancer (SCLC). Combining poly(ADP-ribose) polymerase (PARP) inhibition with the DNA alkylating agent temozolomide has shown activity in both preclinical models and early phase clinical trials. **Method:** This is a single-arm phase 1/2 study combining the PARP inhibitior olaparib (tablet formulation) with temozolomide in patients with SCLC. Key eligibility criteria include histologically or cytologically confirmed incurable SCLC which progressed following ≥ 1 platinum-based chemotherapy. In cohort 1, olaparib and temozolomide are administered orally on days 1-7 of 21-day cycles. After cohort 1 completed enrollment, cohort 2 was added in a protocol amendment, in which olaparib is administered continuously days 1-21 and temozolomide is administered days 1-7 of 21-day cycles. For each cohort, the phase 1 portion is a conventional 3+3 design, with the primary objective to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). The primary objective of the phase 2 dose expansion portion is to determine the objective response rate (ORR). Response assessments are performed every 6 weeks, with treatment continued until progression, unacceptable toxicity, or investigator's discretion. Treatment post-progression is allowed for patients with ongoing clinical benefit. **Result:** Between October 2015 and April 2018, 50 patients were enrolled to cohort 1. The median age was 63 (range 39-85), median number of prior therapies was 2 (range 1-7), and 72% were platinum sensitive. The RP2D was olaparib 200 mg PO BID d1-7 and T 75 mg/m2 QD d1-7. The confirmed ORR was 41.7%. After a median follow-up of 7.1 months among 22 surviving patients, the median progression-free survival (mPFS) was 4.2 months, median overall survival (mOS) was 8.5 months, and median duration of response (mDoR) was 4.3 months. The ORR among platinum-sensitive and platinum-resistant patients was 47.1% and 28.6%, respectively, with no significant differences in mPFS, mOS or mDOR. The most common grade 3/4 treatment related adverse events were neutropenia (38%), anemia (28%) and thrombocytopenia (26%). Among 41 pts treated at the RP2D, dose reductions occurred in 44% overall and 64% of those who received at least 3 cycles. Enrollment to the phase 1 portion of cohort 2 began in November 2018 and is ongoing. Updated results from cohorts 1 and 2 will be presented at the meeting. **Conclusion:** Combination olaparib and temozolomide has an acceptable tolerability profile and shows promising clinical activity in relapsed SCLC. Clinical trials identifier NCT02446704.

Keywords: small cell lung cancer, olaparib, PARP Inhibitor

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OA15.02 CARBOPLATIN-ETOPOSIDE VERSUS TOPOTECAN AS SECOND-LINE TREATMENT FOR SENSITIVE RELAPSED SMALL-CELL LUNG CANCER: PHASE 3 TRIAL

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Background: Topotecan is currently the only drug approved in Europe in second line setting for small-cell lung cancer (SCLC). This study investigates whether the doublet carboplatin-Etoposide was superior to topotecan monotherapy as second-line treatment in patients with sensitive relapsed SCLC. **Method:** this open-label, multicenter, phase 3 trial randomized patients with SCLC that responded to first-line platin etoposide doublet treatment but showed evidence of disease relapse or progression at least 90 days after completion of the first-line treatment. Enrolled patients were randomly assigned (1:1) to receive combination chemotherapy (Six cycles of 3-weeks Carboplatin, AUC 5, day 1 and Etoposide 100 mg/Sqm/d 1-3, intra-venous) or oral Topotecan (2.3 mg/Sqm/d 1-5, every 3 weeks). Primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate (ORR), quality of life and tolerance in the intention-to-treat population, (clinical trialgouv: NCT02738346) **Result:** 178 patients were screened and 164 randomized in 36 centers, with 82 assigned to each treatment group (age: 64.5 ± 7.2 years, men: 72.8%, PS 0/1/>1: 34.7%/56.3%/ 9%. Median PFS was significantly longer in combination chemotherapy group (4.7 months, 95% CI: 3.9-5.5) compare to topotecan group (2.7 months, 95% CI: 2.3-3.2), HR: 0.6, 95% CI 0.4-0.8, p < 0.002. The ORR were significantly more important in the combination chemotherapy than in topotecan arm (ORR 49 % vs 25 %, p < 0,002), but without difference in term of median OS, 7.5 months (95% CI: 5.4-8.7) in combination chemotherapy group

versus 7.4 months (95% CI.6.0-9.3) in topotecan arm. Grade 3/4 neutropenia were significantly more common in the topotecan group than in the combination chemotherapy group (35.8% vs 19.7 %, p < 0.001. There is a non-significant trend for more febrile neutropenia in topotecan arm compare to combination arm (13.6 % 6.2 %, p = 0.19, and no difference for grade 3/4 thrombopenia, 35.8 % *vs* 30.9 %, and anemia, 24.6 % vs 21 %, for topotecan and combination arms, respectively. Two treatment-related deaths occurred in the topotecan arm (febrile neutropenia with sepsis), none in the combination arm. Results of quality of life outcomes will be presented at the meeting. **Conclusion:** platin–etoposide re-challenge can be considered as a standard second-line chemotherapy for sensitive relapsed SCLC.

Keywords: second line, phase 3 trial, Small Cell Lung Cancer,

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TUESDAY, SEPTEMBER 10 14:30–16:00

OA15.04 GENOMIC AND TCR INTRATUMOR HETEROGENEITY OF SMALL-CELL LUNG CANCER BY MULTIREGION SEQUENCING: AN ASSOCIATION WITH SURVIVAL

R. Chen[1], Y. Jin[2], J. Li[1], J. Zhang[1], J. Fujimoto[1], W.-C. Lee[1], X. Hu[2], Y. Chen[2], C. Behrens[1], C.-W. Chow[1], E. Parra[1], L. Little[1], C. Gumbs[1], X. Song[1], E. Roarty[1], J. Zhang[1], D. Gibbons[1], J. Heymach[1,3], J.J. Lee[1], W. William Jr[1], B. Glisson[1], I. Wistuba[1], P.A. Futreal[1], L. Byers[1], A. Reuben[1], M. Chen[2], J. Zhang[1]

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Background: Small cell lung cancer (SCLC) is an aggressive cancer. Although sensitive to initial therapy, recurrence is almost inevitable. The molecular mechanisms underlying recurrence are unknown. We have previously demonstrated that complex genomic and T cell receptor (TCR) intratumor heterogeneity (ITH) was associated with increased risks of relapse in non-small cell lung cancers (NSCLC). Genomic ITH and TCR architecture of SCLC and its clinical impact have not been well studied, largely due to lack of tumor specimens as surgery is rarely used to treat SCLC. **Method:** We performed multiregion whole-exome sequencing and TCR sequencing of 49 tumor samples from 18 resected limited-stage SCLCs to delineate the immunogenomic ITH of SCLC. We compared the results to those in NSCLC and assessed the association of genomic and TCR attributes with patient's survival. **Result:** On average, 544 mutations/sample were detected. The median proportion of trunk mutations (mutations identified in all regions within the same tumors) was 80.4% versus 70% in NSCLC (TRACERx, Jamal-Hanjani, NEJM, 2017, p=0.08) and all *TP53* and *RB1* mutations were trunk mutations, suggesting these mutations were early events during carcinogenesis of this cohort of SCLCs. A higher non-synonymous tumor mutational burden (TMB) was associated with a higher T cell density (infiltration) in the tumor (r=0.46, p=0.005). Compared to the TCR repertoire of NSCLC (Reuben, WCLC, 2017), these SCLC tumors demonstrated significantly lower T-cell density (0.05 *versus* 0.24, p<0.0001), richness (diversity, 1,043 *versus* 3,666, p<0.0001) and clonality (reactivity, average 0.02 *versus* 0.15, p<0.0001) despite similar non-synonymous TMB (average 187 in SCLC versus 176 mutations/sample in NSCLC). Only 0.2% to 14.6% of T cells were detectable across all regions from the same tumors, suggesting substantial TCR ITH. Jaccard index (JI), a parameter quantifying TCR ITH was significantly lower in SCLC than in NSCLC (0.06 versus 0.1, p<0.0001) implying higher level of TCR ITH in SCLC than NSCLC. Interestingly, higher T-cell density, richness or clonality appeared to be associated with lower risk of recurrence numerically. Furthermore, higher TCR JI (less degree of ITH) was associated with significantly longer overall survival (HR=0.15, p=0.04). **Conclusion:** Limited-stage SCLC tumors have distinct TCR repertoire and genomic ITH architecture. Overall, SCLC may have a more pronounced immunosuppressive microenvironment and higher level of TCR repertoire ITH than NSCLC. Nevertheless, higher degree of T cell infiltration and clonal expansion as well as more homogeneous T cell response may be associated with more favorable clinical outcome in patients with limited-stage SCLC.

Keywords: small cell lung cancer, intratumor heterogeneity, T cell repertoire

OA15 TARGETED AGENTS AND IMMUNOTHERAPY FOR SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 10 14:30–16:00

OA15.05 BIOLUMA: A PHASE II TRIAL OF NIVOLUMAB AND IPILIMUMAB IN LUNG CANCER – PROSPECTIVE EVALUATION OF TMB IN SCLC PATIENTS

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Background: Therapeutic options and prognosis for patients with small-cell lung cancer (SCLC) remain poor. Treatment with checkpoint inhibition can achieve remarkable responses, but this holds true for a small percentage of SCLC patients only. Recently, tumor mutation burden (TMB) emerged as promising predictive biomarker for nivolumab and ipilimumab combination therapy in terms of tumor response and overall survival in SCLC patients. Here, we present the SCLC TMB cohort of the BIOLUMA trial, which prospectively evaluates TMB as predictive biomarker in SCLC patients. **Method:** BIOLUMA is an investigator initiated multicentre non-randomised phase II trial in 2nd line patients with SCLC. The initial all-comer SCLC cohort was recently amended for inclusion of patients with high TMB only. FFPE tumor tissue is used for TMB pre-screening by whole exome sequencing (WES) at time of first diagnosis. After progression on platinum-based therapy, 4 cycles of nivolumab 1 mg/kg q3w in combination with ipilimumab 3 mg/kg q3w and subsequent nivolumab 240 mg flat dose as monotherapy are given. Primary endpoint is overall response rate (ORR) of the combination therapy. Analysis of sequential tumor biopsies, blood and gut microbiome is performed at different timepoints. **Result:** The SCLC cohort was amended to include TMB high patients only, after two treatment-related deaths in the SCLC all-comer cohort had occurred and emerging data indicated treatment benefit depends on high TMB status for the combination therapy. TMB analysis seems to be feasible for most patients without the necessity of performing an additional tumor biopsy as evaluation of TMB on FFPE tumor tissue which was obtained at first diagnosis was sufficient in 90.1% of cases. To date, 53 patients are enrolled for pre-screening, sequencing result ist pending for 33 and TMB status has been determined for 20 patients. Of these, 45% belong to the TMB high group, while 55% have low or medium TMB. TMB pre-screening for the amended cohort is ongoing and enrolment of TMB high patients in the BIOLUMA trial recently started. **Conclusion:** Combination therapy of nivolumab and ipilimumab shows remarkable clinical results, but is accompanied by high toxicity rates. Thus, in order to ensure a reasonable balance of risks and treatment benefits, it is an unmet need to evaluate predictive biomarker with TMB being the most promising which recently emerged in SCLC. To our knowledge, this is the first clinical trial which prospectively evaluates tumor mutation burden as predictive biomarker in SCLC patients. TMB screening is feasible on tumor material which is routinely obtained at first diagnosis.

Keywords: Tumor Mutation Burden, Immunotherapy, SCLC

Mini Oral Sessions

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.01 SAFETY OF PEMBROLIZUMAB COMBINED WITH STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) FOR PULMONARY OLIGOMETASTASES

S. Siva[1,2], M. Bressel[2], S. Loi[1], S. Sandhu[2], B. Tran[2], J. Mooi[2], J. Lewin[2], A. Azad[2], D. Colyer[2], M. Shaw[2], S. Chander[2], K. Cuff[3], S. Wood[3], N. Lawrentschuk[1], D. Murphy[1], D. Pryor[3]

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Background: Pembrolizumab has demonstrated safety and efficacy in a broad range of tumors. However, safety concerns exist around the combination of pembrolizumab and high dose radiotherapy to the lung, particularly as both have independent risk of pneumonitis. In this interim analysis we assess the safety profile of combination pembrolizumab and SABR to pulmonary oligometastases. **Method:** As part of the ongoing prospective dual-institutional RAPPORT clinical trial (clinicaltrials.gov ID NCT02855203), patients with 1-5 oligometastases from renal cell carcinoma were enrolled between Nov 2016- April 2019. All participants had ECOG performance status 0-1, and signed informed consent. Patients with at least 1 lung oligometastasis were included in this analysis. All patients were planned for a single fraction of 20Gy SABR to each lung oligometastasis, followed 5 days (+/-3 days) later by 8 cycles of 200mg i.v. 3-weekly pembrolizumab (total 24 weeks). When SABR dose constraints were not achievable, conventional hypofractionated radiotherapy could be delivered. At least 1 oligometastasis needed to receive SABR. Adverse events (AEs) were recorded using CTCAE V4.03 until 30 days post last dose of pembrolizumab, and late AEs atrributable to SABR for 24 months after SABR. **Result:** 20 patients with a combined total of 41 lung oligometastases were included in this analysis. The mean age was 61 years, with 15 (75%) male. The number of lung oligometastases were 1 in 9 (45%), 2 in 3 (15%), 3 in 6 (30%), 4 in 2 (10%) patients. SABR was delivered to 39 lung oligometastases (95%) and conventional radiotherapy to 2 oligometastases (5%) using 10 fractions of 3Gy. Twelve patients have completed all eight cycles of pembrolizumab, with five patients having ongoing treatment. Three patients ceased treatment early due to grade 3 pneumonitis (15%) after 3, 6 and 7 cycles of pembrolizumab respectively. These patients had 1, 2 and 1 lung oligometastases, respectively. The worst grade of any treatment related AEs was grade 3 in 4 pts (20%), with 3 attributed to both SABR and pembrolizumab, and 1 atributed to pembrolizumab alone. Three of the four grade 3 events were pneumonitis. A further 3 patients had grade 2 AEs(15%), and 8 patients had grade 1 AEs(40%). There were no grade 4 or 5 adverse events, and five patients (25%) had no treatment related adverse events. **Conclusion:** SABR to lung oligometastases in combination with pembrolizumab was well tolerated, with clinically acceptable rates of grade 3 pneumonitis compared to historical rates reported with pembrolizumab monotherapy.

Keywords: Oligometastases, stereotactic radiotherapy, Immunotherapy

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.02 LUNG STEREOTACTIC BODY RADIOTHERAPY AND CONCURRENT IMMUNOTHERAPY: A MULTI-CENTER SAFETY AND TOXICITY ANALYSIS

S. Tian[1], J. Switchenko[2], P. Patel[1], J. Shelton[1], S. Kahn[1], R. Pillai[1], C. Steuer[1], T. Owonikoko[1], M. Behera[1], W. Curran[1], K. Higgins[1]

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Background: Radical treatment of metastases with stereotactic body radiotherapy (SBRT) in patients with advanced malignancies is an emerging treatment paradigm. SBRT is increasingly used in patients receiving immune checkpoint inhibition (ICI); however, limited toxicity data for this treatment approach exists. The purpose of this study was to evaluate the safety and tolerability of lung SBRT with concurrent ICI. **Method:** Records from a single academic institution were reviewed to identify patients treated with lung SBRT and concurrent (within 30 days) ICI; a contemporaneous cohort receiving lung SABR without ICI were included as a reference cohort. Treatment-related adverse-effects (AE) occurring within 30 days (acute) and 180 days (subacute) of SBRT were graded via CTCAE v5.0. **Result:** 110 patients were included; 47 received SBRT with concurrent ICI (49 SBRT courses, 61 lesions) between August 2015 and January 2019. 63 received SBRT without ICI (68 courses, 79 lesions). For the SBRT+ICI cohort, median age at treatment was 64 years, median follow-up was 6.7 months. 70% were lung, 15% were melanoma, 6.4% were from head and neck primaries. 90% were treated for metastatic consolidation/oligo-progression, 10% received SBRT for locally advanced/recurrent disease. 65.3% of patients received prior RT. 36.7% received prior lung RT, 40% of which were overlapping. 67% received ICI monotherapy, 16% ICI/chemotherapy, and 16% ICI/ICI combinations. 24.5% received ICI between SBRT fractions; 38.8% received ICI both before and after SBRT. Grade 3 (G3) and any grade pneumonitis rates were 8.2% and 30.6%; there were no G4-5 events. ICI was discontinued due to toxicity in 22.4% of patients. Receipt of ICI/ICI combinations increased the risk of any grade pneumonitis (62.5% vs 24.4%, p=0.04); but not G3 pneumonitis. Risk of G3 pneumonitis was higher in the SBRT+ICI vs SBRT alone cohort (8.2 vs 0%, p=0.03); but not any grade pneumonitis (30.6% vs 29.9%, SBRT+ICI vs SBRT p=0.75). Median time to onset was 3.4 months from end of SBRT in both groups. Risk of G3 and any grade pneumonitis was not predicted by ICI agent, timing of ICI administration, prior RT, prior lung RT, lesion centrality, number of target lesions, or smoking status. Overall acute G3+ AE rates were 2% (SBRT+ICI) and 0% (SBRT). Subacute G3+ AEs occurred in 26.5% (SBRT+ICI) and 2.9% (SBRT) of patients. **Conclusion:** Concurrent ICI, especially ICI/ICI combinations, increased the risk of G3 pneumonitis with lung SBRT. However, SBRT+ICI appears safe and tolerable compared to SBRT alone. Strategies integrating SBRT and ICI warrant additional investigation.

Keywords: Immunotherapy, pneumonitis, SBRT

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.03 INTERIM SAFETY ANALYSIS OF THE PHASE IB TRIAL OF SBRT TO ALL SITES OF OLIGOMETASTATIC NSCLC COMBINED WITH DURVALUMAB AND TREMELIMUMAB

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Background: Oligometastatic NSCLC represents a unique subset of patients (pts) with limited burden of metastatic disease. Prior early studies have demonstrated that combining local ablative and systemic therapies in pts with oligometastatic disease leads to improved progression-free survival (PFS). The immunostimulatory effects of SBRT and potential synergy with immune checkpoint inhibitors has prompted enthusiasm in combining the two; however, the toxicity is unknown. **Method:** In this phase Ib study, a cohort of 21 pts with oligometastatic NSCLC receive SBRT to all sites of disease between 30 and 50 Gy in five fractions and durvalumab 1500 mg IV + tremelimumab 75 mg IV every 4 weeks x 4 cycles in a sequential fashion, followed by durvalumab maintenance until progression, unacceptable toxicity or patient wishes. Eligible patients had 1-6 metastatic extracranial lesions, all of which were suitable for SBRT, ECOG performance status 0-1, no actionable driver mutation, and no prior immunotherapy.The primary endpoint is safety of this combination. The period for evaluating dose-limiting toxicities (DLTs) is from the time of first administration of SBRT until 28 days post completion of the first dose of durvalumab and tremelimumab. Grading of DLTs follows CTCAE version 4.03. A DLT will be defined as any Grade≥ 3 toxicity. Secondary endpoints include PFS and overall survival. Correlative studies of baseline TMB, PD-L1 expression on post-SBRT biopsy and immune biomarkers on circulating tumor cells will be correlated with outcomes. In this interim analysis, we assess the safety of the first nine patients enrolled. **Result:** Nine pts enrolled from 2/2018-3/2019. Median follow-up: 2.8 months (range 1.5-8.2 months). Characteristics included: median age 72 years (range 56-

81 years), female/male 2/7, squamous/nonsquamous 2/7, median number of sites treated 2, CNS involvement 3/9. Most toxicities were Grade (G) 1/ 2. Severe adverse events (AEs) included: G4 elevated CK (1). Severe immune-related (ir)AEs: G3 rash (1), G3 AST (2), G3 ALT (1), G3 amylase (1), G3 lipase (1). One DLT reported due to grade 3 AST > 7 days (recovered). One additional pt discontinued treatment due to grade 3 irAE. There were no treatment-related deaths. Two patients (22%) died of disease progression. **Conclusion:** There were no unexpected safety signals in the first nine patients enrolled. The incidence of grade 3 or greater irAEs was similar to those seen in the treatment of advanced NSCLC, and no additional toxicity is observed with the addition of SBRT to date. The study continues to enroll and results will be updated.

Keywords: Oligometastatic NSCLC, SBRT, immunotherapy

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.05 PROGRESS OF ACCOMPANYING GGN BEYOND PULMONARY RESECTION FOR NON-SMALL CELL LUNG CANCER

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Background: The aim of this retrospective study was to review the natural course of synchronous ground-glass nodule (GGN), which was left after the curative resection of non-small cell lung cancer (NSCLC) in other lobe. **Method:** Between 2008 and 2017, a prospectively collected retrospective data of 2276 patients who underwent curative resection for NSCLC was reviewed. Among them, GGN was detected in 126 patients beside resected lung. Defined by high-resolution computed tomography (HRCT) or thin-section of computed tomography (CT), twenty patients with nearly solid nodule or GGN with higher CT ratio (> 0.75) was excluded, thereafter the data of 98 patients (4.3%) was included in the study. Demographic data of patients including age, gender, and smoking history were collected for analysis. In addition, risk factor including characteristics of GGN, histopathology and staging of resected tumor, adjuvant treatment, and any other medical history were evaluated for risk factor analysis. **Result:** Median duration of follow-up was 36 months (range; 11 – 120). The size of GGN has been decreased in 10 patients (10.2%), stationary 48 patients (50.0%), while an increasing in size of GGN was observed in 40 patients (40.8%). Among them, five patients were recommended reoperation (12.5%), and the other 35 patients were in clinical observation (87.5%). In mutivariate analysis, existence of solid component, smoking history, and multiple GGNs in one lobe were independent prognostic factor.

Table : Multivariate binary logistic analysis of tumor growth

Variables	All tumor[a]			Adenocarcinoma		
	HR	CI	p-Value	HR	CI	p-Value
Age at diagnosis	1.04	0.98 – 1.09	0.174	1.03	0.97 – 1.09	0.356
Part-solid GGN	3.22	1.08 – 9.56	0.036	4.11	1.29 – 13.12	0.017
Male gender	1.81	0.56 – 5.83	0.320	1.68	0.50 – 5.63	0.397
Smoking[b]	3.45	1.33 – 8.98	0.011	5.10	1.76 – 14.80	0.003
Multiple GGNs in one lobe	0.08	0.01 – 0.74	0.026	0.07	0.01 – 0.69	0.023

a. Histopathology of primary resected tumor

b. Smoking history more than 10 pack-year

GGN : ground-glass nodule

HR : hazard ratio

CI : confidence interval

Conclusion: During the follow-up, 40.8% of GGN showed a growth in size, emphasizing that patients with part-solid GGN and with smoking history should be in careful observation.

Keywords: Ground-glass Nodule, Non-Small Cell Lung Cancer, Postoperative surveilance

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.06 PROGNOSTIC FACTORS OF OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER FOLLOWING RADICAL THERAPY: A MULTICENTER-ANALYSIS

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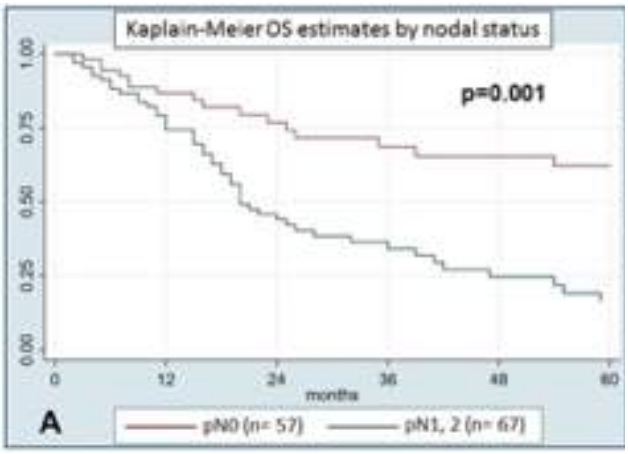
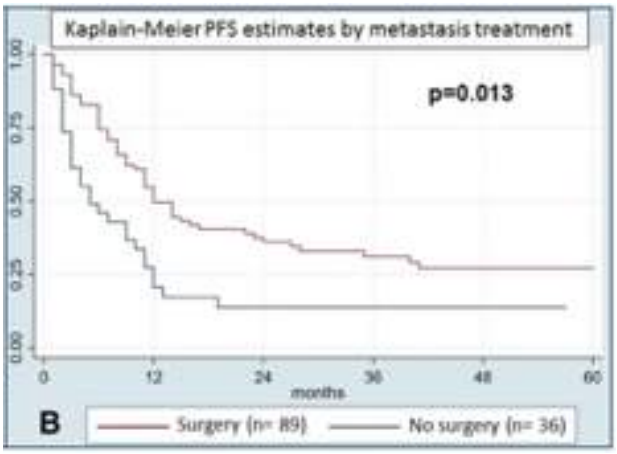
Background: Patients with oligometastatic non-small cell lung cancer (NSCLC) may benefit from radical therapy. We aimed to identify factors related to better prognosis, in a multicenter analysis of patients who underwent surgery of primary tumours, in combination with radical treatment of metastatic sites, and chemo- or chemoradiation. **Method:** We retrospectively reviewed the records of oligometastatic patients who all underwent anatomical resection of primary tumor, treated at 4 centers, (August 2001-November 2018). Oligometastasis was defined as ≤5 synchronous metastases in ≤2 organs. Radical metastatic treatment was surgery (n=48), radiotherapy (n=36) or a combination (n=41). Univariate analysis and multivariate Cox proportional hazards model were used for identification of prognostic factors on overall survival (OS) and progression-free survival (PFS). Survival was estimated by Kaplan-Meier analysis. P-value < 0.05 was considered significant. **Result:** We treated 125 patients; 72 (58%) were male, aged 60±9.8 years, with 88 (70%) adenocarcinoma, and following pathological (pN) stage: pNx: 1 (1%), pN0: 57 (46%), pN1: 23 (18%), pN2: 44 (35%). Brain metastasis was most common (n=76; 61%) followed by adrenal (n=13; 11%) and bone (n=12; 10%). Systemic therapy was administered in 102 (82%). Median follow-up was 60 months (95%, CI: 41-86). One-, 2-, 3-, and 5-years OS was 80%, 58%, 49% and 36% respectively. Several patient-related and treatment-related factors showed a correlation with OS at univariate analysis. Multivariate analysis showed that patients ≤60 years (HR 0.47, 95% CI:0.28-0.78, p=0.004), and/or pN0, compared to pN1,2 (HR 0.38, 95% CI: 0.22-0.66, p=0.001), had a significant survival benefit (Figure 1A). Bone metastasis were associated with worse prognosis (HR 2.122, 95% CI: 1.00-4.48, p=0.05). Twenty-eight patients were ≤60 years with pN0, and had 1- and 5-year survival of 100 and 83%. PFS at 1-, 2-, 3- and 5-years was 41%, 29%, 25% and 23% respectively. In the multivariate analysis, absence of mediastinal lymphnode involvement (HR: 0.483, 95% CI: 0.305-0.764, p=0.002) and surgical treatment of metastasis (HR: 0.553, 95% CI: 0.347-0.880, p=0.013) remained independently associated with better outcome (Figure 1B). The administration of treatments after first progression was strongly associated with better prognosis (HR: 0.252, 95% CI: 0.076-0.834, p=0.013).





Conclusion: Our experience demonstrates, in a multicenter setting, that radical treatment of selected oligometastatic NSCLC results in excellent 5-year survival. Nodal status correlates with both OS and PFS. Surgical metastasectomy appears to improve PFS, but multimodality treatment, especially in case of recurrence, remains mandatory. These data might contribute to develop future combined strategies in the era of immunotherapy.

Keywords: synchronous oligometastasis, surgical therapy, multimodality treatment

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.07 PROGNOSTIC FACTORS OF SURGICAL TREATMENT IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS IN OLIGOMETASTATIC STAGE-M1B OF DISEASE

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Background: Non-small cell lung cancer in stage IV is rarely the subject of surgical treatment. Most cases are considered as inoperable and qualified for palliative treatment. Long-term results in this group of patients are poor despite systemic oncological treatment. A special group of patients are patients with a single metastasis beyond the lung (grade M1b), in which in some cases surgery may significantly improve the prognosis. The aim of the study was to determine the prognostic factors of surgical treatment of non-small cell lung cancer in stage IVA with a single distant metastasis (oligometastatic stage-M1b) **Method:** A retrospective study was based on data from the National Register of Cancer of the Lung conducted by the Polish Group of Lung Cancer. The study included 387 patients (242 men and 145 women) between 41 and 87 years of age (median 60.4 +/- 8.4 years) with established NSCLC and single synchronous metastasis most often to: second lung (55.5%), brain (24.8%) and adrenal glands (14.5%). All patients underwent resection of the pulmonary parenchyma and resection of the metastatic focus. The size of the primary tumor was respectively: 1-2 cm in 16.0%, 2-3 cm in 26.4%, 3-5 cm in 23.5%, 5-7 cm in 12.4% 7-10 cm in 14, 0% and over 10cm in 7.8%. The features of N0, N1, and N2 were diagnosed in 69.8%, 15.5% and 14.7% of patients respectively. Radical oncology R0, R1 and R2 were obtained in 96.1%, 2.1% and 1.8% of cases respectively. Anatomical resection was performed in 70% and minor resection in 30% of patients. Preoperative chemotherapy was used in 7.5% of cases, and postoperative in 21.2% of patients. **Result:** The 5-year survival in the entire M1b group was 27.3%. Multivariate analysis showed that the negative prognostic factors were male gender (HR = 1.56, 95% CI-1.16-2.1, P <0.003), age> 50 (HR = 1.39, 95% CI-0.87-2.22, P <0.002), tumor size (HR = 34.32, 95% CI-2.39-7.82, P <0.001), feature N1 (HR = 1.53, 95% CI-1.02-2.29, P <0.04) and the N2 trait (HR = 2.71; 95% CI -1.8-4.06, P <0.001). Patients undergoing anatomical resection vs lower (HR = 0.5, 95% CI-0.35-0.72, P <0.001) and postoperative preoperative chemotherapy (HR = 0.69, 95% CI-0.48-0.97, P <0.034) have better prognosis. The number of lymph nodes removed during the procedure is also significantly affected - 5-year survival at 1-5 removed nodes was 24.6%, and in the case of 6-10 nodes 32.4%. **Conclusion:** Surgical treatment of NSCLC in the M1b stage in a selected group of patients allows for the improvement of long-term results. Negative prognostic factors are gender, age, tumor size and metastases to lymph nodes. The scope of resection in this group of patients should be the same as in the lower stages with the predominance of anatomical resection and mediastinal lymphadenectomy. Post-operative chemotherapy may have a beneficial effect on long-term results.

Keywords: metastatic lung cancer, surgery

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.09 CONCOMITANT SBRT AND EGFR-TKI VERSUS EGFR-TKI ALONE FOR OLIGOMETASTATIC NSCLC: A MULTICENTER, RANDOMIZED PHASE II STUDY

P. Peng[1], Y. Chen[2], G. Han[3], R. Meng[4], S. Zhang[4], Z. Liao[5], Y. Zhang[1], J. Gong[1], C. Xiao[3], X. Liu[3], P. Zhang[1], L. Zhang[1], S. Xia[1], Q. Chu[1], Y. Chen[1], L. Zhang[1]

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Background: NSCLC patients harboring EGFR mutation generally develop resistance to EGFR TKI less than one year. Prior studies indicated that local consolidative therapy is associated with improved outcomes in patient with limited metastatic NSCLC. Radiotherapy is one of the ideal control methods for locally progressed patients, however, the optimal intervention time in order to slow the occurrence of EGFR-TKI resistance for advanced NSCLC patients with EGFR-sensitive mutations is still unclear. Our preliminary clinical and animal studies suggest that early combined radiotherapy prior to EGFR-TKI resistance can significantly improve the prognosis of patients. Our hypothesis is that the optimal intervention time of radiotherapy for EGFR mutation patients is 3 months after the beginning of EGFR-TKI. **Method:** This is a prospective, multicenter, randomized controlled study to evaluate stereotactic body radiation therapy (SBRT) as a potential treatment for limited stage IV NSCLC (primary plus up to 3 metastatic sites) with sensitive EGFR mutation. The patients did achieve partial response or stable disease after three months treatment of the first-generation EGFR-TKI would be randomized to TKI combined SBRT (TS) or TKI alone. The primary endpoint was PFS (the time from the beginning of EGFR-TKI treatment to disease progression or death). The secondary endpoint was overall survival (OS) and safety. TKI wasn't interrupted during the irradiation. **Result:** A total of 61 patients were enrolled from Feb, 2017 to Jan, 2019. Median follow up was 22.3 months. Patients who TS (n: 30) had a significantly longer median PFS compared to those with TKI alone (n: 31) (PFS: 17.4 vs. 8.9 months P =0.042). T790M mutation was observed in 57.9% acquired resistance patients for TS group, and 39.3% for TKI alone group. Median PFS of T790M mutated patients was 17.4 months compared to 10.3 months of TKI alone group (P = 0.007). Multivariable analysis revealed that radiation fields were positively associated with PFS, 21.8 months for just primary tumor; 10.6 months for metastatic lesions and 18.3 months for primary and metastatic lesions (P= 0.006). OS data was not yet mature. None experienced >= grade 3 SBRT related toxicities. **Conclusion:** A trend of improved long term PFS was noted in patients receiving SBRT for primary tumor combined EGFR TKI at the third month after the beginning of TKI. Moreover, this data suggested that benefit from radiation might be associated with delay the occurrence of T790M mutation. Further studies are required to investigate the molecular mechanisms underlying this association. Clinical Trial information: NCT03595644

Keywords: SBRT, TKI, oligometastatic NSCLC

MA01.10 ADDITIONAL LOCAL CONSOLIDATIVE THERAPY SHOWED SURVIVAL BENEFIT THAN EGFR-TKIS ALONE IN BONE OLIGOMETASTATIC LUNG ADENOCARCINOMA PATIENTS

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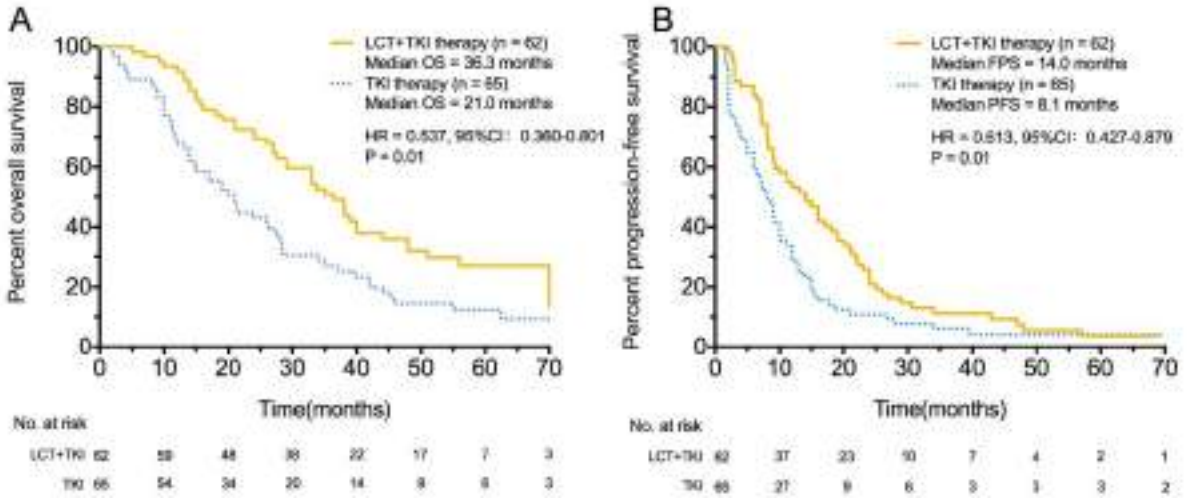
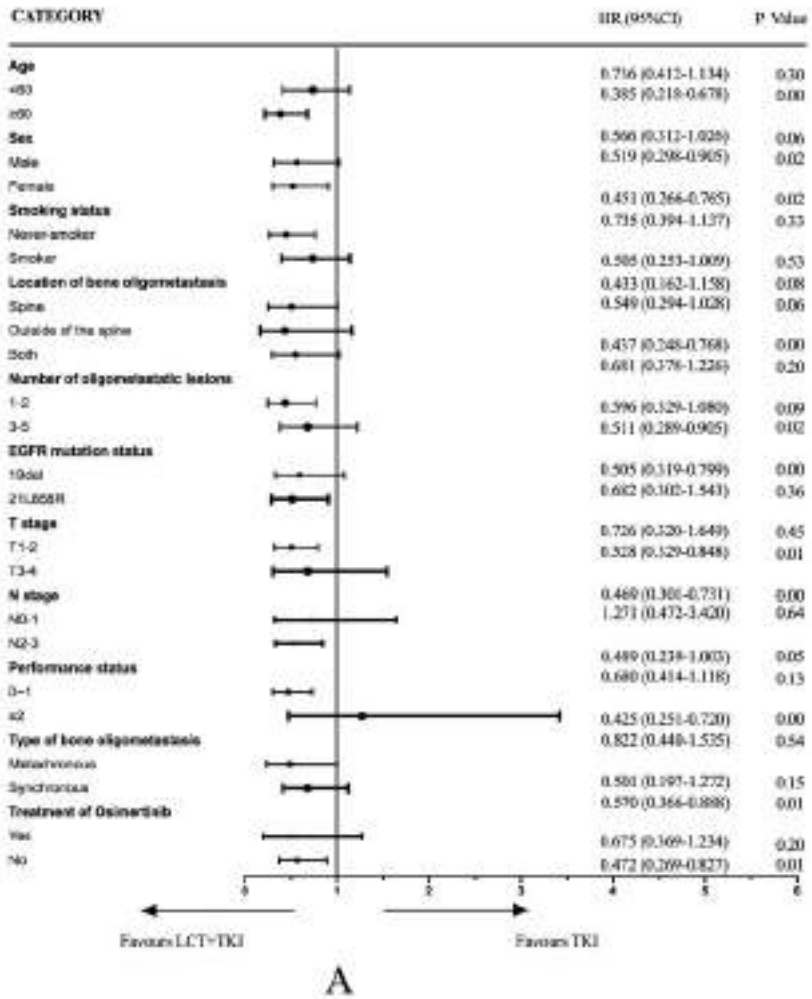
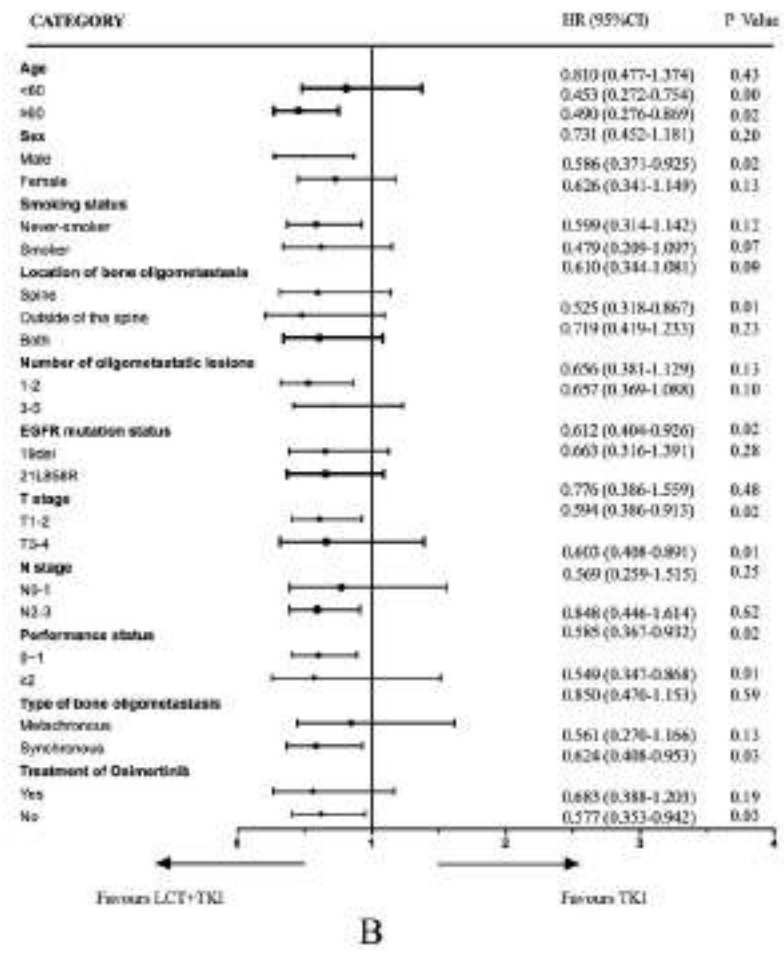
Background: Whether epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKIs) plus local consolidative therapy (LCT) has better survival benefit than EGFR-TKIs alone remains controversial in lung adenocarcinoma patients with EGFR mutation and bone oligometastases. **Method:** We conducted a retrospective study to assess the effects of LCT on bone oligometastases lung adenocarcinoma patients with EGFR mutation. The primary endpoint was overall survival (OS); The secondary endpoints was progression-free survival (PFS). **Result:** A total of 127 lung adenocarcinoma patients with EGFR mutation and bone oligometastases were identified. There were 65 patients received EGFR-TKIs alone (monotherapy group) and 62 patients received EGFR-TKIs plus local consolidative therapy (LCT) (combination group). Addition of LCT was associated with a significantly longer OS (36.3 *vs.* 21.0 months, P=0.01, hazard ratio [HR]=0.537, 95% confidence interval [CI]:0.360-0.801, p=0.01) and PFS (14.0 *vs.* 8.1 months, P=0.01, HR=0.613, 95%CI: 0.427-0.879, p=0.01) in the whole cohort (Figure 1). All subgroups showed OS benefit in faver of combination therapy except for PS scores greater than or equal to 2 group, and all subgroups analyzed derived PFS benefit in favor of combination therapy (Figure 2). **Conclusion:** In patients with EGFR-mutant lung adenocacinoma and bone oligometastases, LCT plus EGFR-TKIs therapy was associated with significantly longer OS and PFS than EGFR-TKIs therapy alone, indicating that LCT plus EGFR-TKIs therapy might be a better therapeutic option for those patient population.







B

Keywords: Bone oligometastases, Local consolidative therapy, Epidermal growth factor receptor mutation

MA01 OLIGOMETASTATIC DISEASE
SUNDAY, SEPTEMBER 8 10:30–12:00

MA01.11 IMPROVING SURVIVAL IN LUNG CANCER PATIENTS WITH OLIGOMETASTATIC DISEASE PROGRESSION USING STEREOTACTIC BODY RADIATION THERAPY

L. Raez[1], M. Castillo[2], A. Botero[1], A. Falchook[3], I. Castellon[3], B. Hunis[1]

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Background: In patients (pts) with stage IV non-small cell lung cancer (NSCLC) receiving systemic therapy, stereotactic body radiation therapy (SBRT) can eliminate oligometastatic disease progression (OMP). This allows NSCLC pts to continue the same systemic therapy, and its is especially important when the therapy is well tolerated as is the case for many pts receiving immunotherapy (IMMUNO) and targeted therapy (TARGET). The purpose of this study is to quantify the progression free survival (PFS) and overall survival (OS) of pts receiving systemic therapy who experience OMP that is treated with SBRT, and subsequently continue the same systemic therapy. **Method:** Retrospective review of one hundred pts with metastatic NSCLC undergoing chemotherapy (CHEMO), IMMUNO or TARGET that had OMP defined as less than 4 sites of metastasis and underwent SBRT were evaluated for PFS and OS. PFS1: Time between initiation of systemic therapy and development of OMP. PFS2: Time between OMP treated with SBRT and development of further PD requiring a change in systemic therapy. Pts received IMMUNO for second line and beyond. SBRT doses were determined based on the disease site and dose tolerance of the adjacent organs. SBRT was delivered in 1-5 fractions on consecutive days or every other day. Radiation dose was determined by target volume and adjacent dose-limiting organs. **Result:** OMP presented as brain metastasis (BM) in 45 pts and extracranial metastasis (EM) in 55 pts. 34 pts were receiving CHEMO, 34 TARGET and 32 IMMUNO at the time of OMP. Pts with BM that received SBRT were able to continue the same therapy for a period of 6.5-9 extra months due to the control of BM. Pts with EM that have developed PD were able to continue the same therapy an 17-21 extra months due to the ablation of OMP by SBRT. For the entire cohort PFS was: 16.5m for BM and 34m for EM and the OS were: 31m and 53m respectively.

Location of oligo-metastatic progression (OMP)	Median PFS1	Median PFS2	PFS	Median OS
Extracranial (N=55)	13	21	34	53
chemo	7	17	24	47
Immuno	13.5	20.5	34	49
Target	12	21	33	53
Brain (N=45)	9	7.5	16.5	31
Chemo	5.5	6.5	12	25.5
Immuno	7	8	15	27
Target	11	9	20	47

Conclusion: PFS and OS may be prolonged due to the use of SBRT in pts that develop OMP. This intervention allowed patients to continue with the same systemic treatment. Our CHEMO cohort is composed of long term survivors under therapy and may not represent the average PFS/OS of pts on CHEMO. Prospective trials are needed to verify these results.

Keywords: Radiation therapy, oligometastatic disease, Immunotherapy

MA02.01 RECCURRENCE PATTERN AFTER ADJUVANT CUSTOMIZED CHEMOTHERAPY BASED ON BRCA EXPRESSION LEVEL (SCAT TRIAL)

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Background:•Postop platinum-based CT improves outcomes in completely resected NSCLC with nodal involvement, (St II-IIIA). Customization is feasible in adjuvant setting (tissue availability). Analysis of expressionin genes involved in DNA repair could be use to select CT regiment. •BRCA1 plays an important role in DNA repair pathways and functions as a differential regulator of response to cisplatin and antimicrotubuleagents. SCAT trial results found that for low BRCA1 levels subgroup Cis-Gemcitabine was superior to Cis-Docetaxel and in high BRCA1 levels subgroup Docetaxel single agent without platinum achieved similar survival to Cis-Doc. Analysis of recurrence pattern in different subgroups of the trials has been performed **Method:** From Jun/2007 to May/2013 591 patients were screened and 500 p were included (108 in Control arm treated with Cisplatin-Docetaxel and 392 in Experimental arm treated with Cisplatin-Gemcitabine, Cisplatin-Docetaxel or Docetaxel alone according terciles BRCA1 expression level). With a cut-off September 30th 2018 and a median follow-up of 60 months, recurrence pattern are analysed in each arm and subgroup treatment and comparison are made for incidence of risk of recurrence, single/multiple recurrence, thoracic/extrathoracic and site of metastases (liver, bone, brain) **Result:** Cumulative recurrence 232/456 evaluable patients (p) (50.8%). Recurrence were seen in 182/354 patients treated in experimental arm and in 50/102 p treated in the control arm (RR 1.04; 0.83-1.30) (p=0.672). Majority of recurrences 159/232 (68.5%) were single site recurrence. Intrathoracic recurrences in 121/232 (52%) while extrathoracic metastatic disease 111/232 (47.8%). No significant differences were seen for single/multiple, intra/extrathoracic recurrences between experimental and control arm. More frequent distant metastatic sites were: bone (42 p), brain (38 p) and liver (11 p) In the experimental group between different treatments no significant differences were found for the overall metastatic rate or for the single/multiple, intrathoracic/extrathoracic recurrences. For specific metastatic sites related to experimental treatment a significant reduction of risk of brain metastases were found in the experimental group with high level BRCA1 treated with Docetaxel single agent (p=0.0016) **Conclusion:** For NSCLC resected patients with lymph node involvement (Stages II-IIIA) risk of recurrence remains high with cumulative rate > 50%. There were no differences in the Relative Risk (1.04) of recurrence when control and experimental arm are compared. Majority of recurrences were single site (68.5%) and intrathoracic (52%) but distant metastases developed in 47.8% os p. More frequent metastatic site was bone, followed by brain and liver. Brain metastases risk were significant lower for patients with low BRCA1 expression treated with single agent Docetaxel

Keywords: Brain metastases, adjuvant chemotherapy, Recurrence pattern

MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.02 TOXICITY OF LUNG SABR IN PATIENTS WITH COEXISTING INTERSTITIAL LUNG DISEASE

T. Finazzi[1], M. Ronden[2], E. Nossent[2], H. Tekatli[2], I. Bahce[2], B. Slotman[2], F. Spoelstra[1], S. Senan[1]

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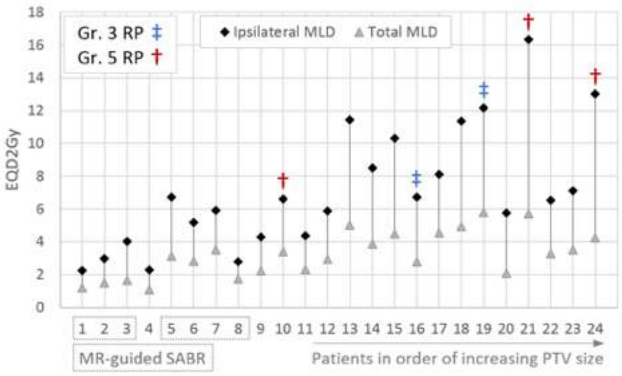
Background: Patients with lung tumors and coexisting interstitial lung disease (ILD) are at increased risk of toxicity following stereotactic ablative radiotherapy (SABR). We report on our institutional experience with SABR in such patients. **Method:** Institutional patients undergoing lung SABR with coexisting ILD were identified. ILD subtypes were determined by a pulmonologist specializing in ILD. From late 2015, patients were routinely counseled about the increased treatment risks. Magnetic resonance (MR-) guided SABR was used to reduce target volumes from 2016. Overall and progression-free survival (OS, PFS) were estimated using the Kaplan-Meier method, and dosimetric predictors of radiation pneumonitis (RP) were analyzed based on total lung minus planning target volumes (PTV). **Result:** Twenty-four SABR patients treated for lung cancer (n=22) or metastasis (n=2) between 2007-2018 were identified. Median patient age was 74 years, and the commonest ILD diagnosis was idiopathic pulmonary fibrosis. The commonest fractionation schemes were 60 Gy in 8 fractions (n=11), or 55 Gy in 5 fractions (n=6), and SABR was delivered on a Linac (n=17) to a motion-encompassing internal target volume, or with MR-guided SABR (n=7). At median follow-up of 36.9 months (95% CI, 15.8 to not reached), median OS and PFS were 16.6 and 13.3 months, respectively, and 12-month local control was 88.9%. Five patients (20.8%) developed grade ≥3 RP, of which 3 (12.5%) were fatal. Patients with grade ≥3 RP had a higher total lung V20Gy, and a higher ipsilateral and total mean lung dose (MLDEQD2; Fig. 1) than those without (p <.05).



Conclusion: Our findings confirm that ILD patients have a poor prognosis and are at high risk for developing severe RP following SABR. Treatment should be preceded by patient counseling by an experienced ILD team. Careful attention must be given to limiting lung doses, and MR-guided SABR is our preferred approach in such patients.

Keywords: interstitial lung disease, stereotactic radiotherapy, toxicity

MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.03 IMPACT OF COEXISTING INTERSTITIAL LUNG DISEASE ON RESECTED NON-SMALL CELL LUNG CANCER PATIENTS

J.G. Lee[1], S.Y. Park[1], C.Y. Lee[1], K.S. Narm[2], S.H. Song[3]

[1]*College of Medicine, Yonsei University, Seoul/Korea, Republic of,* [2]*Eulgi University, School of Medicine, Daejeon/Korea, Republic of,* [3]*Ilsan Hospital, Ilsan/Korea, Republic of*

Background: Patients with interstitial lung disease(ILD) have higher incidence of lung cancer. Treatment for this group is challenging, and long term outcome is poor. We investigated the outcome of patients with lung cancer and ILD after surgical resection, along with risk factor of survival and acute exacerbation.Patients with interstitial lung disease(ILD) have higher incidence of lung cancer. Treatment for this group is challenging, and long term outcome is poor. We investigated the outcome of patients with lung cancer and ILD after surgical resection, along with risk factor of survival and acute exacerbation. **Method:** Between Januery 2002 and August 2016, total 3413 patients underwent pulmonary resection for lung cancer, among them 74 patients had combined ILD. The demographics, operative and survival data were reviewed. **Result:** Mean age was 68±7 years-old for 74 ILD patients. 51 (68.9%) patients received video-assisted thoracic surgery (VATS). Lobectomy and sublobar resection were performed to 58 (78.4%) and 15 (20.3%) patients, respectively. 30 (41.5%) patients experienced respiratory complication during early postoperative period. 30-, 90- days mortality and 5-year survival rate were significantly worse than patients without ILD in the same study period (8.1%, 21%, and 21.2% vs. 1.3%, 3.1%, and 73.8%, respectively, p<0.001). Patients with ILD who experienced respiratory complication showed significantly worse 5-year survival than those who has not (18.2% vs. 44.9%, p<0.001). The leading cause of death was cancer related (47.8%), followed by postoperative complications (23.9%). Among 23 patients who received adjuvant therapy, 10 patients died during or shortly after adjuvant therapy. Open thoracotomy (HR 4.02, p=0.017) was risk factor for respiratory complication. Sublobar resection showed similar survival rate in each stage (stage I, p=0.825 and stage II-III, p=0.633) and lower rate of respiratory complication than lobectomy, although statistically not significant (26.7% vs. 43.1%, p=0.246). **Conclusion:** Interstitial lung disease increased the risk of pulmonary resection for lung cancer. Thoracotomy was associated with higher rate of respiratory complication. Sublobar resection showed similar survival with lower respiratory complication rate compared to lobectomy. Adjuvant therapy should be considered after careful weighing of risk and benefit.

Keywords: Lung cancer, interstitial lung disease, long term outcome

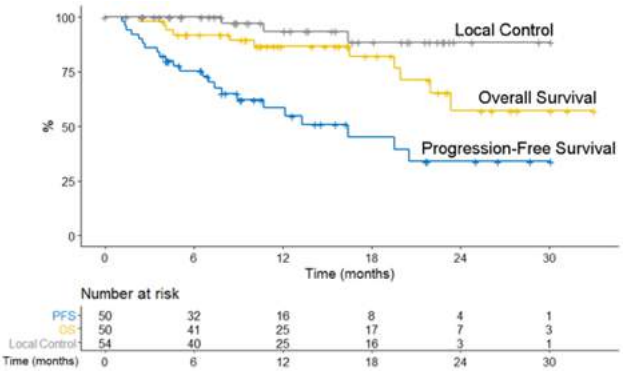
MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.05 PATIENT SELECTION AND EARLY CLINICAL OUTCOMES OF MR-GUIDED SABR IN 54 LUNG TUMORS

T. Finazzi, C. Haasbeek, F. Spoelstra, M. Palacios, M. Admiraal, A. Bruynzeel, B. Slotman, F. Lagerwaard, S. Senan

Amsterdam University Medical Centers, Location VUmc, Amsterdam/ Netherlands

Background: Magnetic resonance (MR-)guided stereotactic ablative radiotherapy (SABR) with daily replanning was performed for patients in whom treatment delivery was challenging due to tumor location, motion or pulmonary comorbidity. We describe patient characteristics and early clinical outcomes using this novel approach. **Method:** 50 consecutive patients (54 lung tumors) underwent MR-guided SABR at a single center between 2016-2018 for either primary lung cancer (n = 29 tumors) or lung metastases (n = 25). Patients had one or more factors predisposing to toxicity, including a central tumor location (n = 27 patients), previous thoracic radiotherapy (n = 17), and interstitial lung disease (n = 7). A daily 17-second breath-hold MR scan was acquired in treatment position, followed by on-table plan adaptation. Gated delivery was performed using repeated breath-holds under continuous MR-guidance. Local control, overall (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method, with PFS defined as time to disease progression or death from any cause. **Result:** Breath-hold SABR delivery was well tolerated, with all but one patient completing the planned schedule. With daily replanning, a biologically equivalent dose (BED10Gy) ≥100Gy to 95% of the planning target volume was delivered in 51 tumors (94%). Median follow-up was 15.8 months (95% CI, [11.4-22.5]). Local control, OS and PFS at 12 months were 93.4%, 86.7% and 58.4%, respectively (Fig. 1). In-field recurrences developed in 2 patients who were re-irradiated for a local recurrence after previous SABR, and one marginal recurrence was observed. Overall rates of any grade ≥2 and ≥3 toxicity were 24% and 4%, respectively. No grade ≥4 toxicity was seen. Commonest toxicities were grade ≥2 radiation pneumonitis (8%) and chest wall pain (8%; including one rib fracture).



Conclusion: Early follow-up of the largest patient cohort to date undergoing thoracic MR-guided SABR indicates low toxicity rates, and promising local tumor control.

Keywords: MR-guided radiotherapy, SABR, stereotactic radiotherapy

MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.06 DOSE-VOLUME FACTORS PREDICTING AIRWAY STENOSIS AFTER SBRT FOR ULTRA-CENTRAL LUNG TUMORS

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Background: The safety of SBRT is uncertain for ultra-central tumors (near the proximal airways or esophagus). One potential toxic effect of ultra-central SBRT is stenosis of the proximal airways, which can lead to airway obstruction and lung collapse. Predictors of such toxicity in this population are urgently needed. We therefore studied dose-volume correlates of airway stenosis after ultra-central SBRT. **Method:** 88 patients with tumors abutting the proximal bronchial tree (PBT) or PTVs overlapping esophagus (n = 76 and 23; 11 met both criteria) were included. 53 (60%) had primary/ locally recurrent lung cancer, and 35 had lung metastases. All had 5, 8 or 15 fractions of image-guided radiotherapy with BED ≥84Gy (α/β=10). The lobar bronchi (LB) were contoured from the takeoff from the main bronchus to the bifurcation into segmental bronchi. The primary endpoint was grade 2 or higher lobar bronchial stenosis (LBS), defined as radiographic evidence of narrowing or complete obstruction of at least one lobar bronchus (CTCAE v4). Dose-volume histograms (DVHs) using linear-quadratic equivalent doses in 2 Gy fractions were calculated for the LB with α/β = 3 Gy. Mean equivalent doses (MEDs) to the LB were tested for correlation with LBS using a Cox proportional hazards model, and the log rank test with patient data split at the median value of the MEDs to the LB. Statistical significance was defined as p < 0.05. **Result:** Median follow up was 14.3 months. There were 24 cases of LBS (27%). Median time to onset of LBS2+ was 8.6 months after end of treatment (range 2-19 months). LBS was significantly correlated with MED to the LB (p = 0.02). Incidence of LBS was significantly different in patients with MED to the LB < or > the median value of 35.4 Gy (p = 0.004 log-rank test), with actuarial rates of 19% and 55% respectively at 14 months, and 19% and 70% respectively at 24 months; and with raw rates of 15.9% and 38.6% respectively. **Conclusion:** We observed

a high rate of lobar stenosis after ultra-central SBRT. Incidence of lobar stenosis was significantly correlated with dose to the lobar bronchi. In particular, mean equivalent dose to the lobar bronchi was significantly correlated with LBS. Our analysis suggests that limiting the mean equivalent dose to the lobar bronchi to < 35.4 Gy results in a two year actuarial incidence of LBS of <19%, and a raw incidence <16%.

Keywords: Ultra-central SBRT Stenosis

MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.07 A PHASE I TRIAL OF AN IMMUNE CHECKPOINT INHIBITOR PLUS STEREOTACTIC ABLATIVE RADIOTHERAPY IN PATIENTS WITH EARLY STAGE NON-SMALL CELL LUNG CANCER

M. Daly[1], A. Monjazeb[1], A. Mirhadi[2], D. Eastham[3], F. Lara[1], J. Riess[1], E. Wiegner[4], K. Kelly[1]

[1]*University of California Davis Comprehensive Cancer Center, Sacramento/United States of America,* [2]*Samuel Oschin Comprehensive Cancer Institute, Los Angeles/United States of America,* [3]*Joint Radiation Oncology Center, David Grant USAF Medical Center, Travis AFB/United States of America,* [4]*Mercy Medical Group, Sacramento/United States of America*

Background: Stereotactic ablative radiation therapy (SABR) is the standard-of-care for medically inoperable, early stage non-small cell lung cancer (NSCLC), but regional and distant failures remain problematic. Based on *in vivo* preclinical data showing synergy between radiation and immune checkpoint inhibitors (ICI) and the known efficacy and mild toxicity profile of ICI in Stage III and IV NSCLC, we conducted a phase I study to determine the safety, tolerability and maximum tolerated dose of neoadjuvant, concurrent, and adjuvant atezolizumab with SABR for high risk early stage NSCLC (NCT02599454). **Method:** Eligible patients had histologically confirmed T1-3 NSCLC with one or more features predictive of increased recurrence risk: diameter ≥1 cm, SUV ≥6.2 on FDG PET, or moderately/poorly differentiated histology. Patients were medically inoperable or refused surgery, and had a Zubrod PS ≤2. Patients received 6 cycles of atezolizumab IV in 21 day cycles. A 3+3 dose finding design was employed with three dose levels: 3 mg/kg, 10 mg/kg, and 1200 mg flat dosing. SABR was delivered starting cycle 3 to 50 Gy over 4-5 fractions. Patients were restaged after cycle 2, prior to SABR. Dose limiting toxicity (DLT) was assessed during the first 9 weeks of treatment. **Result:** From April 2016-June 2018, a total of 15 patients enrolled, with 12 evaluable for DLT assessment. Three patients chose to discontinue treatment due to travel issues (1 pt), a COPD exacerbation (1 pt) and grade 2 liver function tests (LFTs) (1 pt). One patient on dose level 2 developed DLT, a grade 3 rash requiring discontinuation of protocol therapy. No other DLTs occurred, resulting in a recommended dose of 1200 mg for future studies. Eleven patients completed protocol treatment. Other grade 3 toxicities include transient lymphopenia in 4 patients. One patient each developed grade 2 pneumonitis, grade 2 hypothyroidism, and grade 2 hyperthryoidism. Three patients had a radiographic partial response and 1 patient had a minor response following 2 cycles. No patient had progressive disease prior to SABR. Results of correlative blood and tissue studies will also be reported. **Conclusion:** Neoadjuvant, concurrent, and adjuvant atezolizumab in combination with SABR for early stage NSCLC is well-tolerated, with radiographic PR prior to SABR in 25% of our cohort. Overall efficacy data is premature. Enrollment to an expansion cohort is ongoing, and this combination will be tested in an upcoming randomized phase III trial SWOG/NRG S1914. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Lung Cancer Research Program under Award no. W81XWH-15-2-0063.

Keywords: Lung cancer, SBRT, Immunotherapy

MA02 MISCELLANEOUS TOPICS IN THE MANAGEMENT OF EARLY STAGE LUNG CANCER
SUNDAY, SEPTEMBER 8 10:30–12:00

MA02.09 PROGNOSTIC IMPACT OF IMMUNE CELL BIOMARKERS IN SURGICALLY RESECTABLE NON-SMALL CELL LUNG CANCER

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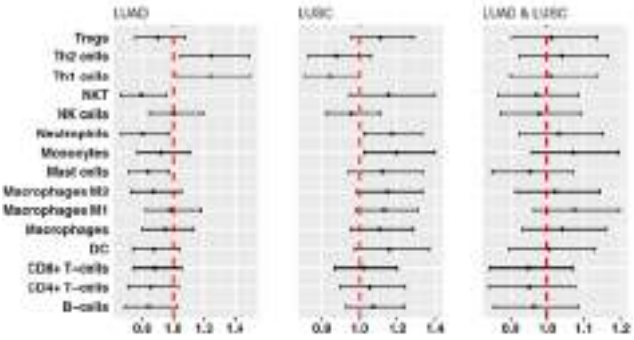
Background: Immune cells within the tumor microenvironment (TME) play an important role in the development, progression and eventual outcomes of non-small cell lung cancer (NSCLC). The relative balance of immune effector and regulatory cell subpopulations may tilt the TME to be either detrimental or supportive of tumorogenesis and will have a profound impact on the tumor's eventual destiny. In early-stage lung cancer, the role of individual immune cell subtypes in the TME on survival outcomes following surgical resection is unknown. **Method:** This project made use of The Cancer Genome Atlas (TCGA) Program data. We computed sample-specific scores for different immune cells using xCell, a new model for estimating different immune cell types from RNAseq data, for all stage I-IIIA NSCLCs. Then, we assessed the association between each cell type and survival with Cox Regression, while adjusting for important clinical variables (i.e., stage, age, gender, smoking status). We stratified the analysis according to histological subtype. **Result:** There were 910 surgically resected early-stage NSCLC analyzed, of which 438 were adenocarcinomas (LUADs) and 472 were squamous cell (LUSC) samples. Higher levels of natural killer cells, neutrophils, and mast cells within tumors were associated with significantly improved survival in LUAD patients, whereas no immune cell type was associated with survival for LUSC patients or the combined analysis. *Figure 1: Adjusted Survival According to Estimated Immune Cell Infiltration*



Hazard ratios are adjusted for stage, gender, age and smoking status **Conclusion:** Innate and adaptive immune cells within the TME may have prognostic value in early-stage NSCLC patients undergoing surgical resection. However, the role of individual immune cells may vary according to histological subtype. Prospective research should continue to assess the association of the immune cell composition of the TME with clinical outcomes.

Keywords: Biomarker, tumor microenvironment (TME), Immune Cell

MA02.10 DIFFERENT PROGNOSTIC IMPACT OF LYMPHOVASCULAR INVASION BETWEEN LOBECTOMY AND SUBLOBAR RESECTION IN STAGE IA NON-SMALL CELL LUNG CANCER: A PROPENSITY SCORE–MATCHED ANALYSIS

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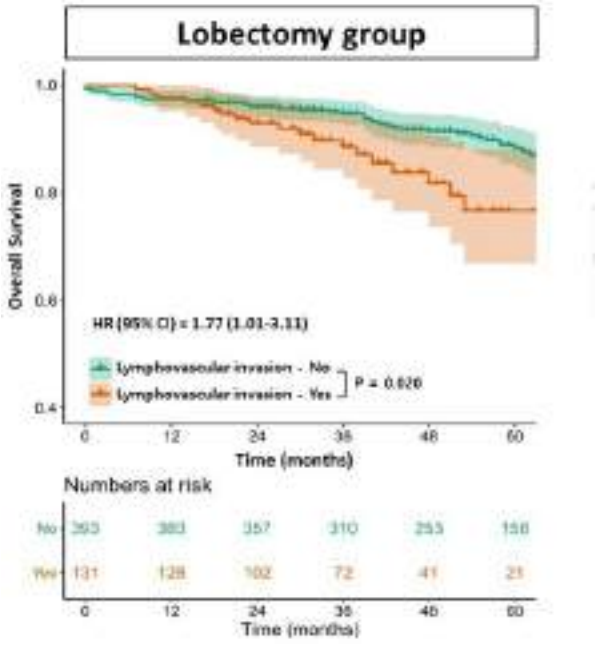
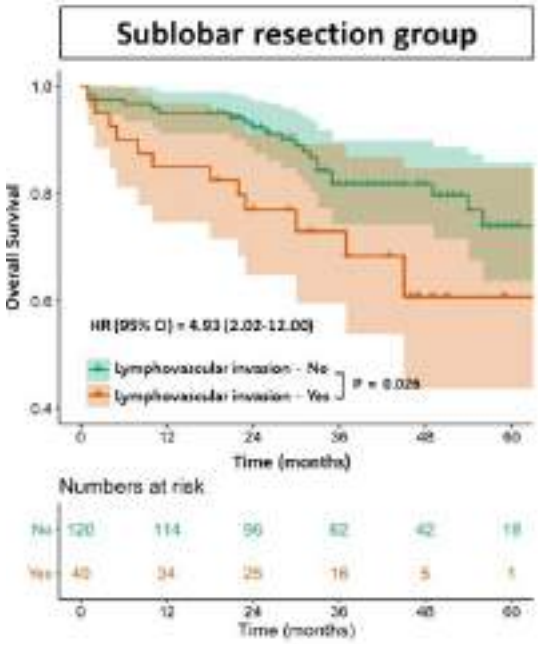
Background: Lymphovascular invasion (LVI) has been reported as a risk factor in patients with stage I Non-Small Cell Lung Cancer (NSCLC). Although lobectomy is a standard treatment, sublobar resection may be performed in patients with stage IA NSCLC. This study aimed to evaluate the prognostic effect of LVI in stage IA patients who underwent lobectomy and sublobar resection. **Method:** We retrospectively reviewed data from 2134 patients with stage IA NSCLC from 2007 to 2016. By using the Cox proportional hazard regression model, we calculated the prognostic impact of LVI quantitatively. To reduce the effects of observed confounding between LVI-positive and negative patients, propensity score matching (PSM) was applied in patients with lobectomy and sublobar resection, respectively. **Result:** Among patients with stage IA NSCLC (n=2134), 184 (8.6%) were pathologically diagnosed with LVI, which were 144 (8.9%) in lobectomy group (n=1614) and 40 (7.7%) in sublobar resection group (n=520). In multivariable analysis, LVI was a significant risk factor for both overall survival (OS) and recurrence-free survival (RFS) (OS: hazard ratio [HR], 2.03; 95% confidence interval [CI], 1.39–2.96; p < .001; RFS: HR, 2.31; 95% CI, 1.68–3.17; p < .001). After PSM, the prognostic impact of LVI was shown much greater in patients with sublobar resection (HR = 1.77 and 2.51 for OS and RFS) than those with lobectomy (HR = 4.93 and 4.25 for OS and RFS). **Conclusion:** The presence of LVI significantly affected OS and RFS in stage IA NSCLC patients. Survival outcomes were more affected by the presence of LVI in patients with sublobar resection than those with lobectomy. Subsequent completion lobectomy could be considered in patients diagnosed with LVI after sublobar resection.





Keywords: Lymphovascular invasion, Non-Small Cell Lung Cancer, stage IA

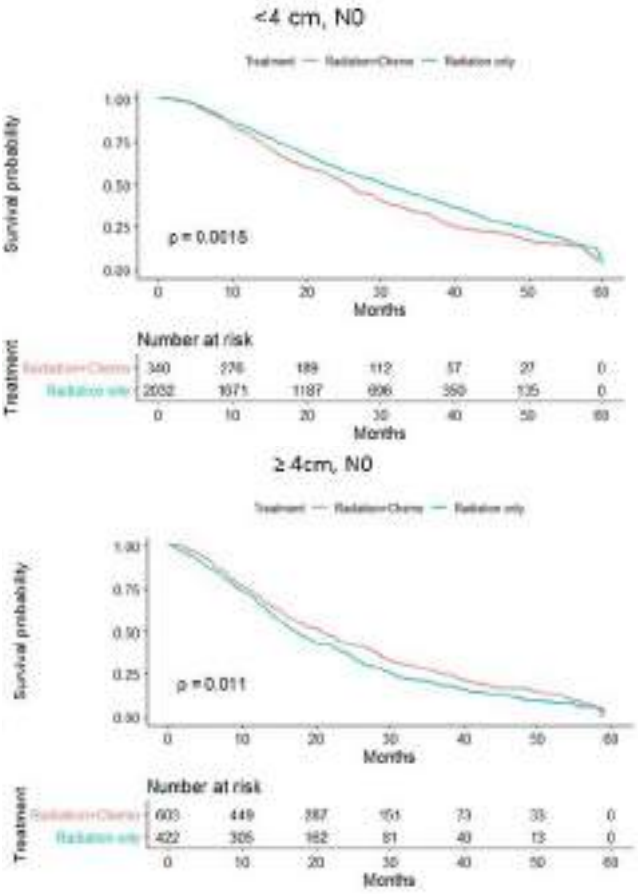
MA02.11 ADJUVANT CHEMOTHERAPY FOLLOWING SBRT FOR EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC) IN OLDER PATIENTS

A.K. Ganti, A. Kusi Appiah, V. Ernani, C. Zhang, W. Zhen, A. Marr, L. Smith

University of Nebraska Medical Center, Omaha/United States of America

Background: Adjuvant chemotherapy following surgery has been shown to be beneficial in NSCLC >4 cm in size, regardless of age. We have recently shown that adjuvant chemotherapy improves overall survival following stereotactic body radiotherapy (SBRT) in patients with tumors ≥4 cm in size. We aim to evaluate the role of adjuvant chemotherapy following SBRT in older patients (>70 years) with early stage NSCLC. **Method:** Patients (>70 years) diagnosed with clinical stages I-II NSCLC (AJCC 7th Edition) from 2004 to 2013, who received SBRT, were identified using the National Cancer Database (n=7,934). The Kaplan-Meier method was used to estimate overall survival (OS) distributions and the log-rank test was used to compare distributions by treatment strategy. Clinical stages I and II were subdivided according to the TNM staging and log-rank tests was used to compare survival distributions by treatment strategy within each subgroup. **Result:** There were 3991 male patients (50.3%), and 6219 (78.4%) had stage I disease. Among stage I patients, 670 (10.8%) received adjuvant chemotherapy (defined as chemotherapy within 90 days of completion of SBRT), compared to 742 stage II patients (43.3%) received adjuvant chemotherapy. Median OS was better with SBRT in patients with stage I disease (25.2 vs. 19.9 months; p<0.001); while patients with stage II NSCLC had better OS with SBRT + chemotherapy (19.9 vs. 14.6 months; p<0.001). On multivariate analysis, after adjusting for age, gender and facility type, patients with stage I NSCLC who received SBRT alone had better overall survival [HR for death: 0.79 (95% CI, 0.73, 0.87)]. SBRT alone was associated with an increased risk of death in patients with stage II disease [HR: 1.37 (95% CI, 1.23, 1.53). When patients with N0 disease were evaluated based on tumor size, those with tumors ≥4 cm had better OS with SBRT + chemotherapy (18.5 vs. 15.5 months; p=0.003). In contrast, patients with tumors <4 cm did better with SBRT alone (median OS of 24.1 vs. 20.3 months; p<0.001)

Overall Survival



Conclusion: Adjuvant chemotherapy following SBRT is associated with improved OS in patients >70 years of age and tumors ≥4 cm in size or lymph node involvement.

Keywords: SBRT, Older patients, adjuvant chemotherapy

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.01 THE IMPACT OF EARLY STEROIDS ON CLINICAL OUTCOMES IN PATIENTS WITH ADVANCED NSCLC TREATED WITH IMMUNE CHECKPOINT INHIBITORS- A CANCERLINQ COHORT

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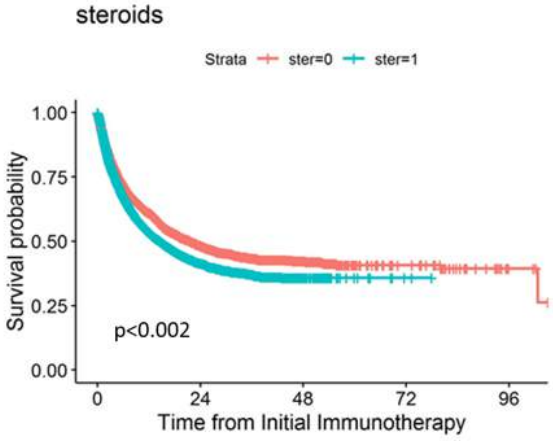
Cleveland Clinic, Cleveland/United States of America

Background: Immune checkpoint inhibitors (ICIs) have changed the treatment paradigm for patients with NSCLC, however only a fraction of patients have objective responses to these agents. Identifying clinical factors that influence efficacy of ICIs is crucial for optimal patient selection for treatment. Since ICIs produce anti-tumor responses by reinvigorating cytotoxic effector T cells, one can surmise that patients who receive steroids within a short interval of initiating ICIs will have less robust anti-tumor responses. Clinical trials usually exclude patients receiving steroids for this reason. In clinical practice, patients with NSCLC often receive corticosteroids for various indications such as brain metastases, appetite stimulation, autoimmune disorders, or COPD. By analyzing data obtained from a large real world cohort of patients with NSCLC, we aim to study the impact of early steroids (within 30 days) on clinical outcomes in patients with advanced NSCLC treated with ICIs. **Method:** Using the Cancerlinq Discovery Database which consists of data aggregated from the electronic medical records of oncology practices, 11,143 patients with advanced NSCLC treated with ICIs were identified. Of these, 1581 patients were prescribed or administered ≥ 10 mg of prednisone or equivalent corticosteroid dose within the first 30 days of initiating ICIs. To account for prognostic heterogeneity within the population, we created matched cohorts of patients that exhibited similar prognostic clinical characteristics such as age (using 65 years as a cutoff) and gender. Association between time on treatment with ICIs and early steroid use was evaluated using the Student's t-test. Overall survival (OS) was estimated using the Kaplan-Meier method and analyzed using the Cox proportional-hazards model. **Result:** The cohort consisted of a predominantly white population (53.4%), with a median age of 76 years and a slight male predominance (54.9%). The median time on ICI treatment was 3.8 months. Patients who received steroids within the first 30 days had a shorter time on treatment- median of 3.36 months vs 3.86 months for those without steroid use (p= 0.023). Early steroid use was also associated with significantly worse overall survival [HR 1.16, 95% CI (1.05, 1.28) p<0.002]. Figure: Kaplan-Meier survival analyses of patients with NSCLC treated with ICIs according to early steroid use



Conclusion: The use of ≥ 10 mg of prednisone equivalent corticosteroid dose within 30 days of initiating ICIs was associated with shorter time on treatment and worse overall survival in this large real world cohort of NSCLC patients. It is prudent that clinicians judiciously prescribe corticosteroids upon initiation of ICIs.

Keywords: Immunotherapy, steroids

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.02 GENETIC VARIANTS IN ERAP1 AND NCF2 IN THE MHC CLASS I RELATED GENES ARE ASSOCIATED WITH NON-SMALL CELL LUNG CANCER SURVIVAL

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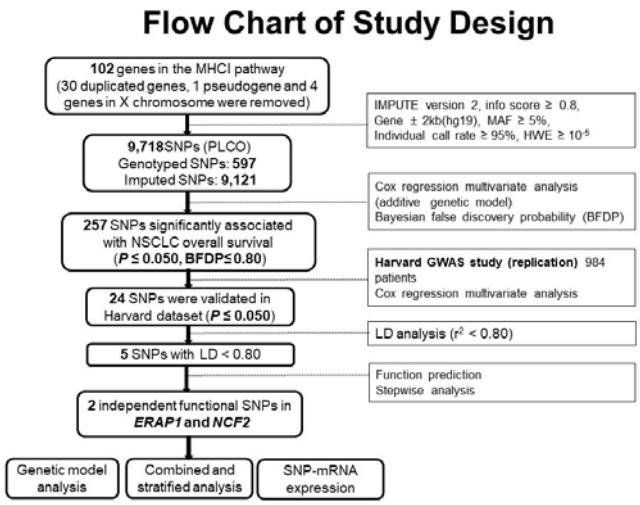
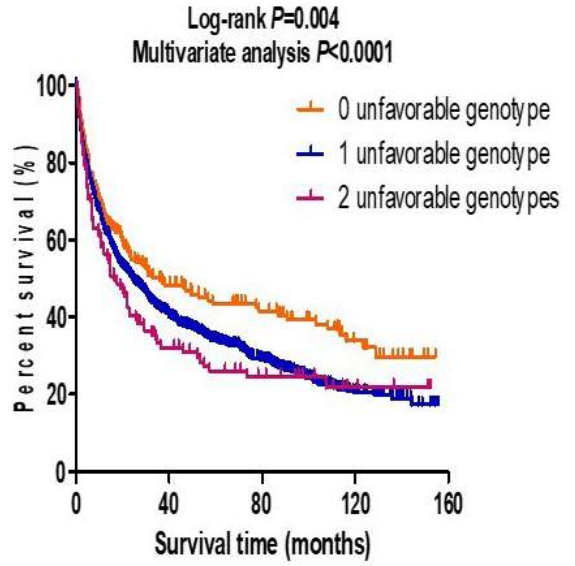
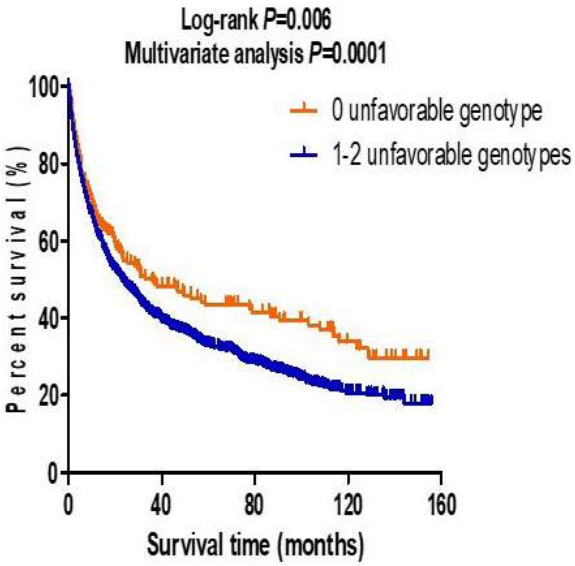
Background: Adaptive immunity, particularly the presence of tumor-infiltrating $CD8^+$ T cells, is crucial in the control of tumor cells and preventing overall cancer progression. However, the process of $CD8^+$ T cells recognizing and killing tumor cells depends on the expression of MHC class I (MHCI) complex presented on tumor cell surface. **Method:** In the present study, we performed a two-phase analysis of two independently published genome-wide association studies (GWASs) to evaluate associations between genetic variants in the MHCI-related gene-set and overall survival (OS) of patients with non-small cell lung cancer (NSCLC). In the discovery GWAS dataset, we performed multivariate Cox proportional hazards regression with Bayesian false-discovery probability for multiple test corrections and evaluated associations between 9,718 single-nucleotide polymorphisms (SNPs) in 102 genes and survival of 1,185 NSCLC patients. After validation in another GWAS dataset, we performed linkage disequilibrium, function prediction and a multivariate stepwise Cox proportional hazards regression analysis. **Result:** We found that two independent, potentially functional SNPs in two genes (*ERAP1* rs469783 T>C and *NCF2* rs10911362 C>T) were significantly associated with NSCLC survival, and their meta-analysis showed an adjusted hazards ratio (HR) of 0.83 [95% confidence interval (CI) =0.77–0.89] and $P_{meta} = 8.2\times10^{-7}$; 1.31 (1.06-1.73) and P_{meta} =0.0009; respectively. A genetic score of unfavorable genotypes of these two SNPs revealed a decreased OS in a dose–response manner (P_{trend} <0.0001). Further expression quantitative trait loci (eQTL)

analysis showed significant associations between the genotypes and mRNA expression levels. Furthermore, the expression levels of these genes in tumor and normal tissues were different and had an effect on patient survival as well.







Conclusion: Taken together, the genetic variant of the *ERAP1* rs469783 and *NCF2* rs10911362 from the MHCI pathway genes may be a promising predictor of survival in NSCLC patients via *ERAP1* and *NCF2* expression alteration.

Keywords: NSCLC, MHC-I, single-nucleotide polymorphism

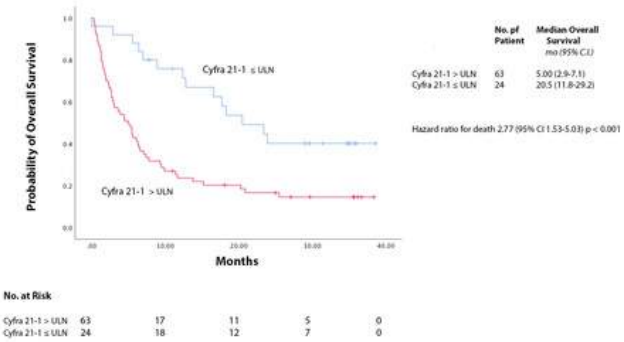
MA03.03 CEA AND CYFRA 21-1 AS PROGNOSTIC BIOMARKERS OF BENEFIT FROM NIVOLUMAB AND AS A TOOL IN TREATMENT MONITORING IN ADVANCED NSCLC

F.G. Dall'Olio[1], F. Abbati[1], F. Facchinetti[2], F. Gelsomino[1], B. Melotti[1], M. Massucci[1], S. Buti[1], M. Veneziani[3], M. Tiseo[2], A. Ardizzoni[1]

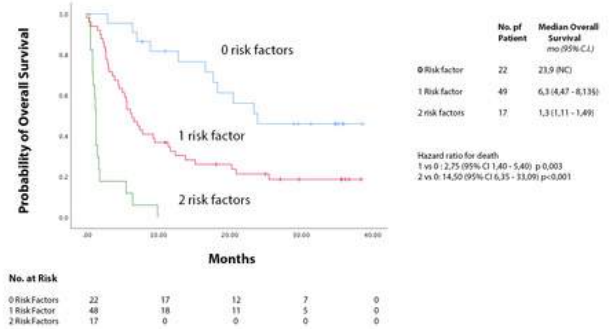
[1]*Policlinico di Sant'Orsola - University of Bologna, Bologna/Italy,* [2]*University of Parma, Parma/Italy,* [3]*Azienda Ospedaliero-Universitaria di Parma, Parma/Italy*

Background: To assess the role of pre-therapy levels of Carcinoembryonic antigen (CEA) and Cytokeratin-19 Fragments (CYFRA 21-1) as prognostic marker in advanced NSCLC patients treated with nivolumab, and their change as an early predictor of treatment outcome. **Method:** This is a retrospective cohort study including all patients with stage IIIB – IV NSCLC who received nivolumab after first-line chemotherapy in 2 Italian institutions. Median Overall Survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR) and Time to Treatment Failure (TTF) were chosen as endpoints. **Result:** 100 patients were included. Cyfra 21-1 > ULN resulted correlated with OS (FIG.1A) both in univariate (HR 2.77, 95% CI 1.53 – 5.30, p 0.001) and multivariate analysis (HR 2.72, 95% CI 1.44 – 5.16, p 0.002). The only other factor correlated with OS in multivariate was ECOG PS (0-1 vs 2) (HR 5.46, 95% CI 3.07 – 9.91, p< 0.001) (Table 1). ECOG PS (0-1 vs 2) and CYFRA 21-1 (≤ 3.5 vs > 3.5) where combined to create a prognostic score (FIG.1B). Median OS was 23.9 months for patients without risk factors, 6.3 months with one (HR 2.75, 95% CI 1.40 – 5.40 p 0.003) and 1.3 months with 2 risk factors (HR 14.50, 95% CI 6.35 – 33.09, p< 0.001). Early 20% reduction after 3rd cycle was correlated with OS for CEA, HR 0.05 (95% CI 0.01–0.41), p 0,003 and borderline for CYFRA 21-1, HR 0.29 (95% CI 0.09 – 1.01), p 0.052. (FIG.1C-1D).

1A

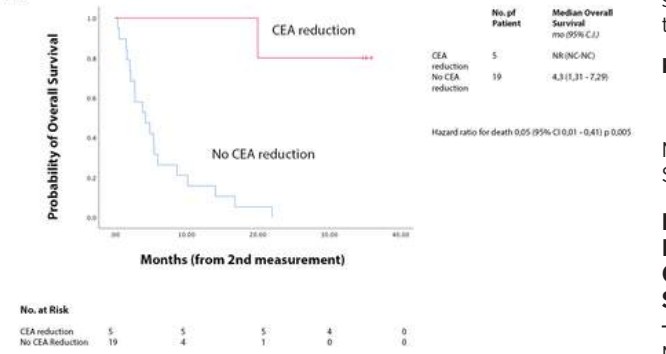


1B



MINI ORAL SESSIONS

1C



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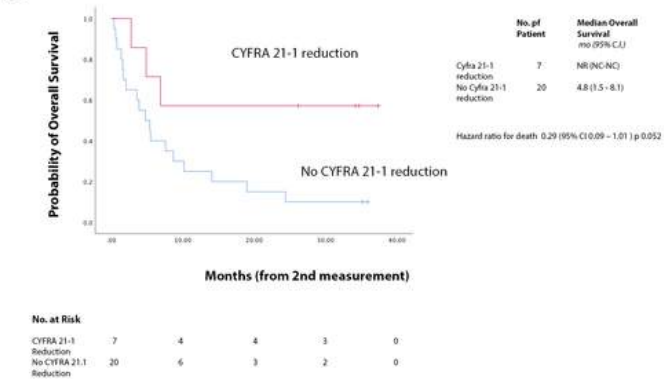

	Univariate		Multivariate	
Covariate	**HR (95% CI)**	**P value**	**HR (95%CI)**	**P value**
ECOG PS 2 vs 0-1	5.40 (3.21 – 9.09)	< 0.001	5.46 (3.07 – 9.91)	< 0.001
Cyfra > vs ≤ ULN	2.77 (1.53 – 5.03)	0.001	2.72 (1.44 – 5.16)	0.002
Liver metastasis yes vs no	2.19 (1.26 – 3.78)	0.005		0.102
Neutrophil/lymphocyte ratio ≥ 4 vs < 4	1.99 (1.23 – 3.20)	0.005		0.105
KRAS mutated vs wild type*	0.39 (0.21 – 0.74)	0.004		0.262
Bone metastasis yes vs no	1.75 (1.10 – 2.79)	0.018		0.362
Response to previous therapy yes vs no	0.51 (0.29 – 0.91)	0.023		0.376
CEA > vs ≤ ULN	1.41 (0.88 – 2-25)	0.150		0.418
Stage IV vs IIIB	1.63 (0.75 – 3.54)	0.22		0.449
Squamous vs non squamous	0.79 (0.48 – 1.28)	0.334		0.689
Smoker vs never smoker	0.88 (0.65 – 1.18)	0.386		0.694
Second-line vs third or more	0.94 (0.60 – 1.47)	0.77		0.843
Brain metastasis yes vs no	1.16 (0.66 – 2.04)	0.603		0.594

Conclusion: Our data suggests that Cyfra 21-1 pre-therapy assessment, both alone and in combination with other factors in a prognostic/predictive score, may provide clinicians with further information on the prognosis of patients treated with nivolumab. CEA and CYFRA 21-1 repeated measures could be useful as an early surrogate marker of clinical benefit. Further analysis are warranted to confirm these findings.

Keywords: NSCLC, Checkpoint inhibitors, Serum Tumor Markers

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.05 BRAF MUTATIONS ARE ASSOCIATED WITH INCREASED BENEFIT FROM PD1/PDL1 BLOCKADE COMPARED WITH OTHER ONCOGENIC DRIVERS IN NON-SMALL CELL LUNG CANCER

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[1]The University of Texas MD Anderson Cancer Center, Houston/United States of America, [2]UT MD Anderson Cancer Center, Houston/United States of America, [3]Foundation Medicine, Cambridge/United States of America, [4]Genentech Inc., South San Francisco/United States of America, [5]Genentech, Inc., South San Francisco/United States of America, [6]Hoffmann-La Roche Limited, Mississauga/Canada, [7]University of Texas MD Anderson Cancer Center, Houston/United States of America, [8]MD Anderson Cancer Center, Houston/United States of America

Background: PD-1/PD-L1 immune checkpoint blockade (ICB) has revolutionized the treatment of non-small cell lung cancer (NSCLC), but only a minority of patients achieve durable clinical benefit. Although classic *EGFR/ALK* alterations are correlated with ICB resistance, it is unknown if patients with other molecular subtypes of NSCLC also derive poorer outcomes from ICB. We investigated if there are oncogene-driven NSCLC associated with higher response rates (RR) and progression-free survival (PFS) to ICB. **Method:** Two independent retrospective cohorts of oncogene-driven NSCLC treated with ICB monotherapy were analyzed for clinical outcome: MD Anderson (MDACC) and Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-CGDB). PD-L1 expression (Dako 22C3 - FoundationCore) and tumor mutational burden (TMB - FoundationCore; TCGA and MSK-IMPACT – cbioportal.org) were compared across distinct molecular subtypes of NSCLC to determine differences in clinical outcome. **Result:** Among five oncogene defined groups from the MDACC cohort, *BRAF*-mutant NSCLC had the highest response rate (RR) (RECIST 1.1) (P<0.01) and PFS (P<0.01) when treated with ICB (Table). These differences remained significant after adjusting for PD-L1 expression. Classic *EGFR* and *HER-2* mutant NSCLC had the lowest RR and PFS (Table). Similar results were observed in the independent FH-CGDB cohort where *BRAF*-mutant NSCLC had longer real-world (rw) PFS and OS to ICB monotherapy (Table). PD-L1 expression (tumor score ≥1% and ≥50%) and TMB were higher in *BRAF*-mutant NSCLC compared to *EGFR* and *HER-2* (P<0.01). *BRAF* V600E NSCLC had lower TMB compared to non-V600E (5.9 vs 13.7 mut/Mb, P<0.01), but both had high PD-L1 expression (≥1%: 72% vs 61%; ≥50%: 42% vs 32%).

	KRAS	BRAF	Classic EGFR	EGFR exon 20	HER2
MDACC cohort					
Patients – N	87	10 (V600E 3 / non-V600E 7)	28	25	15
RR – %	24.3	62.5	4.5[b]	10[b]	8.3
Median PFS – mo (95% CI)	2.76 (2.23-3.30)	7.37 (not estimable)[a]	1.78 (1.18-2.37)	2.73 (1.71-3.75)	1.88 (1.63-2.12)
FH-CGDB					
Patients – N	503	68 (V600E 32 / non-V600E 36)	52	42	25
Median rwPFS - mo (95% CI)	3.55 (3.15-4.24)	6.0 (2.89-11.6)	2.17[b] (1.77-2.63)	2.66[b] (2.23-5.13)	1.87[b] (1.31-4.34)
Median rwOS – mo (95% CI)	10.28 (8.51-12.02)	16.07 (8.64-NA)	5.29[b] (3.25-17.68)	9.89[b] (3.68-20.86)	10.81 (4.17-NA)
FoundationCore cohort – N	NA	188 (V600E 74 / non-V600E 114)	386	96	57
TMB – mean (mut/Mb)	NA	10.6[a]	3.7	3.8	5.8
PD-L1 TPS ≥ 50% (%)	NA	36[a]	19	23	16

a: *P*<0.01 vs all groups; b: *P*<0.05 for pairwise comparison vs BRAF.

Conclusion: NSCLCs with *BRAF* mutations are associated with increased benefit from ICB when compared to tumors harboring other targetable oncogenic drivers. Oncogene driver mutations are associated with distinct patterns of TMB and PD-L1 expression. These findings highlight the importance of developing mutation-specific clinical trials in NSCLC.

Keywords: braf, Immunotherapy, Non-Small Cell Lung Cancer

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.06 EFFICACY RESULTS OF SELECTIVE AXL INHIBITOR BEMCENTINIB WITH PEMBROLIZUMAB FOLLOWING CHEMOTHERAPY IN PATIENTS WITH NSCLC

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Background: The RTK AXL is implicated in epithelial-to-mesenchymal transition, negative regulation of anti-tumour immunity and resistance to multiple therapies including immune checkpoint inhibitors. Bemcentinib (BGB324) is a first-in-class, oral, highly selective and potent AXL inhibitor which has been demonstrated to enhance anti-PD1 therapy. **Method:** This phase II trial (Cohort A, NCT03184571) enrolled 48 advanced lung adenocarcinoma patients with progression on or after no more than one prior line of platinum-based chemotherapy. Patients with EGFR/ALK mutations were included in this study and must have progressed on or after at least one standard targeted therapy. The primary endpoint was ORR according to RECIST v1.1. Additional endpoints included efficacy according to biomarker expression, DCR, PFS, OS, and safety. Tumour biopsies were analysed for PD-L1 expression (22C3 pharmDx), AXL by IHC, and infiltrating immune cells. **Result:** As of April 2019, the trial was fully recruited: median age 65 (range 39-82) yrs, 61% male, 76% smokers or ex-smokers. At time of writing, a total of 210 treatment cycles had been completed by all patients. 17 patients were ongoing. 17 of 32 biomarker-evaluable patients (53%) were PD-L1 negative, 13 (41%) had TPS 1-49%, and 2 (6%) had TPS ≥50%. Of 28 biomarker-evaluable patients, 14 (50%) expressed AXL on their tumours. Among patients who had at least 1 evaluable on-treatment scan: 5 responses were observed in 13 AXL positive patients (38%), and 7 in 30 patients with TPS 0-49% (23%). There were 10 responses observed among 34 evaluable patients overall (29%). In Stage 1, two of the 4 AXL positive responses are ongoing; mDoR is not mature in the AXL positive patients. mPFS was 5.9 mo in AXL positive patients (n=10, 3.0-NR) and 4.0 mo (95% CI 1.9-NR) overall (n=24). mOS was not mature. The most common TRAEs (occurring in ≥10% of patient in both stages) were transaminase increases (34%), asthenia/fatigue (30%), diarrhoea (26%), nausea (13%), anaemia (11%), decreased appetite (11%), and pruritus (11%). All cases of transaminase increase were reversible and resolved with concomitant administration of systemic corticosteroids and interruption of study treatments. **Conclusion:** Patients had predominantly low or no PD-L1 expression; approximately half were AXL positive. The combination of bemcentinib and pembrolizumab was well tolerated and showed promising efficacy in previously treated IO-naïve NSCLC patients, particularly in those with AXL positive disease, including PD-L1 negative patients. Mature ORR for both stages, as well as 12-month OS for stage 1 will be presented at the meeting.

Keywords: Pembrolizumab, bemcentinib, AXL

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.07 FIRST-LINE ATEZOLIZUMAB CHEMOIMMUNOTHERAPY IN ADVANCED NON-SQUAMOUS NSCLC PATIENTS HARBORING EGFR/ALK GENETIC ALTERATIONS

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Background: Management of advanced non-squamous non-small cell lung cancer (NSCLC) is an area in dire need of therapeutic innovation. In recent years, multiple randomized clinical trials (RCT) have combined atezolizumab, programmed death ligand 1 (PDL-1) antibody, with chemotherapy as first-line treatment of advanced non-squamous NSCLC. In patients with EGFR/ ALK genetic alterations, PDL-1 or programmed death receptor 1 (PD-1) inhibitors monotherapy previously failed to demonstrate survival benefits compared to standard chemotherapy. The purpose of our study is to explore the efficacy of atezolizumab in combination with chemotherapy for first-line treatment of advanced non-squamous NSCLC harboring EGFR or ALK genetic alterations. **Method:** We conducted a comprehensive literature search using PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019. RCTs utilizing first-line atezolizumab combination regimen in patients with advanced non-squamous NSCLC were incorporated in the analysis. A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for progression-free survival (PFS) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q -statistic. Random effects model was applied. **Result:** 3 RCTs (IMpower – 130, 132 and 150) including 2101 patients with advanced non-squamous NSCLC were eligible. The study arm used standard chemotherapy regimens in combination with atezolizumab while control arm used only standard chemotherapy regimens. The randomization ratio was 2:1 in IMpower130 study and 2:1 in other studies. The I^2statistic for heterogeneity was 0, suggesting homogeneity among RCTs. 1949 patients were EGFR/ ALK wild type and 152 patients from Impower 130 and 150 were positive for EGFR/ ALK genetic alterations. The pooled HR for PFS was statistically significant at 0.62 (95% CI: 0.56-0.69; P < 0.0001) in patients with EGFR or ALK genetic alterations, favoring first-line atezolizumab chemoimmunotherapy regimen. In the EGFR/ ALK wild type population, the pooled HR for PFS was 0.63 (95% CI: 0.43 to 0.94; P = 0.02). **Conclusion:** Our meta-analysis demonstrated that atezolizumab in combination with chemotherapy significantly improved progression-free survival compared to standard chemotherapy in patients with advanced non-squamous NSCLC, regardless of the presence or absence of EGFR/ ALK genetic alterations.

Keywords: advanced non-squamous non-small cell lung cancer, first-line atezolizumab chemoimmunotherapy, EGFR/ ALK genetic alterations

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.09 DRAMATIC RESPONSES TO IMMUNE CHECKPOINT INHIBITORS IN MET EXON 14 SKIPPING MUTATION (METEX14MUT) NON SMALL CELL LUNG CANCERS

M. Mayenga[1], I. Monnet[2], M.-A. Massiani[3], J.-B. Assié[2], L. Tabeze[1], S. Friard[1], S. Fraboulet[1], A.-C. Metivier[1], C. Chouaid[2], L. Zemoura[4], E. Longchampt[4], S. Melaabi[5], L.-J. Couderc[1], H. Doubre[1]

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Background: METex14 mutations occur in 2-3% of Non-Small-Cell Lung Cancers (NSCLC), with a higher prevalence in patients aged over 70-years-old, non-smokers and women. Crizotinib, a MET-inhibitor, allows remarkable, but often short, tumor responses. Immune Checkpoint Inhibitors (ICIs) have become pivotal treatments in NSCLC but seem less efficient in non-smokers and in case of oncogenic addiction. We report durable strong responses in four non-smoker women (A, B, C, D) and two smokers (E, F) treated by ICIs in a second-line setting for NSCLC harboring METex14 mut. **Method:** We studied the clinical and biological characteristics and the tumor response after ICIs for each patient. The complete DNA sequencing of the tumor was available after the beginning of ICIs (explaining why crizotinib was not proposed in second line). PDL1 expression on tumor cells was evaluated by antibody clone E1L3N (Cell signaling Technology). **Result:** Table 1 summarizes patient and tumor characteristics, and the evolution during ICIs:Nivolumab for all patients except E (pembrolizumab). There were neither EGFR, BRAF, KRAS mutations, nor ALK or ROS translocations (except minority KRAS mutation for C). No concurrent MET amplification was found.

	Age at diagnosis (years)	Histological subtype	Metastatic site	First line treatment	MET Mutation	PDL1 expression	Time between diagnosis and ICI	Time under ICI	Tumor response
A	69	Adenocarcinoma	None then adrenal	Cisplatin - Pemetrexed	c.3082+1 G>A	70%	5,5 months 12 months when rechallenging	24 months (ongoing)	Complete
B	71	Adenocarcinoma	Brain Then brain, lung and pleura	Carboplatin -Pemetrexed	c.3082+1 G>C	20%	10,5 months	23 months	Partial
C	71	Sarcomatoid carcinoma	Bone	Carboplatin -Paclitaxel	c.3082G>A KRAS c.34G>A (minority)	40%	4,5 months	24 months	Complete
D	69	Adenocarcinoma	Pleural	Cisplatin -Pemetrexed -Bévacizumab	non available	40%	34 months	40 months (ongoing)	Partial
E	80	Adenocarcinoma	pancreas, brain	Carboplatin -Pemetrexed	c.3082+1 G>C	90%	5 months	16 months (ongoing)	Partial
F	57	Adenocarcinoma	None (locally advanced)	Cisplatin – Pemetrexed+ radiotherapy	non available	non available	24 months	18 months (ongoing)	Partial

Partial or complete response was rapidly (2 months) obtained in five patients, while pseudo-progression was first observed in D. After a grade 3 diarrhea and diabetic ketoacidosis, ICI was stopped in A but the reintroduction one year later did not cause any toxicity. The tolerance was excellent for the 5 other patients. Response was maintained from 16 to 40 months and treatment is ongoing in four patients. C stopped ICI after 26 months (Complete response on PETscan). B had an isolated bone progression after 7 months of ICI which benefited from a local radiotherapy. After almost 2 years of ICI, a multisite progression occurred and crizotinib was proposed. **Conclusion:** ICIs should be discussed in the treatment of METex14 mut NSCLC.

Keywords: MET exon 14 mutations, Immune checkpoints Inhibitors, Non small cell lung cancers

MA03.10 PROSPECTIVE EVALUATION OF A PROGNOSTIC CLINICO-MOLECULAR SCORE (DEMO) TO PREDICT OUTCOME OF ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

A. Prelaj[1], C. Proto[1], G. Lo Russo[1], D. Signorelli[1], R. Ferrara[1], M. Mensah[1], G. Galli[1], A. De Toma[1], G. Randon[2], F. Pagani[2], M. Brambilla[2], B. Trevisan[1], M. Ganzinelli[1], N. Zilembo[1], F. De Braud[2], V. Torri[3], M. Garassino[1], G. Sozzi[2], M. Boeri[2]

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Background: We have already reported three different molecular (MSC: plasma miRNA-*signature* classifier, *Boeri, Clin Cancer Res 2019*) and clinico-biochemical scores (DiMaio: *Di Maio, EJC 2010*; EPSILoN: *Ann.Onco 2018 supp*) able to differently predict prognosis in advanced non-small cell lung cancer (aNSCLC) patients treated with immunotherapy (IO). Exploiting the ability of each test we developed a combined clinico-biological composite score called DEMo (DiMaio EPSILoN MSC). Objective of the study is to prospectively evaluate the prognostic value of DEMo in aNSCLC patients treated with IO. **Method:** We enrolled 127 consecutive aNSCLC patients treated with IO in first (n=37) and further-lines (n=90) at Istituto Nazionale dei Tumori, Milan. All patients had complete clinico-laboratoristic data necessary for both scores: DiMaio (ECOG-PS, sex, histology, stage, uses of platinum-based therapy at first-line and response to first-line) and EPSILoN (ECOG-PS, Smoke, Liver, LDH, NLRatio). MSC was prospectively evaluated in plasma samples collected prior starting IO and the risk level were assessed. Progression-free survival (PFS) and overall survival (OS) in strata of MSC/DiMaio/EPSILoN alone or DEMo and overall response rate (ORR), were considered as endpoints. Kaplan Meier were used to generate survival curves and Cox hazard model were employed to perform multivariate analyses. **Result:** In multivariate analyses, adjusted for age, sex, pack/year and ECOG-PS, patients with high MSC and high DiMaio and EPSILoN scores reported a lower PFS (MSC: HR 1.72 CI95% 1.06 – 2.77, p=0.027; DiMaio: HR 2.63 CI95% 1.40 – 5.00, p=0.002; EPSILoN: HR 2.17 CI95% 1.16 – 4.16, p=0.014) and OS (MSC: HR 2.17 CI95% 1.29 – 3.70, p=0.003; DiMaio: HR 3.57 CI95% 1.66 – 7.69, p=0.001; EPSILoN: HR 2.50 CI95% 1.15 – 5.26, p=0.020). DEMo stratified patients into four risk groups according to the presence of 3–2–1–0 bad markers (High MSC/DiMaio/EPSILoN or none). Groups had 0%–0%–32.2%–53.3% 1-year PFS (p<0.0001) and 4.4%– 19.4% – 66.9% – 75.4% 1-year OS (p<0.0001). We further compared 0/1 to 2/3 combined groups. At the multivariate Cox model group 2/3 had a mPFS 1.9 vs 9.4 mo compared to group 0/1 (HR 3.70 CI95% 2.08 – 6.67, p<0.0001) and mOS 4.1 vs 22.4 mo (HR 4.76 CI95% 2.56 – 9.10, p<0.0001). Regarding ORR, DEMo group 0/1 had a 3.86 (CI95% 1.76-8.47) fold higher probability to respond compare to 2/3 group (p=0.0007). **Conclusion:** DEMo composite biomarker is able to predict better prognosis compared to each single score and can be a useful tool for guiding IO treatment choices. In particular, DEMo allowed a good selection for those patients who are less likely to benefit from IO.

Keywords: NSCLC, immunotherapy, prognostic score, DEMo, EPSILON

MA03 CLINOMICS AND GENOMICS
SUNDAY, SEPTEMBER 8 10:30–12:00

MA03.11 CHEMOTHERAPY AFTER PD-1 INHIBITORS VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH NON–SMALL CELL LUNG CANCER (WJOG10217L)

E. Miyawaki[1], R. Kato[2], H. Hayashi[2], Y. Chiba[2], J. Shimizu[3], T. Ozaki[4], D. Fujimoto[5], R. Toyozawa[6], Y. Akazawa[7], M. Okuno[8], S. Morikawa[9], T. Ohira[10], T. Harada[11], R. Ushio[12], A. Kubo[13], T. Harada[14], N. Kimura[15], H. Yamaguchi[16], K. Nishikawa[17], N. Yamamoto[18], K. Nakagawa[2]

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Background: Studies have suggested that chemotherapy after immune checkpoint inhibitors may confer an improved response in patients with non–small cell lung cancer (NSCLC). However, potential selection bias in such studies has not been addressed. We therefore applied propensity score analysis to investigate the efficacy of subsequent chemotherapy after PD-1 inhibitors (CAP) compared with chemotherapy alone. **Method:** We conducted a multicenter retrospective cohort study for patients with advanced or recurrent NSCLC who were treated at 47 institutions across Japan between 1 April 2014 and 31 July 2017 with chemotherapy (docetaxel with or without ramucirumab; S-1; or pemetrexed) either after PD-1 inhibitor therapy (CAP cohort) or alone (control cohort). The primary end point was objective response rate (ORR). Inverse probability weighting (IPW) was applied to adjust for potential confounding factors, including age, sex, smoking status, performance status, histology, EGFR or ALK genetic alterations, brain metastasis, and recurrence after curative radiotherapy. **Result:** A total of 1439 patients (243 and 1196 in the CAP and control cohorts, respectively) was available for unadjusted analysis. Several baseline characteristics—including age, histology, EGFR or ALK alterations, and brain metastasis—differed significantly between the two cohorts. After adjustment for patient characteristics with the IPW method, ORR was 18.9% for the CAP cohort and 10.8% for the control cohort (ORR ratio, 1.75; 95% confidence interval [CI], 1.25–2.45; P = .001). Median PFS was 3.5 and 2.6 months for the CAP and control cohorts, respectively (hazard ratio [HR], 0.862; 95% CI, 0.743–0.998; P = .048). The PFS rate at 3, 6, and 12 months was 53.3%, 28.5%, and 4.6%, respectively, for the CAP cohort, and 44.3%, 19.7%, and 6.1% for the control cohort. Median OS was 9.8 months for the CAP cohort and 10.3 months for the control cohort (HR, 0.979; 95% CI, 0.813–1.179; P = .822). **Conclusion:** After adjustment for selection bias using propensity score–weighted analysis, CAP showed a significantly higher ORR and longer PFS compared with chemotherapy alone, with the primary end point of ORR being achieved. However, these results did not translate into an OS advantage, and no PFS benefit was apparent at 12 months despite the improvement observed at 3 and 6 months. Our findings suggest that prior administration of PD-1 inhibitors may result in a synergistic antitumor effect with subsequent chemotherapy, but that such an effect is transient. CAP therefore does not appear to achieve durable tumor control or confer a lasting survival benefit.

Keywords: non-small-cell lung cancer, propensity score, chemotherapy after PD-1 inhibitors

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.01 DEVELOPMENT OF AN IN VIVO PLATFORM TO IDENTIFY NOVEL MECHANISMS GOVERNING LUNG CANCER RESPONSE TO IMMUNOTHERAPY

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Background: Immune checkpoint inhibitors (ICIs) have emerged as a promising therapy for the treatment of advanced stage lung cancer. While these agents elicit durable responses in some patients, most do not respond. An improved understanding of the mechanisms governing ICI response in a complex *in vivo* setting has potential to reveal novel therapeutic combinations to enhance ICI efficacy and associated biomarkers indicative of response. We have developed a syngeneic lung tumour model for *in vivo* CRISPR/Cas9 screens to deduce novel tumour-intrinsic mediators of response to anti-PD1 therapy. **Method:** To delineate physiologically relevant ICI response mechanisms, an *in vivo*, syngeneic and orthotopic lung tumour model with an intact immune system is required. For this purpose, we have developed the *KRAS*-mutant Lewis Lung Carcinoma (LLC) model. Flow cytometry and immunohistochemistry were used to characterize immune cell composition in resected tumours and *in vivo* experiments were conducted to determine the effects of anti-PD1 treatment on LLC tumour growth. **Result:** Luciferase-tagged LLC cells were implanted into the lungs of syngeneic C57BL/6 mice using orthotopic injection and mice reached humane endpoints 10-14 days post injection. Immunophenotyping of dissociated tumours revealed changes in the proportions of myeloid and lymphocyte populations relative to tumour-naïve lungs. CD8+ T-cells were present and tumour cells expressed PDL1 suggesting LLC has the capacity to respond to ICI. Consistent with these observations, orthotopic LLC growth was delayed in mice treated with anti-PD1 therapeutic antibody compared to anti-IgG2a isotype control, demonstrating that LLC is an appropriate model for identifying mechanisms that confer sensitivity and/or resistance to ICI therapy. Based on these findings, we generated LLC-Luciferase cells stably expressing Cas9. Since genome-wide screens are not feasible with this *in vivo* tumour model, we are synthesizing a custom, focussed guide RNA (gRNA) library. Genomic analyses have identified ~500 candidate immunomodulatory genes expressed in LLC and clinical lung tumours that will be targeted to determine the effects of inactivating these candidates on anti-PD1 response. **Conclusion:** This platform will enable high-throughput genetic screens to elucidate novel tumour-intrinsic determinants of ICI response *in vivo*. Our discoveries will have potential to inform novel biomarkers predictive of response, and putative targets for new combination therapies to enhance the anti-tumour effects of ICIs. Collectively, this work will improve our understanding of the biological mechanisms governing ICI sensitivity, thereby stimulating the development of new strategies to maximize therapeutic benefit from ICIs in lung cancer patients.

Keywords: Immunotherapy, CRISPR screen, Lewis lung carcinoma

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.02 MOLECULAR PROFILING OF ADENOCARCINOMA AND SQUAMOUS CELL LUNG CANCER AT SINGLE CELL RESOLUTION

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Background: Adenocarcinoma and squamous are two main subgroups of lung cancer: adenocarcinoma (ADC) accounts for 30-50% and squamous cell carcinoma (SCC) accounts for nearly 30% of all cases respectively. ADC and SCC have different pathological phenotypes and respond differently to various therapies, including immunotherapy. However, the underlying molecular mechanism of such differentiated drug responses still needs to be further characterized. **Method:** To achieve high resolution of both tumor cells and their tumor microenvironment (TME), we used single cell RNA sequencing method to characterize ADC and SCC tumors from Stage IV NSCLC patients. Tissue biopsy samples from 21 patients (12 patients with ADC, 9 with SCC) were collected. For each sample, single cell RNA sequencing was performed on an average of 1930 cells. A graph-based clustering approach was used to classify cells into different cell types based on their gene expression patterns. The cellular subtypes of both cancer cells and TME in ADC and SCC samples were analyzed. **Result:** ADC and SCC show distinct patterns at single cell resolution. Cancer cells from all ADC patients form two closely related clusters, while cancer cells from SCC patients show high intra-and inter-patient heterogeneity. Gene Ontology (GO) analysis demonstrated that ADC samples are enriched in genes of neutrophil degranulation and activation, while SCCs are enriched in genes related to epidermal cell differentiation and glutathione metabolic process. Genes related to cancer progression and metastasis, such as LSD1 and FASCIN, are normally expressed at higher level in SCC than in ADC. Furthermore, ADC samples contain higher percentage of a specific myeloid cell population, while SCC has higher percentage of fibroblasts, demonstrating the difference also in TMEs of ACD versus SCC. **Conclusion:** The significantly higher level of heterogeneity for SCC can be a possible reason for poor responses to standard lung cancer therapies, including immunotherapy. Accurate characterization of SCC with single cell resolution could hold the key to more effective therapeutic strategies.

Keywords: Adenocarcinoma, squamous cell carcinoma, single cell sequencing, immunotherapy, heterogeneity

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.03 LUNG TUMORSPHERES CHARACTERIZATION REVEALS CANCER STEM-LIKE CELLS POTENTIAL TARGETS AND PROGNOSTIC MARKERS IN NON-SMALL CELL LUNG CANCER

A. Herreros-Pomares[1,2], E. Jantus-Lewintre[1,2,3], S. Calabuig-Fariñas[1,2,4], J.D. De-Maya-Girones[5], R. Lucas[4], A. Blasco[2,6], R. Guijarro[2,6], M. Martorell[2,6], E. Escorihuela[1,2], M.D. Chiara[7], E. Durendez-Saez[1,2], C. Gandia[5], R. Sirera[2,3], R. Farràs[5], C. Camps[1,2,4,6]

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of death cancer-related worldwide due to late diagnosis and high resistance against treatments. This resistance has been associated to cancer stem-like cells (CSCs), a highly tumorigenic subpopulation for which the identification of targets and biomarkers is still under development. **Method:** Tissue samples from 8 NSCLC patients were successfully established and cultured using a sphere-forming assay for CSCs enrichment. Adherent counterparts were used as differentiated control cells. Proliferation, chemorresistance, invasion and differentiation capacities were tested *in vitro*, whereas tumor initiation capacity was determined *in vivo*. The expression of 44 CSCs-related genes was assessed by qPCR and protein expression of the best contributors to distinguish adherent cells from tumorspheres was determined by immunoblot and immunofluorescence. The prognostic role of these genes was evaluated in a cohort of 661 resected NSCLC patients from TCGA and validated in an independent cohort of 114 resected lung adenocarcinoma patients. **Result:** Patient-derived tumorspheres showed unlimited exponential growth, high resistance against chemotherapy, great invasion and differentiation capacities *in vitro* in addition to a higher tumorigenic potential than adherent cells *in vivo*. The expression of 17 genes was significantly overexpressed in lung tumorspheres, being *NANOG, NOTCH3, CD44, CDKN1A, SNAI1,* and *ITGA6* the best contributors. Proteins encoded by these genes were consistently increased in tumorspheres from adenocarcinoma patients and showed differential localization and expression patterns. The expression of *CDKN1A, SNAI1* and *ITGA6* was associated to prognosis based on Cox regression analysis (Z-score > 1.5), so their absolute regression coefficients from a multivariate model were used to calculate a gene expression score. Kaplan-Meier survival analysis showed that patients with high score have shorter OS in the entire cohort [37.7 vs. 60.4 mo., $p = 0.001$] and the adenocarcinoma subcohort [36.6 vs. 53.5 mo., $p = 0.003$], but not in squamous cell carcinoma one. Multivariate analysis indicated that this gene expression score was an independent biomarker of prognosis for OS in both, the entire cohort [HR: 1.498; 95% CI, 1.167-1.922; $p = 0.001$] and the adenocarcinoma subcohort [HR: 1.869; 95%

CI, 1.275-2.738; p = 0.001]. The prognostic value of this score was confirmed in an independent cohort of 114 lung adenocarcinoma patients (42.90 vs. NR mo, p = 0.020). **Conclusion:** Proteins encoded by *NANOG, NOTCH3, CD44, CDKN1A, SNAI1,* and *ITGA6* are potential targets against lung CSCs. Elevated gene expression levels of *CDKN1A, SNAI1* and *ITGA6* are associated with worse prognosis. Funded by CB16/12/00350 from CIBEROnc, PI12-02838, and PI15-00753 from ISCIII and Fundacion Arnal Planelles.

Keywords: adenocarcinoma, prognosis, cancer stem cell

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.05 DECIPHERING THE MOLECULAR MECHANISMS UNDERLYING THE PROGRESSION OF BRONCHIAL PREMALIGNANT LESIONS

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Background: The mechanisms underlying the progression of bronchial lesions to squamous cell lung cancer remain undefined. Previously, we hypothesized that bronchial lesions presented individually or combined with each other in the bronchi of non-small cell lung cancer (NSCLC) patients mirror the different scenarios of the premalignant process: individual basal cell hyperplasia (iBCH) – the stoppage at hyperplasia, BCH plus squamous metaplasia (SM) – the progression of hyperplasia to metaplasia, and SM plus dysplasia – the progression of metaplasia to dysplasia. In this study, we aimed to assess the molecular profile of BCH, SM, and dysplasia depending on their co-occurrence in the bronchi of NSCLC patients and to identify mechanisms that are involved in the different scenarios of the premalignant process. **Method:** The samples of lung tissue were obtained at a distance of 4-5 cm from the tumor during surgery of 21 NSCLC patients. Normal bronchial epithelium, BCH, and SM, as well as dysplasia, were isolated from tissue sections using laser microdissection PALM (Carl Zeiss). The microdissected samples underwent whole genome (One Step WGA, Bioron) and transcriptome (Ovation PicoSL WTA System V2, Nugen) amplification and sequenced using the SeqCap EZ Human Oncology Panel (Roche) and profiled using SurePrint G3 Human GE v2 8x60K microarrays (Agilent). Additionally, the samples were sequenced using the Pico Methyl-Seq Library Prep Kit (Zymo Research). Changes in gene expression were confirmed using immunohistochemical staining. **Result:** Genetic alterations were observed already at the early stages of the premalignant process in the bronchial epithelium; however, their number varied from sample to sample. For example, one case of BCH showed more than 10 deleterious mutations in the *GRM5*, *MAML2*, *SP1*, *ETV4*, and other genes, whereas other BCHs carried single alterations. No significant differences were found in the mutational landscape between the iBCH and BCH combined with SM. Bisulfite sequencing demonstrated significant changes in the methylation status of the *SAPCD2* and *ST14* genes in BCH. Importantly, these changes differed between various forms of BCH. Sequencing of SM and dysplasia is in progress and results will be presented later. Gene expression profiling showed differences in the activity of immune response genes between the iBCH and BCH combined with SM and the cell cycle and cilium assembly genes between SMs co-presented with BCH and dysplasia. Overall, the transcription profile of SM co-presented with BCH was closer to BCHs, whereas SM co-detected with dysplasia was similar to dysplasia. Several genes were identified to be expressed specifically in different forms of BCH and SM, among which *CCDC114*, *MAP7D2*, and *LIFR* were confirmed by immunohistochemistry. The loss of CCDC114 and MAP7D2 in SM may serve as an indicator of its progression to dysplasia. **Conclusion:** Taken together, this study demonstrates the significant differences between various types of BCH and SM. These differences support the hypothesis that the isolated and combined forms of the bronchial lesions mirror the different scenarios of the premalignant process as well as explore the mechanisms underlying the progression of hyperplasia and metaplasia to dysplasia. The study was supported by RFBR (#17-29-06002) and the Russian President Fellowship (#SP-1549.2018.4).

Keywords: premalignant lesion, Squamous Cell Lung Cancer, molecular profile

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.06 LUNG EPITHELIUM WHOLE TRANSCRIPTOME SIGNATURES THAT REFLECT INCIDENT LUNG CANCER CASE-CONTROL STATUS

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Background: Focusing early detection and prevention efforts on those at high risk for lung cancer is central to leveraging such strategies. Notably, that risk persists even after removal of a lung cancer, as reflected in lung recurrences, which are common, and usually occur remote from the surgical removal site. This implies risk for future incident lung cancer is represented in the biology of broad areas of lung epithelium, before, during, and after diagnosis. Given that somatic mutations in the bronchial tree are known to persist for decades, there is a suggestion that smoking transforms the entire epithelium at several somatic and gene regulatory levels. *We hypothesize* that the normal lung epithelium contains expression and epigenetic epithelial signatures that are representative of donor case-control status, that is poised for carcinogenesis. **Method:** Methods:As a first step, in order to identify differentially expressed genes (DEGs) associated with aging, smoking and cancer case-control status, we analyzed RNA-seq transcriptome data of laser capture microdissected (LCM) bronchial and alveolar epithelium separately, in paired tissue sets of 40- and 74 respective individuals, summarized here. Read count was the main normalization variable. We also measured differentially methylated sites (DME) by whole genome bisulfite genome sequencing (WGBSeq), covering >60% of the genome/methylome [as of this deadline, these methylome data are not yet fully analyzed]. Result:Mean subject age for 77 total subjects was 65 (+/-9.9), 19% current-, 76% former, 5% never smokers. For each cell type, we modeled gene expression level as a result of aging, gender, smoking and case-control status. We put all four clinical variables age, gender, smoking status, case-control status) along with cell type (alveolar/bronchial) into the model, to avoid potential confounding effects. We discovered 175 DEGs discriminating case-control status (FDR p<0.05) in alveolar and bronchial cells combined, and 420 case-control DEGs with bronchial cells alone. Bronchial cells displayed 31 DEGs discriminating current versus former smokers (FDR-adjusted P<0.05). Gene ontology (David) clusters for case-control discrimination in these "normal" bronchial epithelia included energetics pathways (GO 0042776/0006754; ATP biosynthesis) as well as transcriptional and translational regulation pathways; KEGG clusters also included oxidative phosphorylation pathways (hsa00190), among others. **Conclusion:** There is a donor case-control discriminant expression signature for human lung bronchial captured cells, emphasizing bioenergetically-deranged metabolic pathways, among others. If confirmed in larger studies that measure deranged metabolites directly, metabolomics biomarkers representing bioenergetics and other pathways may serve to define those individuals whose epithelia is tilted toward carcinogenesis, and therefore are at increased risk for lung cancer.

Keywords: transcriptome, case-control, normal lung epithelium

MA04.07 INHIBITION OF CXCR2+ NEUTROPHIL MIGRATION AS A TARGETED THERAPY IN KRAS-DRIVEN LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma (LUAD) accounts for 40% of all lung cancer cases. Although driver mutations in the K-RAS oncogene occurs in 25% of all LUAD cases, to date, there are no available targeted therapies. Infiltrating neutrophils in LUAD are indicative of the worst survival outcomes. The C-X-C motif chemokine receptor 2 (CXCR2) mediates their recruitment to the tumour microenvironment where they promote a pro-tumorigenic environment. CXCR2 ligand expression is higher in KRAS-driven LUAD compared to the other most frequently mutated oncogenes. Therefore, we hypothesize that K-RAS-driven LUAD may be the best candidate for a CXCR2 targeted treatment strategy. **Method:** The PREdiction of Clinical Outcomes from Genomic Profiles (PRECOG) is a dataset of gene expression and survival outcome. The dataset includes data from approximately 18 000 human patients with 39 different malignancies. The dataset was used to determine whether high neutrophil infiltration, CXCR2 expression and CXCR2 ligand expression were associated with poor survival outcomes in LUAD. A 100 patient LUAD tissue microarray was built and stained for neutrophil elastase and CXCR2 by immunohistochemistry. Kaplan-Meier curves were used determine the effect of high neutrophil or CXCR2+ cell infiltration in the LUAD tumour microenvironment on survival outcome. The Cancer Cell Line Encyclopedia (CCLE) is an online dataset that provides gene expression and genotype data from 947 human cancer cell lines (36 cancer types). Expression data of all LUAD cell lines (n=70) from CCLE was obtained for all known CXCR2 ligands. The expression of CXCR2 ligands in K-RAS, EGFR, ALK and ROS-1-driven LUAD cell lines was compared. Microfluidics devices were used to compare the neutrophil recruitment to K-RAS, EGFR, ALK and ROS-1-driven LUAD cell lines. The neutrophil recruitment to each of the cell lines was compared in the presence and absence of CXCR2 inhibition. **Result:** Using the PRECOG dataset, we found that CXCR2 expression in neutrophils is at least 18-fold greater than its expression in other immune cell types. Using all the LUAD cell lines (n=70) available on the CCLE, we found that K-RAS-driven LUAD is the highest CXCR2 ligand expresser as compared to EGFR, ALK and ROS1-driven LUAD. Moreover, using PRECOG, we found that poorer survival outcome is associated with high expression of eight out of nine known CXCR2 ligands ($p < 0.05$). In addition, high neutrophil infiltration in LUAD is associated with the worst survival outcome compared to other immune cell infiltrates ($p < 0.001$). In accordance with the PRECOG data, the presence of infiltrating neutrophils in a 100 patient LUAD tissue microarray is associated with poorer survival outcome when compared to patients with no infiltrating neutrophils ($p < 0.05$). Neutrophil migration to K-RAS, EGFR, ALK and ROS1-driven LUAD cell lines was examined in microfluidics devices and found to be highest in K-RAS-driven LUAD. CXCR2 inhibition reduced neutrophil migration only in K-RAS-driven lung adenocarcinoma ($p < 0.05$). **Conclusion:** CXCR2 inhibition could be an exciting potential targeted treatment for patients with K-RAS-driven LUAD. CXCR2 inhibition is in clinical trials for metastatic melanoma, pancreatic, breast and head and neck cancer. Current evidence suggests that CXCR2 inhibition is safe and tolerable.

Keywords: K-ras, lung adenocarcinoma, CXCR2

MA04.09 STUDY OF EXOSOMES IN NSCLC FOR BIOMARKERS SEARCHING

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Background: Exosomes are small membranous vesicles secreted by a most type of cells (especially in tumoral processes), around 40-130 nm of size, that carry relevant information to distant tissues and being able to modulate its physiology. Exosomes have been detected in different clinical samples and may play a key role in NSCLC, participating in several processes such as horizontal transfer of RNA from tumor to microenvironmental cells, angiogenesis, pre-metastatic niche formation, immunosuppression; and could also be key elements in stem cell differentiation (from different origins). The principal objective of this study was to analyze the exosomes cargo from NSCLC cell lines and primary cultures with diverse characteristics under different growth conditions: suspension cultures with cancer stem cells (CSCs) features and monolayer cultures. **Method:** Primary cultures from resected NSCLC patients and NSCLC cell lines were successfully established. Differentiated tumor cells were cultured under adherent conditions (2D) whereas CSCs were established in suspension cultures (3D tumorspheres). Exosomes isolation was performed by ultracentrifugation. Exosomes characterization was carried out through nanovesicles tracking analysis (NTA) and electron microscopy; and the determination of surface markers through immunoblot and flow cytometry. Exosomal DNA was extracted in order to determine the mutational status of the *EGFR* and *RAS* genes by BEAMing Digital PCR (*Sysmex)*. Transcriptomic analysis has been carried out from exosomal RNA through whole genome gene expression microarrays, (*Affymetrix*). The data was normalized by Robust Multi-Array Average (RMA) and analyzed using Transcriptome Analysis Console (TAC), MultiExperiment Viewer (MeV) software and Partek Genomics Suite. Statistical significance was established at ($p \leq 0.01$). **Result:** In reference to the characterization, NTA and electron microscopy showed that exosomes were obtained free of cellular debris and their size ranges from 108-125 nm, according to the size of tumor-derived microvesicles. Exosomal surface markers analyzed by immunoblot and flow cytometry were detected in samples, confirming proper isolation. Mutational analysis of EGFR and RAS genes performed on exosomal DNA shown the same pattern displayed by the origin cells. Transcriptomic analysis of the exosomal content showed that the expression of mRNAs, miRNAs and precursors were significantly different between 3D and 2D-derived exosomes. Finally, a pathway enrichment analysis was carried out to know in which biological processes (cancer-related) are involved. Significant differential expressions were also found between mRNAs, miRNAs and pre-miRs present in exosomes from adenocarcinoma (ADC) vs. squamous cell carcinoma (SCC). Interestingly, 7 miRNAs differentially expressed in exosomes (miR-200c; miR-29a; miR-339; miR-224; miR-31; miR-21; miR-33a) had already been identified as overexpressed in tumor tissue from NSCLC patients by our group. Moreover, miR-339 y miR-21 were related to prognosis ($p < 0.05$) in ADC group. **Conclusion:** Differences in exosomal mRNA, miRNAs and pre-miRs expression have been observed between: i) lung-tumorspheres vs. more differentiated tumor cells and ii) ADC vs. SCC cultures. In addition, the same mutational pattern was detected in exosomes as compared with their parental cultures. Therefore, exosomes can be a useful source for biomarkers analysis in NSCLC. Supported by grant GV/2018/026, PI18/00266, & Asociación Española Contra el Cáncer (AECC Valencia).

Keywords: NSCLC, liquid biopsy, exosomes

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.10 DEVELOPMENT AND VALIDATION OF A GENE EXPRESSION-BASED PROGNOSTIC SIGNATURE IN EARLY-STAGE SQUAMOUS CELL CARCINOMA OF THE LUNG

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Background: Squamous cell carcinoma of the lung (SqCCL) accounts for about 30% of all lung cancers and is usually associated with smoking. The clinical outcomes of early stage SqCCL are heterogeneous; while 60% of Stage I and II SqCCL patients never present with recurrence after surgery, the remaining will ultimately succumb to the disease. Therefore, a robust prognostication tool is an unmet clinical need. Here, we describe the development and validation of a gene expression-based prognostic signature in Stage I and II SqCCL patients. **Method:** A total of 673 primary tumour samples obtained from surgically resected Stage I and II SqCCL patients were included in this study. The Cancer Genome Atlas (TCGA) cohort contained 365 patients with gene expression data generated using RNA sequencing (RNAseq). Five data sets (GSE30219, GSE37745, GSE50081, GSE4573, GSE14814) containing 308 patients profiled using Affymetrix microarrays were obtained from the Gene Expression Omnibus (GEO) database; batch effect mitigation of gene expression data was performed using ComBat. An additional cohort of consecutive Stage I and Stage II SqCLC patients was assembled at the Tom Baker Cancer Centre (TBCC), University of Calgary and gene expression was profiled using RNAseq. We performed a two-stage development of the gene signature by performing penalized elastic net Cox regression analysis in the TCGA training cohort followed by refinement of the gene list in the compiled GEO database patients. Final validation was performed using the in-house TBCC cohort. Progression-free survival (PFS) and overall survival (OS) were the primary and secondary outcomes of interest, respectively. **Result:** All datasets used in this study were found to consist of patients with comparable clinical characteristics. A gene expression signature associated with PFS was developed in TCGA cohort that significantly stratified patients into high and low risk groups. The signature was refined in the complied GEO database cohort and validated in the U of C cohort. The signature also effectively stratified patients into high and low risk groups based on OS. We are currently performing multivariable analysis of the refined gene signature, adjusting for covariates of known prognostic value. **Conclusion:** Our signature, if prospectively validated, will guide clinical decision making in SqCCL. Effective risk stratification using our signature may identify Stage I patients that will benefit from adjuvant therapy and stage II patients that could be spared adjuvant treatment following surgical resection.

Keywords: squamous cell carcinoma of the lung, Gene Expression, prognostic signature

MS04 MODELS AND BIOMARKERS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA04.11 BIOLOGICAL AND PROGNOSTIC IMPLICATIONS OF THE LONG NON-CODING TRANSCRIPTOME IN TUMOUR-INFILTRATING IMMUNE CELLS

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Background: The lung tumour microenvironment is defined by complex infiltration patterns of immune cells which can contribute to both tumour progression and rejection. The advent of targeted immunotherapies has transformed cancer therapy, leading to durable regression even in late-stage lung tumours. Single-cell RNA sequencing and deconvolution of bulk tumour samples have provided insight into the transcriptomes of tumour-infiltrating immune populations and the regulatory networks that promote cytotoxicity and exhaustion transcriptional programs. Long non-coding RNAs (lncRNAs) have emerged as master regulators of gene expression in tumour cells, but their role in immune cells remains undercharacterized. We sought to delineate lncRNA expression profiles in healthy and lung tumour-infiltrating immune cells in order to better understand transcriptional reprogramming in tumour-infiltrating immune cells and to explore their potential as biomarkers of patient outcome and response to immunotherapy. **Method:** RNAseq profiles of flow-purified adaptive and innate immune subsets were analysed for lncRNA expression, yielding 4919 expressed lncRNAs. Immune lncRNAs were then mapped to tumour and paired non-malignant lung adenocarcinoma samples (TCGA n=108, BCCA n=72) and associated with infiltrating immune populations by deconvolution and methylation-based purity scores. Associations with tumour immunogenicity were assessed by somatic mutational load and expression of tumour-associated antigens. Immune-specific expression of lncRNAs was confirmed in an external single cell RNAseq dataset of lung adenocarcinomas (n=5). **Result:** We found that lncRNA expression patterns display markedly greater cell-type specificity than protein-coding genes in healthy samples, supporting their role in cell-intrinsic transcriptional regulation. 323 immune lncRNAs were differentially expressed in lung tumours compared to matched non-malignant tissue, with enriched expression of immune lncRNAs in tumours with high antigenic load. Many of these genes were positively correlated with CD45 expression and negatively correlated with tumour purity, suggestive of immune cell-restricted expression patterns. Furthermore, a substantial proportion of these genes showed decreased expression in microdissected tumour samples, suggesting that immune-derived lncRNAs may account for gene expression patterns observed in bulk tumour data. We validated these findings in a scRNAseq dataset and analysed co-expression patterns of immune lncRNAs with immune cell markers in order to identify specific immune cell phenotypes and assess the interaction of immune lncRNAs with cytotoxicity and exhaustion transcriptional networks. We identify immune lncRNAs which may regulate expression of important immune genes related to NK and CD8+ T cell cytotoxicity, as well as immune lncRNAs which predict patient outcome and response. **Conclusion:** We present an atlas of lncRNAs expressed in innate and adaptive immune cells, emphasizing the multifaceted roles of lncRNAs in homeostasis and anti-tumour immunity. We highlight the potential of immune infiltrate to confound differential expression analysis of bulk tumour RNAseq data, with consideration needed for tumour purity and immune infiltration levels. Our data provide a resource that will facilitate further identification of functionally and clinically useful lncRNAs.

Keywords: Immune, Genomics

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.01 SECOND OR THIRD LINE ANTI-PD-1 THERAPY AFTER MULTIMODALITY THERAPY INCLUDING TOTAL PLEURECTOMY IN MALIGNANT PLEURAL MESOTHELIOMA

L. Lang-Lazdunski[1], Y.Z. Zhang[2], S. Popat[3], M. O'Brien[4], J. Steele[5], T. Newsom-Davis[6], A. Scherpereel[7], H. Bouchaab[8], A. Rice[9], A. Nicholson[10]

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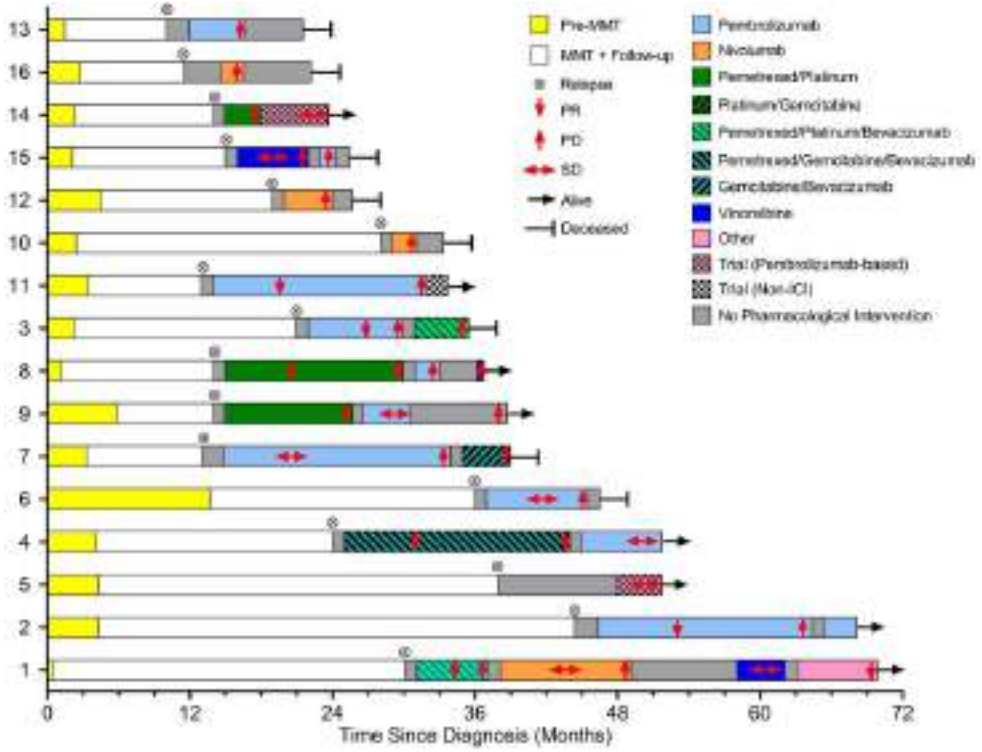
Background: Surgical resection plays an important role in the management of selected patients with malignant pleural mesothelioma (MPM). Early experience with anti-PD-1 immunotherapy showed promise in MPM, but it is yet uncertain if it can improve outcomes when tumour relapses following surgical resection, radiotherapy and chemotherapy. We reviewed our experience in patients who received Pembrolizumab or Nivolumab following multimodality therapy. **Method:** Retrospective study including patients with histologically-proven MPM having completed multimodality therapy and received anti-PD-1 immunotherapy as 2nd or 3rd line treatment. Data were retrieved from a prospective mesothelioma database. Histopathology, BAP1, MTAP and PD-L1 (22C3) immunohistochemistry were performed on surgical specimens and reported by a senior pathologist. All patients had chest computed tomography and positron emission tomography (PET-CT) as part of their normal follow-up. Response evaluation was determined using RECIST 1.1 criteria. **Result:** 16 patients received anti-PD-1 immunotherapy between August 2015 and March 2019.

All patients had total pleurectomy/decortication, prophylactic radiotherapy (21Gy/3) and systemic chemotherapy based on pemetrexed and platinum. Median age was 68.5 years, with male predominance (13/16). 56% had epithelioid type, 44% had biphasic type. Median time to starting immunotherapy was 20 months (range 11-42) following surgery. Median ECOG performance status was 0. Twelve patients received Pembrolizumab and 4 received Nivolumab. Median number of cycles of anti-PD-1 therapy received was 5 (range 1-33). Disease control rate at 12 weeks was 56.2% and 7 (43.7%) patients had disease progression. Adverse events were observed in 6 patients (one Grade 3). Eight patients were alive by 1st April 2019. Median OS from starting immunotherapy was 13.5 months. Three patients received treatment for 14 months or more. Five patients started further therapy after discontinuing immunotherapy. **Conclusion:** In our cohort, second or third-line anti-PD-1 immunotherapy showed efficacy with DCR comparable to non-surgical setting. Further studies are warranted to validate our preliminary findings.



Keywords: Mesothelioma, Immunotherapy, multimodality therapy

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.02 LOG ODDS OF POSITIVE LYMPH NODES PREDICTS OVERALL SURVIVAL AND THE BENEFIT OF POSTOPERATIVE RADIOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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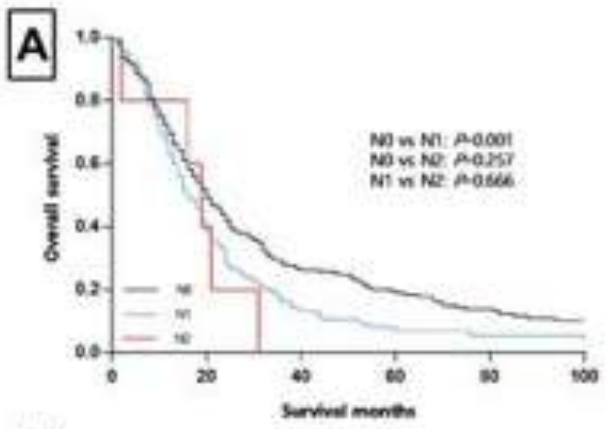
Background: Nodal categories of malignant pleural mesothelioma (MPM) are mostly adopted from lung cancer staging criteria and the N descriptors in the eighth edition of TNM staging system have not been fully verified. We aimed to evaluate the effectiveness of the current N descriptors and a novel prognosticator—the log odds of positive lymph nodes (LODDS)—in predicting overall survival (OS) and postoperative radiotherapy (PORT) benefit in MPM. **Method:** Patients in the Surveillance, Epidemiology, and End Results (SEER) database with MPM undergoing surgery and lymph nodes examination were extracted and restaged according to the 8th edition TNM staging system. LODDS was calculated as $\log_e$[(positive nodes count+0.5)/(negative nodes count+0.5)]. X-tile software determined the optimal cut-point for LODDS. Log-rank tests along with Cox regression analyses were adopted for survival analyses. Harrell's C-index statistic measured discriminatory ability and prognostic performance. **Result:** A total of 534 patients were enrolled in this study. N descriptors were unevenly distributed. Most cases were staged as N0 (51.9%) and N1 (47.0%), with only 1.1% staged as N2. The eighth edition N descriptors failed to clarify the survival difference between adjacent categories and were incapable of predicting PORT benefit. The cut-points for LODDS were classified as follows: LODDS1 (≤-2.61), LODDS2 (-2.56≤LODDS≤0.62), and LODDS3 (≥0.87). The median survival of LODDS1 was 23.1 months compared with 17.9 months (HR=1.397, *P*=0.005) and 13.0 months (HR=2.317, *P*<0.001) for LODDS2 and LODDS3, respectively. The survival curves stratified by LODDS separated nicely without overlapping and the benefit of PORT was limited to cases with LODDS3 (≥0.87). LODDS also provided better C-index than the conventional N descriptors.



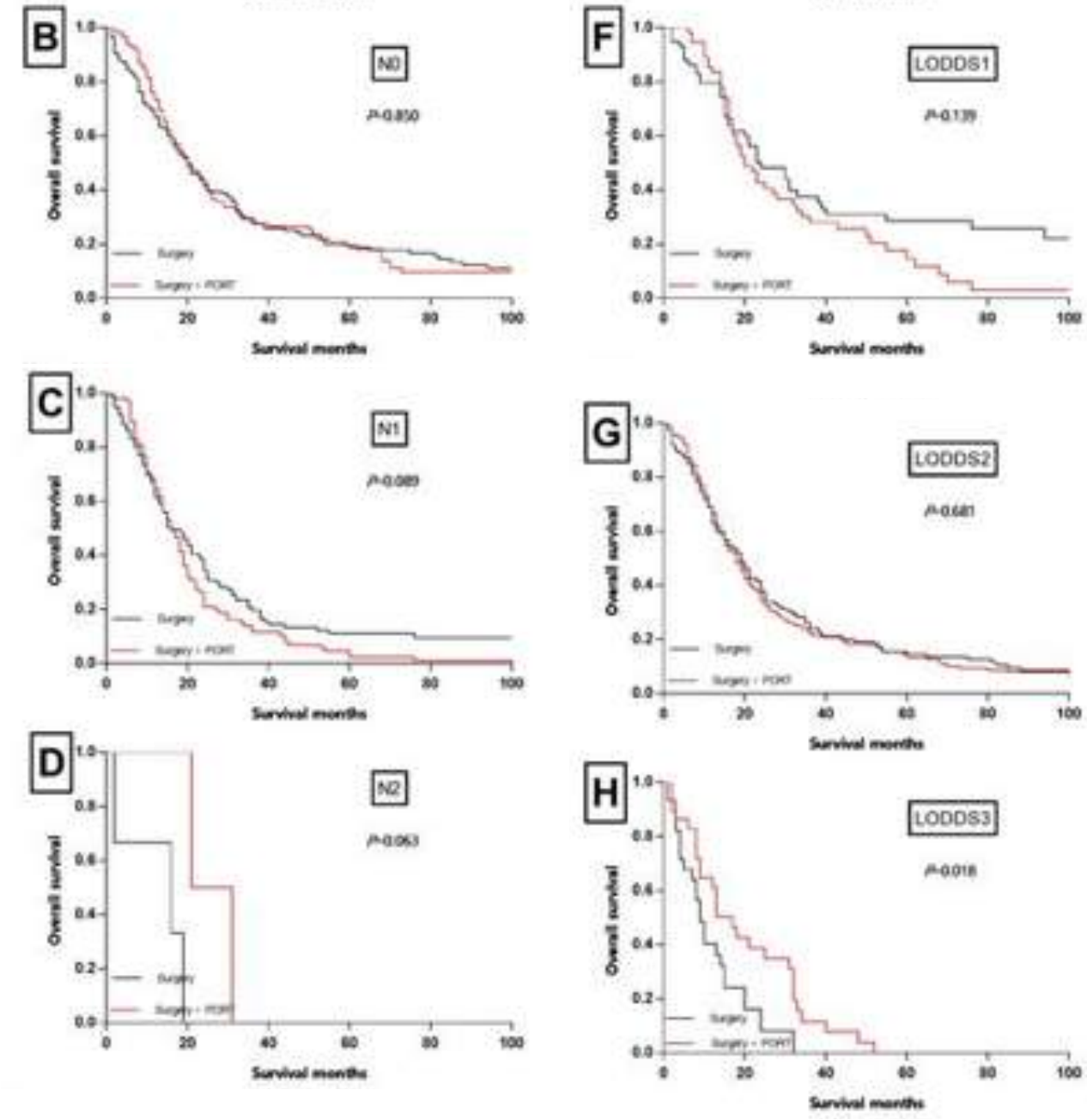


Figure 1 Survival curves stratified by (A) N stages, (B) treatment modality in N0, (C) treatment modality in N1, (D) treatment modality in N2, (E) LODDS, (F) treatment modality in LODDS1, (G) treatment modality in LODDS2, and (H) treatment modality in LODDS3.

Conclusion: LODDS performs better than N descriptors for predicting survival and benefits of PORT in resected MPM, and it could be considered as a potential parameter to compensate for defects in the 8th AJCC TNM staging for MPM.

Keywords: malignant pleural mesothelioma, LODDS, staging

MA05.03 IMPACT OF TIME TO SURGERY ON OUTCOMES IN PATIENTS UNDERGOING OUTRIGHT RESECTION FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: We hypothesized that a longer interval to surgery would be associated with worse overall survival for patients with malignant pleural mesothelioma (MPM). **Method:** The National Cancer Database (NCDB) for patients with cT1-3N0-1M0 MPM who underwent surgery without induction therapy. Patients with interval of <1 or >180 days were excluded. Patients were grouped into quartiles based on distribution of time intervals to surgery: Q1 (1-30 days), Q2 (31-50 days), Q3 (51-80 days), and Q4 (>80 days). The primary outcome was overall survival. Secondary outcomes were upstaging to pN2 and margin-positive (>R0) resection rate. Survival was estimated using the Kaplan-Meier and Cox Proportional Hazards methods. Nodal upstaging and >R0 resection rates were modeled with multivariable logistic regression. **Result:** A total of 812 patients met study criteria. The median interval from diagnosis to surgery was 52 days. The unadjusted median survival for Q1, 2, 3, and 4 was 16, 19, 20, and 27 months, respectively (log-rank p=0.004). In multivariable analysis, increased time to surgery was not associated with worse overall survival (Table 1), and Q4 (>80 days) was independently associated with improved survival compared to Q1. When modeled as a continuous variable, an increased time to surgery was associated with a small but clinically insignificant increase in survival (AHR 0.997; 95%CI 0.995-0.999; p=0.005). In a multivariable regression of factors predicting pathologic upstaging to N2, increased time to surgery was significantly associated with upstaging (adjusted odds ratio [AOR] for Q4 compared to Q1: 2.26; 95%CI 1.04-5.28). In a separate regression of >R0 resection, an increased interval to surgery was not associated with margin-positive resection (AOR 0.70; 95%CI 0.41-1.21). **Conclusion:** An increasing interval from diagnosis to definitive surgery for MPM was not associated with worse overall survival or margin-positive resection, but was associated with higher likelihood of pathologic nodal upstaging in this analysis.

Variable	Adjusted HR	95% CI	P value
Interval (ref:Q1) Q2 Q3 Q4	1.07 0.96 0.74	0.84-1.36 0.76-1.22 0.58-0.95	0.61 0.75 0.02

Keywords: Mesothelioma, surgery, Outcomes

MA05.05 POST-DISCONTINUATION TREATMENTS IN IFCT-GFPC-0701 MAPS TRIAL: REAL-WORLD EFFECTIVENESS OF 2ND-LINE (2L) TREATMENTS FOR MESOTHELIOMA

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Background: MAPS phase 3 trial assessing the addition of bevacizumab to pemetrexed-cisplatin doublet set a new standard of care in malignant pleural mesothelioma (MPM) patients, showing 18.8 months median overall survival (OS) with triplet combo. While both arms were well balanced in terms of 2L treatments, the size of the OS benefit from second-line treatments remains controversial. **Method:** Long-term survival data were collected in the 342 MAPS patients alive at the end of the first-line (1L) treatments, in both arms. Median OS and 2-year survivals were calculated from the initiation of 2L. Multivariate analysis using Cox model included the stratification variables of the MAPS trial, along with the treatment arm (with or without bevacizumab). **Result:** 342/442(77.4%) patients received 2L treatment for disease progression after MAPS trial, of which 324 received chemotherapy (CT), 18 palliative radiotherapy (RT), while 100/442 (22.6%) remained untreated. 160/342 patients (46.8%) had a platinum-based doublet CT. 163 patients (47.7%) received a single-drug CT. 172/324 (53.1%) received a pemetrexed-containing regimen (alone or with platinum), 84 (25.9%) a gemcitabine-based CT, 16 (4.9%) vinorelbin alone, 48 (14.8%) gemcitabine alone, while in 12 (3.7%) single-agent bevacizumab was resumed. Median age was lower in patients with doublet CT (64.4 years, IQR 60.2-68.9) vs. single-drug CT patients (66.3 years, IQR 61.5-70.3), patients receiving RT (68.5 years, IQR 63.3-70.5) or untreated patients (67.8 years, IQR 63.4-71) (p=0.007). There were more PS=2 patients (10%) in the untreated group, compared with 0.6%, 1.8% and 5.6% in those receiving doublet, monotherapy or radiotherapy, respectively (p<0.001). A lower proportion of patients receiving 2L doublet CT had sarcomatoid/biphasic MPM (11.2%) compared with 21.5%, 38.9% and 25% in those with single-arm agent, RT or untreated, respectively (p=0.002). When compared with those treated with 2L single-agent, patients with 2L doublet had more frequently objective response (11.9 vs. 3.1%, p=0.005) and disease control (60.3 vs. 34.6%, p<0.0001). From the date of 2L therapy initiation, median OS was 3.2 months, 95%CI [1.7-5.0] for RT vs. 7.0 months 95%CI[5.6-7.8] for single-agent CT, or 12.2 months 95%CI [9.5-14.1] for doublet CT. HRs were adjusted for 1L treatment type (bevacizumab-containing or not), PS, smoking, and histology. Adj.HR (single-agent vs. doublet) was 1.21, 95% CI(0.96-1.53), p=0.11. Adj.HR (monotherapy vs. RT) was 0.39, 95%CI[0.24-0.65], p=0.0003. Adj.HR (combination CT vs. RT) was 0.32 95%CI[0.19-0.54], p<0.0001. 1-year OS was 11.8%, 95%CI [0.0-27.1], 48.7%, 95%CI [39.9-57.5], and 32.9%, 95%CI [25.1-40.6], in patients with RT alone, single agent CT or combination CT, while 2-year OS was 0%, 14.2%, and 20.0% respectively. **Conclusion:** Second-line monotherapy only gave a 7-months median OS in MPM patients, comparing unfavorably to 11.9 and 15.9-months median OS with 2nd/3rd-line nivolumab or nivolumab+ipilimumab respectively, in the IFCT-1501 MAPS-2 randomized phase 2 trial. Conversely, 2L platinum-based chemo, in younger fit patients, still gave a 12.2-months median OS, not statistically different from monotherapy in the multivariate analysis, as a consequence of PS influence, although clinically meaningful. Based on these results, immunotherapy might be preferred for 2L/3L MPM patients, while monotherapy CT shows limited survival benefit.

Keywords: Mesothelioma, second-line, Chemotherapy

MA05.06 FEASIBILITY AND SAFETY OF TRANSARTERIAL CHEMOPERFUSION FOR ADVANCED PLEURAL MESOTHELIOMA: INTERIM RESULTS OF A PHASE 2 STUDY

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Background: Transarterial chemoperfusion (TAC) treatment selectively delivers relatively high concentration of chemotherapy to the targeted tissue's arterial bed maximizing antitumoral effect and minimizing systemic side effects. Advanced malignant pleural mesothelioma (MPM) carries a poor prognosis. The current prospective study investigates the disease control rate, overall survival and adverse events of TAC treatment in patients with recurrent, advanced MPM. This interim analysis reports the feasibility and safety of TAC in advanced MPM. **Method:** Eligibility criteria included progressive disease following at least one line of chemotherapy and with disease site amenable to TAC. The number of prior treatments was 1.95±1.4 (range: 1-6). Patients had TAC treatment in every 4 weeks with cisplatin (35 mg/m^2), methotrexate (100 mg/m^2) and gemcitabine (1000 mg/m^2) via the ipsilateral internal mammary artery and/or descending thoracic aorta. Response rate was evaluated by modified RECIST for mesothelioma. Survival was defined from date of trial enrollment. **Result:** 23 patients, 3 female and 20 males (age 71±6.5 years) were treated between 3/2016-1/2019. Histology was epitheliod 19, sarcomatoid 3, and biphasic 1. At the data cutoff date (January 31, 2019) 15 patients had died and 128 TAC treatments had been performed; 82 via radial artery access

and 42 via femoral artery access. The median number of treatments was 4/patient (range 1-18). There was no treatment related mortality. Major complication rate was 1.6% (1 fever, 1 ischemic stroke, fully recovered). There were 110 events of minor complications; the most common was chest wall pain during TAC into the internal mammary artery (52), followed by nausea (20). The disease control rate was 70% (1 PR, 15 SD, 7 PD). In addition, clinical benefits of localized tumor shrinkage in the chemoperfused area were observed. Median progression free survival was 4.6 months (95% CI 1.1-8). Median OS was 7.9 months (95% CI 3.6-12.3). **Conclusion:** TAC treatment with triplet chemotherapy in every 4 weeks is feasible and safe. The treatment has promising disease control rate in this group of heavily pretreated patients with MPM. ClinicalTrials.gov Identifier: NCT02611037

Keywords: advanced stage, transarterial chemoperfusion, Mesothelioma

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.07 EFFICACY AND SAFETY OF RE-TREATMENT WITH TREMELIMUMAB AND DURVALUMAB WITHIN THE NIBIT-MESO-1 STUDY

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Background: Targeting immune-checkpoint inhibitors (ICI) had proven effective in a variety of tumor types. However, primary and secondary resistance to treatment is emerging as a major limitation of ICI therapy, and scattered information is available on the therapeutic efficacy of re-treatment in ICI-resistant subjects. Here we investigated the efficacy and safety of re-treatment with tremelimumab and durvalumab in malignant mesothelioma (MM) patients who developed resistance to these agents in the phase II NIBIT-MESO-1 study (Calabrò L et al, Lancet Resp Med 2018). **Method:** Patients eligible for re-treatment *per* the NIBIT-MESO-1 protocol were those who completed 4 dosing cycles of tremelimumab combined with durvalumab, and achieved partial response (PR) or stable disease (SD), followed by progressive disease (PD) during the maintenance with durvalumab or the follow-up phase. Subjects who met the re-treatment criteria received tremelimumab (1 mg/Kg, i.v.) and durvalumab (20 mg/Kg, i.v.) every 4 weeks (Q4W) for 4 doses (re-induction phase), followed by durvalumab (20 mg/Kg, i.v.) Q4W for additional 9 doses (maintenance phase). Objective response rate (ORR), disease control rate (DCR), *per* immune-related (ir)-modified RECIST criteria, overall survival (OS), and safety were evaluated. Adverse events (AEs) were recorded according to CTC v4.0. **Result:** Seventeen (42.5%) of the 40 MM patients enrolled in the NIBIT-MESO-1 study met the criteria for re-treatment and received therapy. Among them 8 (47%) completed the re-induction phase, 7 (41.2.%) went on maintenance phase, and 1 (5%) entered the follow-up phase. As of April 1st 2019, 16/17 patients were discontinued during re-treatment because of PD, and 7 received additional lines of therapy. Seven out of the 17 (41.2%) re-treated subjects had an irSD, while no ir-ORR were observed. At a median follow-up of 35.8 months, median OS of re-treated patients was significantly (p=0.005) higher (25.6 months, 95% CI: 6.1-45.1) as compared to the 23 subjects who were not re-treated (9.9 months, 95% CI: 7.7-12.1). Grade 1-2 irAEs occurred in 6/17 (35%) re-treated patients, were most frequently dermatological and reversible *per* protocol guideline; no grade 3-4 irAEs were observed. **Conclusion:** Re-treatment with tremelimumab and durvalumab of MM patients who developed resistance to therapy in the course of the NIBIT-MESO-1 study is clinically effective and safe in a sizeable proportion of re-treated subjects. Clinical trial infomation: NCT02588131

Keywords: Mesothelioma, NIBIT-MESO-1, Immune Checkpoint Inhibitors

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.09 REAL-WORLD DATA OF NIVOLUMAB AND PEMBROLIZUMAB IN CHEMOTHERAPY PRE-TREATED MESOTHELIOMA PATIENTS

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Background: Both nivolumab and pembrolizumab have shown positive results in phase II studies in patients following chemotherapy in mesothelioma patients. However, these studies were done in a limited number of patients with strict inclusion criteria, while reports show a difference between real life and study setting. **Method:** In our mesothelioma center, we treated patients that progressed during or after chemotherapy treatment with nivolumab 3mg/kg once every 2 weeks independent of PD-L1 expression or with pembrolizumab 200mg once every 3 weeks when PD-L1 expression was ³1%, both in Early Patient Access programs. All patients were pre-treated with at least one cycle of platinum/folate treatment. CT scan evaluation was done using modified RECIST every 6 weeks. **Result:** In total, we treated 78 patients with nivolumab and 13 patients with pembrolizumab. Median age of the patients was 71 years (29-85) at start of the checkpoint inhibitor treatment, 80 (88%) were male. Performance status was ECOG 0 in 19 patients, ECOG 1 in 57 patients, ECOG 2 in 9 patients. Data analysis thus far showed 9 partial responses (10%) and 31 patients with stable disease (29%) and therefore a disease control rate of 39% at twelve weeks of treatment. Median progression free survival is 2.4 months and median overall survival 6,3 months. Median duration of response had not been reached yet. These data will be updated for the meeting. Two cases of pseudoprogression were seen on checkpoint inhibition therapy where progression according to modified RECIST was followed by response during continuation of PD-1 therapy. Toxicity was in line with historical data. **Conclusion:** We believe that this large dataset, using real-world data, can truly give an insight in the clinical benefit of these immune checkpoint inhibitors. In comparison with the published phase I and II trials on nivolumab and pembrolizumab, the response rates appear to be lower in a real-life setting. However, clinically meaningful and durable responses are seen in a population that has no other proven therapy options.

Keywords: checkpoint inhibition, Mesothelioma, Immunotherapy

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.10 PEMBROLIZUMAB IN THE TREATMENT OF PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA FOLLOWING PROGRESSION AFTER INITIAL CHEMOTHERAPY

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Background: Checkpoint inhibitor (CPI) therapies have demonstrated clinical benefit in patients (pts) with malignant pleural mesothelioma (MPM) and are now included in the NCCN guidelines as an acceptable treatment option. Herein, we report our initial experience treating pts with MPM in the palliative second line or greater setting. **Method:** Between January 2016 and November 2018, 74 pts with biopsy proven MPM were treated with pembrolizumab every three weeks until confirmed disease progression or unacceptable toxicity. Progression-free survival (PFS) and OS were defined as the time from first pembrolizumab dose to recurrence and death, respectively, or to last contact. Response rates (RR) were measured by a dedicated thoracic radiologist using modified RECIST 1.1 criteria. Adverse events were routinely recorded/scored at each follow up visit. according to CTCAE 4.0 with level of attribution to pembrolizumab. **Result:** Demographics of the 74 pt cohort are shown in table 1. Twenty-nine (39%) of pts experienceda total of 39

grade 1-2 adverse events, possibly or definitely related to therapy (Table 2). There was one grade 4pneumonitis that resulted in new requirement for oxygen, which resolved with steroids; and one patient experienced leukoencephalopathy that resulted in death. The overall response rate (including only partial responses by modified RECIST 1.1) for the entire cohort was 26%. Median progression free survival and overall survival for the entire cohort were 2.8 months and 7.9 months, respectively.

Table 1: Demographics		
Age in Years	median (range)	
Min	73	(52-92)
Gender	Patients (N=74)	
Female	29	39%
Male	55	74%
Histology		
Epithelial	58	78%
Sarcomatoid	6	8%
Biphasic	10	14%
# of chemotherapy courses		
0	3	4%
1	42	57%
2	22	30%
3-4	7	9%
# of radiotherapy courses		
0	42	57%
1	30	41%
2-3	6	8%
Surgical Resection		
Have EPD	24	32%
Did not have EPD	50	68%
PDL1		
Negative	21	28%
Positive	12	16%
Not Determined	42	57%

Table 2: Adverse Events	CTCAE 4.0 Grade		
AE Description	1-2	3-4	5
hypothroid	5		
arthralgias	8		
colitis	3		
diarrhea	2		
lip lesion	1		
pneumonitis	2	1	
SICCA syndrome	1		
thrombocytopenia	1		
dermatitis	1		
hypopigmentation	1		
nephritis	1		
fatigue	1		
abdominal pain	1		
uveitis	1		
transaminitis	1		
elvated alk phos	1		
leukoencephalopathy			1
pruritis	3		
hypercalcemia	3		
rash	2		

Conclusion: Pembrolizumab in the Tx of MPM was reasonably well tolerated in this large, single institution experience. RR, PFS and OS appear remarkably similar to recent published data from a registry study of off-label use of pembrolizumab in pts with MPM in Switzerland and Australia (include reference). Ongoing studies include analysis of PDL-1 and other potential immunotherapy response biomarkers.

Keywords: Mesothelioma, Immunotherapy

MS05 UPDATE ON CLINICAL TRIALS AND TREATMENTS
SUNDAY, SEPTEMBER 8 13:30–15:00

MA05.11 SAFETY AND EFFICACY OF NINTEDANIB IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH REFRACTORY/RELAPSING MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive disease with no standard of care after progression to first line pemetrexed and platinum-based chemotherapy. Combinations between anti-angiogenic agents and immunotherapy are being developed as angiogenesis and immunosuppression influence each other leading to a more powerful anti-tumor response. Both Nintedanib and Pembrolizumab have been investigated as single agents or in different treatment combinations in MPM patients with interesting activity. **Method:** The PEMBIB trial is a multi-centric open-label non-randomized basket phase 1 trial evaluating the combination of nintedanib with pembrolizumab in multiple tumor types. The safety and activity of the dose escalation part of the study were reported at AACR & ASCO meetings in 2018 with an established DLT defined as grade 3 alanine and/or aspartate aminotransferase elevation (ALT/AST). The recommended phase 2 dose is set at 150

mg BID of nintedanib with 200 mg flat dose of pembrolizumab. We would like to report the safety and activity of one of the expansion cohorts of patients with relapsing/refractory MPM which has now been completed. Eligible MPM patients were 18 years or older with an ECOG performance status of 0 or 1, histologically proven MPM that relapsed after at least one line of pemetrexed and platinum-based combination, specific anti-angiogenic eligibility criteria such as no radiographic evidence of cavitary/necrotic or tumors with local invasion of major blood vessels. Updated results on the safety profile and efficacy of this anti-angiogenic and anti-PD-1 combination therapy including overall response rate as per RECIST, irRC and mRECIST criteria, disease control rate will be presented at the meeting. **Result:** The first patient from the MPM cohort was enrolled in July 2017 and the last one in April 2019. Thirty-one eligible MPM patients have been evaluable at the data cut off onJuly 2019, one of them had been enrolled since the dose-escalation part at dose level of 200mg. The age at inclusion was 68 (ranging from 38 to 85), 68% of the patients having an ECOG of 1 and 58% of the histological type was epithelioid. The most frequent adverse events (grades 1, 2 and 3) related to any of the combination drugs were liver enzymes increase, fatigue, decreased appetite, nausea, diarrhea and hypothyroidism. There were two cases of myocarditis, one of grade 3 (pembrolizumab related) and one of grade 5(pembrolizumab and nintedanib related). At the time of the data analysis the efficacy data shows six partial responses (overall response rate of 21%) and seventeen stable disease (disease control rate at 61%.). **Conclusion:** The combination of Nintedanib with Pembrolizumab shows promising activity in relapsed MPM patients .The toxicity profile appear consistent with previous reports of anti-angiogenic agents and immunotherapy combination.

Keywords: mesothelioma, nintedanib, pembrolizumab

MA06.01 MEDIASTINAL LYMPH NODE DISSECTION (MLND) V SYSTEMATIC SAMPLING (SS) V NEITHER (NN) IN POPULATION-BASED COHORT

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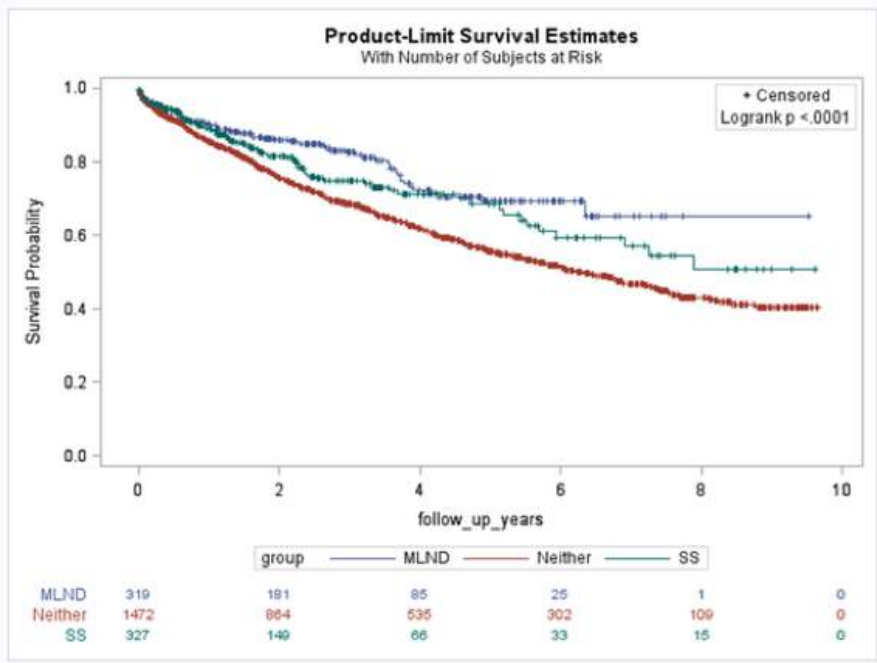
Background: American College of Surgeons' Oncology Group (ACOSOG) Z0030 revealed similar survival after MLND v SS for early-stage non-small cell lung cancer (NSCLC), but a recent meta-analysis of 1,980 patients in 5 randomized controlled trials from 1989-2007 suggested superior survival after MLND, raising doubts about Z0030 findings. We compared survival of patients with MLND v SS v NN in a population-based cohort. **Method:** All resections for NSCLC in all institutions within 4 contiguous United States Hospital Referral Regions from 2009-2018 stratified by ACOSOG Z0030 nodal examination criteria into MLND (stations 2R,4R, 7, 8, 9 and 10R for right-side resections; 4L, 5, 6, 7, 8, 9, and 10L for left-sided), SS (minimum of 4R, 7, and 10R on the right and 5,6,7 and 10L on the left, but MLND definition not met), and NN (neither MLND nor SS). Using appropriate statistical tests, we compared demographic and clinical characteristics, perioperative complication rates and survival, adjusting survival for extent of resection, histology, age, race, sex and insurance. **Result:** 2118 patients met Z0030 eligibility criteria (clinical T1/2,N0/non-hilar N1,M0): 15% had MLND, 15% SS, 69% NN. The distribution of age, race, insurance was similar, but 54% v 51% v 43% of MLND v SS v NN, were female (p=.0002). Use of preoperative PET-CT scans was similar (p=.5797), but invasive staging was used in 21% v 19% v 28% (p<.01), Although the distribution of clinical T,N and aggregate stage was similar (p>.05), 10% of the patients who met neither MLND nor SS criteria had no lymph nodes examined (pathologic NX). The median (interquartile range) number of mediastinal lymph nodes examined was 8(6-12), 5(4-8), 2 (0-5) (p<.001); hilar/intrapulmonary nodes 5(2-9), 6(3-10), 3(1-7) (p<.001). Postoperative complication rates were similar, including rates of cardiac arrhythmia, chylothorax and ICU re-admission. ICU length of stay (LOS) was 1(1-2) days in all groups, hospital LOS was 5(3-7), 5(3-8), 6(4-10) days. The 30-day mortality rate was 4% for all groups. Unadjusted hazard ratio (HR) was 0.80 (0.56-1.10, p=1.664) between MLND and SS; adjusted (a)HR 0.81 (0.58-1.138, p=0.2273). Survival of MLND and SS patients was significantly better than NN (Figure): aHR 0.62(0.48-0.81, p=0.0004) for MLND v NN; aHR 0.76 (0.60-0.98, p=0.0304) for SS v NN.



Conclusion: ACOSOG systematic nodal dissection was achievable and safe in a 'real-world,' population-based cohort. SS was associated with similar survival to MLND in early-stage NSCLC, corroborating Z0030 findings. However, the majority of resections did not attain either criteria, with significantly worse survival.

Keywords: ACOSOG Z0030, Survival, NSCLC

MA06 CHALLENGES IN THE TREATMENT OF EARLY STAGE NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

MA06.02 NSCLC SURGERY OUTCOMES BETWEEN FACILITY TYPES AND ASSOCIATION WITH GUIDELINE DIRECTED SURGICAL QUALITY OF CARE METRICS

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Background: Non-small cell lung cancer (NSCLC) treatment outcomes differ between facility types. Surgical outcome differences may be related to modifiable factors and likelihood of receiving guideline centered care, which could be improved with new policy initiatives. We therefore analyzed the National Cancer Database (NCDB), to determine the variables related to different outcomes between facility types. **Method:** The NCDB is a cancer registry curated by the Commission on Cancer that captures demographic and clinical data for an estimated 80% of NSCLC patients in the United States. A retrospective analysis of the NCDB was performed from 2004-2013 for Stage 1, 2 and 3a NSCLC patients treated with surgery. We compared overall survival between academic comprehensive cancer programs (ACAD) and community cancer programs (CCP) and four surgical quality metrics; lobectomy or greater vs sublobectomy, positive vs negative margin status, whether regional lymph node (LN) surgery was performed and number of nodes removed (less that 10 or equal to or greater than 10), in addition to 16 other demographic and clinical variables known to affect NSCLC survival. Kaplan-Meier estimates, log-rank test, multivariate Cox proportional hazard models and propensity score matching were used to evaluate survival differences while adjusting the effects of covariates. Quality of matching was checked using Wilcoxon rank sign test, chi-square test, and multivariate logistic regression models. **Result:** The total cohort was 75,976 patients. After propensity matching for clinical and demographic variables, median overall survival (OS) for Stage 1, 2 and 3a was 76, 51 and 36 months for ACAD and 67, 43 and 32 months for CCP respectively ($p<0.002$ for all). Overall, selection of lobectomy or greater was the same between facility types ($p=0.645$), but ACAD were more likely to have negative margins (92.3% vs 89.8%, $p<0.00001$), perform LN dissection (89.5% vs 84.3%%, $p<0.00001$) and remove greater than 10 LN (37.4% vs 23.1%%, $p<0.00001$). After contrast matching for the surgical quality metrics, OS for Stage 1, 2 and 3a was 73, 49 and 34 months for ACAD and 67, 43 and 32 months at CCP respectively, with a non-significant P value for Stage 3a sub-cohort. Analysis revealed that the four key surgical quality measures explained 38% of the OS difference in median survival ($p<0.00001$). **Conclusion:** In this large cohort of Stage 1, 2 and 3a NSCLC patients treated surgically, OS was higher at ACAD compared to CCP, which was in part explained by differences in surgical quality metrics. In the era of discussions of nationalized healthcare, policymakers will need to consider the differential treatment outcomes at different centers and consider consolidating treatment for NSCLC at high performing centers or improving the quality care measures of low performing centers.

Keywords: facility type; quality of care

MA06 CHALLENGES IN THE TREATMENT OF EARLY STAGE NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

MA06.03 POOR PULMONARY FUNCTION DOES NOT DEFINE "MEDICAL INOPERABILITY": SHORT AND LONG TERM RESULTS OF A MATCHED LUNG CANCER COHORT

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Background: Patients with suboptimal pulmonary function tests (PFTs) are often denied surgery for NSCLC. However, there is no consensus definition of compromised lung function. This study compared morbidity and survival following surgery in patients with preoperative %predicted FEV_1 or DLCO ≤50% (Low-Group) versus those with both values >50%(High-Group). **Method:** A prospectively-maintained database was reviewed for patients undergoing surgery for NSCLC between 1990–2019. Propensity matching (1:2) was performed based on age, gender, histology, pathologic stage, and comorbidity index. Overall survival (OS) was estimated using Kaplan-Meier analysis and multivariable analysis identified predictors of survival. **Result:** Among 2982 patients with PFT data, 372(12.5%) had FEV_1 or DLCO ≤50%. We matched 321 patients with FEV_1 or DLCO ≤50% to 637 patients with both PFTs >50%. No significant differences were observed in perioperative complications(Table) or 30-day mortality between Low and High groups (0.3% vs. 0.6%, $p=0.668$). The Low group more frequently underwent sublobar resection (41% vs. 22%, $p<0.001$). Median follow-up was 41 months, and median, 3-, and 5-year OS for the Low and High groups was 118 vs.148 months, 79% vs. 82%, and 70% vs. 74%, respectively ($p=0.003$). Patients with both FEV_1 and DLCO ≤50% (n=44) had a median survival of 109 months and 3- and 5-year OS of 77% and 71%. Multivariable analysis identified advanced age (HR=1.03, CI 1.01–1.05), higher clinical stage (HR=1.85, CI 1.22–2.82), and earlier year of surgery (HR=1.06, CI 1.01–1.12) as predictors of poor survival, but not FEV_1 or DLCO ≤50% ($p=0.672$). Among the Low group only, advanced age (HR=1.05, CI 1.02–1.07) and sublobar resection (HR=1.60, CI 1.04–2.45) predicted worse OS.

Matched Patients (N= 958)	Low PFT Group (N= 321)	High PFT Group (N= 637)	P value
Median LOS, days (IQR)	5 (4 – 8)	5 (4 – 6)	< 0.001
Any complication	69 (22%)	115 (18%)	0.202
Pulmonary complications	51 (16%)	74 (12%)	0.064
Cardiovascular complications	22 (7%)	40 (6%)	0.733
Thromboembolic complications	3 (1%)	6 (1%)	1
Infectious complications	8 (2%)	14 (2%)	0.774
Mortality (30-day)	1 (0.3%)	4 (0.6%)	0.668
Median survival, months (IQR)	118 (107 – 132)	148 (139 – 152)	0.003
5-year Overall Survival	70%	74%	

Conclusion: Patients with decreased lung function have comparable perioperative outcomes to patients with normal lung function and experience excellent long-term survival. "Medical inoperability" should therefore be determined by surgeons and not by pulmonary function alone.

Keywords: pulmonary function, surgery, Lung cancer

MA06.05 PREDICTIVE PERFORMANCE OF QUANTITATIVE METABOLIC METRICS OF FDG-PET/CT ON SURVIVAL AND THE EFFECT OF ADJUVANT CHEMOTHERAPY IN LUNG CANCER

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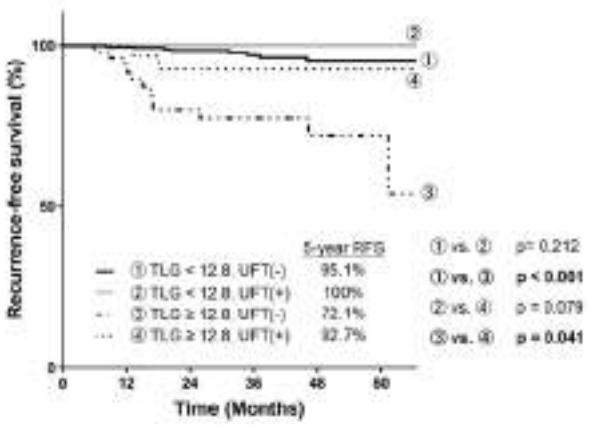
Background: Growing evidence suggests metabolic metrics of tumors, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) on FDG-PET/CT, reflect the malignancy of early-staged lung cancer. We aimed to investigate the role of metabolic metrics in predicting prognosis and response to adjuvant chemotherapy in pathological stage I (the 7th Edition of TNM Staging of Lung Cancer) lung adenocarcinoma (p-I Ad). **Method:** The study included 452 patients with p-I Ad who underwent FDG-PET/CT followed by complete resection between July 2012 and December 2017. In this study, MTV is defined as the total tumor volume with an SUV > 2.5 while TLG is calculated as mean of SUV x MTV. The three metabolic metrics measured by a three-dimensional workstation and clinico-pathological factors were analyzed to identify the factors associated with unfavorable overall survival (OS) and recurrence-free survival (RFS). We assessed whether the metabolic metrics were associated with response to oral adjuvant chemotherapy with uracil-tegafur (AC with UFT) in patients with p-I Ad amenable to the treatment. **Result:** All the three metabolic metrics were significantly correlated with unfavorable OS and RFS on univariate analyses (SUVmax; p=0.047 / p<0.001, MTV2.5; p=0.003 / p<0.001, TLG2.5; p=0.005 / p<0.001). On multivariate analyses, smoking status (p=0.043), the value of serum CEA (p < 0.001), and SUVmax (p=0.001) were independent determinants for poorer RFS while gender (p=0.013) and MTV2.5 (p=0.028) were independent significant factors for unfavorable OS. The receiver operating characteristic areas under the curves for SUVmax, MTV2.5, and TLG2.5 relevant to recurrence were 0.901, 0.849, and 0.872, respectively. Among 239 patients who fitted the criteria of AC with UFT (p-IA > 2cm or p-IB), 80 patients (33.4%) received the treatment (250 mg of tegafur per square meter of body-surface area per day). Although the administration of AC with UFT did not significantly affect RFS and OS (p=0.411 and 0.753), patients with TLG2.5 > 12.8, which value corresponded to the cut-off level, who were not given AC with UFT exhibited worse RFS than those who received the treatment (5-year RFS rate of 72.1% vs. 92.7%; p=0.041).



Conclusion: Metabolic metrics on FDG-PET/CT such as SUVmax, MTV, and TLG enable us to estimate survival outcomes and the effectiveness of AC with UFT in patients with p-I Ad. Patients with metabolically active tumors should be considered high risk, and this information can be useful for the selection of appropriate therapeutic strategy including AC with UFT.

Keywords: FDG-PET/CT, lung adenocarcinoma, adjuvant chemotherapy

MA06 CHALLENGES IN THE TREATMENT OF EARLY STAGE NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

MA06.06 A PHASE III STUDY OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED, NODE-NEGATIVE NON-SMALL CELL LUNG CANCER

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Background: Post-operative UFT (tegafur/uracil) has been shown to prolong survival of Japanese patients with completely resected, p-stage I (T1> 2 cm) non-small cell lung cancer (NSCLC). This trial, the Japan Clinical Oncology Group (JCOG) 0707, aimed at estimating the efficacy of S-1 (tegafur/gimeracil/oteracil) compared to UFT as adjuvant therapy in this population. **Method:** Eligible patients had received complete resection with lymph node dissection for p-stage I (T1-2N0M0, T1> 2 cm, by 5thEdition UICC TNM) NSCLC, within 56 days of enrollment. Patients were randomized to receive: oral UFT 250mg/m^2/day for 2 years (Arm A), or oral S-1 80mg/m^2/day for 2 weeks and 1 week rest, for 1 year (Arm B). The initial primary endpoint was overall survival (OS). Based upon the monitoring in Jun. 2013, which showed the combined OS of the 2 arms better than expected (4-year OS of 91.6% vs. presumed 5-year OS of 70-76.5%), it was judged to be underpowered. The study protocol was amended so that the primary endpoint is relapse-free survival (RFS). With the calculated sample size of 960, this study would detect the superiority of Arm B over Arm A with power 80% and one-sided type I error of 0.05, assuming the 5-year RFS of 75% in Arm A and the hazard ratio of 0.75. **Result:** From Nov. 2008 to Dec. 2013, 963 patients were enrolled (Arm A:482, Arm B:481): median age 66 (range: 33 to 80), male 58%, adenocarcinoma 80%, p-T1/T2 46%/54%. Only 2 received pneumonectomy. ≥Grade 3 toxicities (hematologic/nonhematologic) were observed in 15.9 (1.5/14.7) % in Arm A, and in 14.9 (3.6/12.1) % in Arm B, respectively. 60.0% of the patients in Arm A and 54.7% of them in Arm B completed the protocol treatment (p=0.10). There were 4 cases of deaths during protocol treatment, probably of cardio-vascular origin, with 1 in Arm A and 3 in Arm B. At the data cut-off of Dec. 2018, the hazard ratio (HR, Arm B vs. Arm A) of RFS was 1.06 (95% confidence interval (C.I.): 0.82-1.36), showing no superiority of S-1 over UFT. The HR of OS was 1.10 (95% C.I.: 0.81-1.50). The 5-year RFS/OS rates were 79.4%/88.8% in Arm A and 79.5%/89.7% in Arm B, respectively. Pre-specified subset analyses for gender, age, smoking, stage, tumor side, lymph node dissection area, pleural invasion and histology revealed no remarkable results; S-1 arm was not superior to UFT arm in each analysis. Of the 77 and 85 OS events for Arm A/Arm B, 45 each (58%/53%, respectively) were due to the NSCLC. During the follow-up period, secondary malignancy was observed in 85 (17.8%) and 84 (17.8%) in Arm A and Arm B, respectively. **Conclusion:** Post-operative adjuvant therapy with oral S-1 was not superior to that with UFT in stage I (T>2 cm) NSCLC after complete resection. UFT remains standard in this population. Future investigation should incorporate identification of high-risk population for recurrence, since survival of each arm was so good with substantial number of OS events due to other causes of deaths in this trial.

Keywords: Non-Small Cell Lung Cancer, Adjuvant therapy, Node-negative

MA06.07 E1505: ADJUVANT CHEMOTHERAPY +/- BEVACIZUMAB FOR EARLY STAGE NSCLC: UPDATED CHEMOTHERAPY SUBSET ANALYSIS

H. Wakelee[1,2], S. Dahlberg[3], S. Keller[4], W. Tester[5], S. Aisner[6], J. Rothman[7], J. Patel[8], R. Delaune[9], S. Mcdermott[10], A. Shafqat[11], R. Perez-Soler[12], A. Chapman[5], S. Kasbari[13], A. Traynor[14], T. Evans[15], L. Horn[16], S. Graziano[17], D. Gandara[18], A. Adjei[19], C. Butts[20], N. Leighl[21], S. Ramalingam[22], J. Schiller[23]

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Background: Adjuvant chemotherapy (chemo) for resected early stage NSCLC provides modest survival benefit with limited comparison data between regimens. From this trial we previously reported that adding bevacizumab (B) to adjuvant chemo failed to improve either disease free survival (DFS) or overall survival (OS). Here we update outcomes by chemotherapy regimen with an additional 30 months of follow-up. **Method:** Enrolled patients with resected early stage NSCLC, stratified by stage, histology, sex, and chemo option, were randomized 1:1 to chemo alone or with B (15 mg/kg every 3 weeks for up to 1 year). Chemo consisted of a planned 4 cycles of every 3 week cisplatin with either vinorelbine (V), docetaxel (D), gemcitabine (G) or pemetrexed (P). **Result:** From July 2007 to September 2013, 1501 patients were enrolled with this distribution of chemo: V 25.0%, D 22.9%, G 18.9% and P 33.2%. P was added in 2009 and restricted to non-squamous (NSq) pts. Chemo regimen was chosen (not randomized). Arms were well balanced for known prognostic factors; 28% had Sq histology. Median f/up per chemo group is: V 83.5 months(m); D 89.9m; G 87.8m; P 71.9m. In pooled analysis DFS differed by histology ranging from 29.9m(G)-43.5m(V) for NSq and 59.4m(V)-77.3m(G) for Sq. OS also differed by histology ranging from 80m(D)-98.8m(P) for NSq and 98m(G)-119m(V) for Sq. A non-significant decline in both DFS and OS was seen when B was added to D or V regimens, regardless of histology. Conversely, the addition of B to P improved both DFS (HR 0.74, p= .00994) and OS (HR 0.65, p= .00368). We thus compared outcomes across non-B regimens and though numerical differences were seen in median DFS and OS, these failed to reach statistical significance. Toxicity details were presented previously. **Conclusion:** B did not improve OS when added to adjuvant chemo for patients with surgically resected early stage NSCLC, though variable DFS and OS outcomes by chemotherapy regimen have emerged with longer-term follow-up. These include a significant positive improvement in DFS and OS with B combined with P and trends of worse outcomes when B was added to other regimens. Ongoing molecular analysis of samples will hopefully elucidate the etiology of these differences.

MA06.09 TIMING OF DRIVER MUTATION DEVELOPMENT AND THE GENETIC EVOLUTION OF SEMI-SOLID LUNG NODULES INTO EARLY NSCLC

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Background: The genetic changes that drive the appearance of a ground glass opacity and subsequent development of an invasive solid component within a semi-solid lesion (SSL) are not well understood. Biomarkers that predict the transition to invasive cancer are needed to determine when ground glass lesions will evolve into invasive cancer. **Method:** From a prospective database 65 patients with surgically resected SSL between 2011-2018 were identified. Clinical characteristics and disease free survival was compared between SSL and 155 stage I adenocarcinomas resected during the same time period. Paraffin tissue blocks were obtained from 22 of the SSL and areas of normal lung (NL) ground glass (GG) and solid (S) tumor were identified and microdissected separately from within the same lesion. Next generation sequencing (NGS) was performed on DNA extracted from 19 nineteen matched GG and S samples on twenty-five common lung cancer driver mutations. Affymetrix microarray of over 48,000 transcripts was performed on S, GG, and NL samples from eight patients with SSL. **Result:** No patients with a resected SSL has recurred to date with significant differences in 5-year disease free survival verses stage I adenocarcinomas from the same time period (100% vs 80.9%, log-rank p-value 0.007). Driver mutations in the solid component of SSL were EGFR mutation (43%; L858R 26% and exon 19 deletion 11%), KRAS mutation (21%), and no mutation identified (42%). All driver mutations present in S component of SSL were also identified in GG regions of the same lesion with very similar gene expression profiles. Only 32 transcripts were significantly different between GG and S areas of the same tumor. The greatest difference observed between GG and S portions of the same tumor was significantly higher expression of secreted phosphoprotein 1 (SPP1) in the invasive solid portion suggesting that SPP1 may serve as a biomarker of invasive potential. **Conclusion:** This is the first study to examine the systems genetics of mutations and gene expression from the microenvironments of solid and ground glass areas within the same tumor. Mutations are present in the ground glass portion of a semi-solid tumor suggesting early development of driver mutations. Increased expression of SPP1 emerged as the most promising biomarker of invasive potential of a semi-solid lesion. In other studies SPP1 has been shown to correlate with poor prognosis and is a biomarker that warrants further study.

Keywords: Ground glass opacity, Systems genetics, Semi-solid lesion

MA06.10 STEREOTACTIC ABLATIVE RADIOTHERAPY IN THE MANAGEMENT OF SYNCHRONOUS EARLY STAGE NON-SMALL CELL LUNG CANCERS

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Background: The aim of the study is to evaluate the efficacy and patterns of failure of early stage synchronous non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy (SABR). **Method:** Patients with synchronous NSCLC who received SABR (50 grays in 4 fractions or 70 grays in 10 fractions) to at least one lesion were reviewed. Synchronous lesions were defined as multiple ipsilateral or contralateral intrapulmonary lesions diagnosed within 6 months. **Result:** Out of a total of 912 patients treated with SABR for early stage NSCLC between 2005 and 2015, 82 (9%) had synchronous disease. The median age was 70 years and 34 (41.5 %) patients were males. The median diameter was 2.1 cm (Interquartile range (IQR) 1.6-3 cm) for index lesions and 1.5 cm (IQR 1.1-2.2 cm) for second lesions. At a median follow-up time of 58 months, the 1, 3 and 5-year progression-free survival (PFS) rates were 85.4%, 47.3% and 28.5%, respectively; the corresponding overall survival rates were 95.1%, 66.9% and 52.4% and the 1, 3 and

5-year local recurrence (LR)-free survival rates were 97.3%, 79.6% and 70.8%, respectively. Among the 39 (47.6%) patients with disease progression, intralobal LR was the first site of failure in 15 (18.3%) patients, with a total of 19 local recurrences out of 169 (11.2%) thoracic lesions. Isolated regional recurrence occurred in 3 (3.7%) patients, and distant failure in 221 (25.6%) patients. On multivariate analysis, factors associated with improved PFS were an improved ECOG PS score (HR 10.786; 95% CI 2.845-40.902; p-value <0.001), DLCO (HR 0.947; 95% CI 0.903-0.994; p-value 0.026) and an index lesion pathology of adenocarcinoma (HR 0.167; 95% CI 0.033-0.841; p-value 0.030). Only the ECOG PS score maintained significance (HR 6.165; 95% CI 2.081-18.263; p-value 0.001) on multivariate analysis for OS. No association was found between the use of chemotherapy as part of the initial management strategy and survival outcomes. Similarly, no difference in outcomes was observed whether all lesions were treated with SABR compared to SABR and other modalities. **Conclusion:** SABR achieves promising long-term survival and tumor control rates and may be a potential curative treatment for synchronous early stage NSCLC. Our data indicates that patients presenting with synchronous NSCLC lesions can be approached as having two separate primary lung tumors, and be offered definitive local therapy with aims of cure.

Keywords: Early-stage non-small cell lung cancer, Synchronous lesions, Stereotactic ablative radiation therapy

MA06 CHALLENGES IN THE TREATMENT OF EARLY STAGE NSCLC
SUNDAY, SEPTEMBER 8 13:30–15:00

MA06.11 CT-GUIDED PERCUTANEOUS RADIOTRACER LOCALIZATION AND RESECTION OF INDISTINCT/SMALL PULMONARY LESIONS

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Background: Detection of small pulmonary lesions has increased and often they are difficult to localize and resect. We present our mature experience with preoperative computer-tomography (CT)-guided radiotracer localization followed by resection of these lesions. **Method:** Patients with pulmonary nodule smaller than 1 cm and/or deep below the visceral pleura underwent CT-guided injection of radiotracer technetium macroaggregates (99mTc-MAA) in/close to the lesion. A gamma probe was used to localize the marked area that was resected and in case of primary lung cancer, a lobectomy with nodal dissection was performed. **Result:** Between November 2007 and December 2017, 262 patients (196 men; median age 63 years) underwent preoperative radiotracer injection with a successful marking in all patients. Complications included 35 (13.4%) asymptomatic pneumothoraces, 36 (13.7%) parenchymal hemorrhage suffusions, and 2 (0.7%) mild allergic reaction to contrast medium. In all cases, except for 3, the gamma probe revealed the pulmonary lesion. Mean distance from the pleura was 10 mm (range, 0-40 mm). Pulmonary resection was performed by thoracoscopy in 212 (80.9%) cases, intentional thoracotomy in 42 (16.0%), converted thoracoscopy in 8 (3.1%). Mean pathological nodule size was 9.3 mm (range, 2-25 mm). 166 (63.4%) nodules were nonsolid, 64 (24.4%) were partially solid, and 32 (12.2%) had a solid morphology. Histology showed 16 (6.1%) benign and 246 (93.9%) malignant lesions (218 primary lung cancers). **Conclusion:** Preoperative radiotracer localization of small/indistinct pulmonary lesions is simple and feasible with a high rate of success. It may be an effective and attractive alternative in managing lung lesions.

Keywords: lung cancer surgery, Computed tomography, minimally invasive surgery

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.01 CIRCULATING IMMATURE NEUTROPHILS, TUMOR-ASSOCIATED NEUTROPHILS AND DNLR FOR IDENTIFICATION OF FAST PROGRESSORS TO IMMUNOTHERAPY IN NSCLC

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Background: Neutrophils are active regulators of the antitumor immune response, with pro- and antitumor- properties, but generally are associated with progression (PD) and poor outcomes. We reported that pretreatment dNLR ((neutrophils/[leucocytes-neutrophils]; high>3) correlated with immune checkpoint inhibitor (ICI) outcomes in advanced (a) NSCLC pts. Although neutrophil population is heterogeneous, the immature neutrophils (i.e. CD15+CD244-CD16^{low}, among others) seem to be a key subpopulation linked to PD. Tumor-associated neutrophils (TAN) can be also modulator on the microenvironment. We aimed to assess the role of pretreatment circulating immature-neutrophils and tissue-TAN, combined with dNLR, on ICI outcomes in aNSCLC pts. **Method:** aNSCLC pts treated with ICI at our institution between 11/2012 and 08/2018 were eligible. Pretreatment immunophenotyping of monocytes, monocytic MDSC (mMDSC) and granulocytes (CD15, CD11b, CD33, CD244, CD16, CD14, CD32, CD64, HLA-DR) was prospectively performed by flow cytometry in fresh whole blood in 58 pts; we defined immature-neutrophils as CD15+CD244-CD16^{low}. TAN in the stroma were assessed using H&E staining from archival specimen, available from 80 pts. dNLR was retrospectively collected; available from 343 pts. Correlation between baseline circulating neutrophils phenotype, TAN and dNLR was evaluated as well as their impact on outcomes: progression-free survival (PFS), overall (OS), including death before 12 weeks (12wk-death) (fast-PD) **Result:** 366 pts included; 320 (90%) smokers, median age 63; 280 (77%) nonsquamous, 117 (64%) ≥1%PDL1 and 183 missing. Median PFS (mPFS) was 1.93 months (m) [95%CI, 1.8-2.3] and mOS 8.8m [6.5-11.6]. Overall, 12wk-death rate was 31% [25.9-35.6]. Pretreatment high-dNLR (143/343; 42%) was correlated with poor PFS (P=0.002), OS P=0.0003) and a 12wk-death rate of 43% [34.5-50.9]. Pretreatment high immature-neutrophils (30/58; 53%), defined by logrank maximization method (>0.22%), were also associated with poor PFS (P=0.04), OS (P=0.0007) and a 12wk-death rate of 48.7% [26.7-64.1]. TAN (9/80; 11%) were not correlated with outcomes. There was not a correlation between immature-neutrophils, tissue-TAN and dNLR. When evaluating pretreatment immature-neutrophils and dNLR together, we identified a fast-PD phenotype (high immature-neutrophils/high-dNLR, 10/58; 17%), with a mOS of 1.3m [0.73- not reached (NR)] and 12wk-death rate of 60% [14.5-81.3] compared to a responder-phenotype (low immature-neutrophils/low-dNLR, 12/58; 21%), associated with good outcomes: mOS NR [18.23-NR] (P=0.002). **Conclusion:** Pretreatment high circulating immature-neutrophils (CD15+CD244-CD16^{low}) correlate with early failure to ICI and fast-PD phenotype. The combination of circulating immature-neutrophils and dNLR could improve the identification of this population. The impact of immature-neutrophils on ICI should be more deeply explored.

Keywords: dNLR, immature-neutrophils, Immunotherapy

MA07.02 EARLY CHANGE OF DNLR IS CORRELATED WITH OUTCOMES IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

L. Mezquita[1], I. Preeshagul[2], E. Auclin[3], D. Saravia[4], L. Hendriks[5], H. Rizvi[2], D. Planchard[6], W. Park[4], E. Nadal[7], J.C. Ruffinelli[8], S. Ponce[9], C. Audigier-Valette[10], S. Carnio[11], S. Novello[12], G. Zalcman[13], M. Majem[14], A. Mariniello[15], A.M. Dingemans[5], G. Lopes[16], C. Rossoni[6], J.-P. Pignon[6], N. Chaput[6], M. Hellmann[2], K. Arbour[2], B. Besse[1]

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Background: The [neutrophils/[leucocytes-neutrophils] ratio (dNLR) correlates with immune checkpoint inhibitors (ICI) outcomes in advanced non-small cell lung cancer (aNSCLC) patients. Significance of early dNLR change after the first course of ICI is unknown. **Method:** Patients with NSCLC treated with ICI (PD(L)1+/- CTLA4) between Nov. 2012 and Jun. 2018 at 16 EU/US centers were included. A control group treated with chemotherapy (CT) only was also evaluated (NCT02105168). dNLR was collected at baseline (B) and at cycle 2 (C2). Patients were categorized as low vs high dNLR at each timepoint (defined as < vs > 3, as previously done), and the change between B and C2 (good = low at both timepoints, poor = high at both timepoints, mixed = different at each timepoint). **Result:** 1485 patients treated with ICI were analyzed. PDL1 was negative in 162 (11%), 1-49% in 178 (12%), ≥50% in 201 (14%), and missing in 944 (64%). dNLR at B and C2 did not associate with PD-L1 status. At baseline, dNLR was high in 509 (34%) patients and associated with worse PFS compared to those patients with low dNLR at baseline (HR 1.56, P<0.0001) and OS (HR 2.02, P<0.0001). At C2, dNLR was high in 484 (34%) and similarly associated with worse outcomes compared to patients with low dNLR at C2 (PFS HR 1.64, P<0.0001; OS HR 2.13, P<0.0001). Between B and C2, dNLR remained low in 804 (56%, « good ») or high in 327 (23%, « poor ») or changed in 310 pts (22%, « intermediate »). Those with a good dNLR demonstrated mPFS 5.3, mOS 18.6 mo), followed by those intermediate with mixed dNLR (mPFS 3, mOS 9.2 mo), and finally poor dNLR (mPFS 2, mOS 5mo). Outcomes were independant of PD-L1 expression (adjusted HR for PFS 1.94 for intermediate and 3.16 for poor groups, compared to good dNLR group, P<.001; adjusted HR for OS was 2.08 for intermediate and 3.67 for poor groups, *P*<0.001).A bootstrap tested the stability of OS/PFS prediction (*P*<0.001). In the chemo-cohort (n=173), high C1-dNLR (n=81, 47%) was not associated with OS (*P*=0.84). **Conclusion:** dNLR at baseline, at cycle 2, and the change between these two timepoints associated with outcomes in patients treated with immunotherapy independent of PD-L1, but not in patients treated with chemotherapy alone. dNLR is specifically prognostic in the context of immunotherapy.

Keywords: Immunotherapy, NSCLC, dNLR

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.03 A CIRCULATING MICRORNAS-BASED TEST AS BIOMARKER OF PRIMARY AND SECONDARY RESISTANCE IN PD-L1 ≥50% NSCLC TREATED WITH IMMUNOTHERAPY

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Background: PD-L1 represents the only clinically approved biomarker to select patients for immunotherapy. However, about 20-25% of PD-L1≥50% NSCLC patients do not benefit of ICIs treatment. We showed that a plasma microRNA signature classifier (MSC), reflecting the switch towards an immunosuppressive profile of immune cells, identifies NSCLC patients with worse prognosis after ICIs, irrespective from PD-L1 expression. Aim of this trial is to prospectively define the MSC role as biomarker of primary or secondary resistance in PD-L1≥50% NSCLC treated with ICIs. **Method:** Fifty consecutive advanced NSCLC patients with PD-L1≥50% treated with ICI as first (n=32) or further line were enrolled. Plasma samples, as well as demographics information, smoking history and ECOG PS were collected before starting ICI treatment. The MSC test identified patients at high (H) risk vs intermediate/ low (I/L) risk levels. According to RECIST 1.1 criteria, patients were classified as responders (R), patients with stable disease (SD), and progressors (P). Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) in MSC risk level strata at the baseline were considered as endpoints. For 26 R or SD patients with extended follow-up, additive, not mandatory plasma samples were collected and analyzed at the time of revaluations. To determine changes in the risk level during follow-up, we evaluated changes in the probability of having progressive disease after two consecutive MSC tests, considering all possible combinations. **Result:** Overall 17 (34%) R, 17 (34%) patients with SD, 11 (22%) P and 5 (10%) not evaluable patients were identified. Considering the baseline blood samples 11 (22%) NSCLC patients were MSC H. ORR was 0% in MSC H vs 45% for other patients (p=0.0090). Median PFS was 2.3 months for MSC H vs 10.9 months for other patients (HR=0.38; 95%CI=0.17-0.84; p=0.0174). Median OS was 2.9 months for MSC H vs 22.0 months for other patients (HR=0.18; 95%CI=0.07-0.47; p=0.0004). Data remained significant adjusting for age, sex, pack-years and ECOG performance status: PFS HR=0.31 (95%CI=0.13-0.73; p=0.0072) and OS HR=0.13 (95%CI=0.04-0.39; p=0.0003). Among the 26 patients with longitudinal evaluation of MSC risk level, all the 12 patients reaching progression during treatment showed an increase in the risk level (Sign-test p-value=0.0039). Conversely, when considering the 14 NSCLC patients still maintaining SD or responding to ICIs at the time of the analysis, the risk level decreased for 9 (64%) of them (Sign-test p-value=0.1655). **Conclusion:** These preliminary results suggest that MSC risk level at the baseline and during treatment could help to identify primary or secondary resistance in PD-L1≥50% NSCLC patients treated with ICIs. Ongoing clinical trials are validating these results.

Keywords: microRNA, Circulating biomarkers, Immunotherapy

MA07.05 IMMUNE CHECKPOINT INHIBITOR (ICPI) RE-CHALLENGE: OUTCOMES ANALYSIS IN A FRENCH NATIONAL COHORT OF NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

E. Gobbini[1,2], A.C. Toffart[1], M. Perol[3], J.-B. Assié[4], M. Duruisseaux[5], D. Coupez[6], R. Gervais[7], V. Westeel[8], M. Delaunay[9], F. Guisier[10], R. Veillon[11], V. Gounant[12], E. Giroux Leprieur[13], F.R. Vanel[14], N. Chaabane[15], E. Dansin[16], H. Babey[17], C. Decroisette[18], F. Barlesi[19], N. Girard[20], P. Fournel[21], L. Mezquita[22], Y. Oulkhouir[23], A. Canellas[24], B. Duchemann[25], O. Molinier[26], D. Moro-Sibilot[1], M. Giaj Levra[1]

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Background: ICPis deeply changed the NSCLC therapeutic algorithm in the past few years. Unfortunately, a majority of patients experiences disease progression. ICPi re-challenge could be an attractive option but no data supporting this strategy are available. Here we report outcomes of a large cohort of NSCLC patients treated with ICPi re-challenge. **Method:** We retrospectively collected data about 144 advanced NSCLC patients (diagnosis between 2010 and 2018) from 26 French centers. Patients were re-challenged with ICPi after at least 12 weeks of discontinuation for toxicity, disease progression or clinical decision. Progression Free Survival (PFS) and Overall Survival (OS) were calculated from the start of first or second ICP to disease progression (PFS1;PFS2) and death or last follow-up (OS1;OS2) respectively. **Result:** Median age was 63 year [39 –83], most of patients were male (67%), smokers (87%), adenocarcinomas (62%) and stage IV at diagnosis (66%). Most of patients received the first ICPi round in first or second line (66%) and the second ICPi round in third line or later (79%). In both settings patients received preferentially an anti-PD1 (87%) and no differences were detected regarding brain metastasis or ECOG PS (*P* = 0.7827 and *P* = 0.3164 respectively). The Best Response during the second ICPi was not correlated to that one achieved to the first ICPi (*P* = 0.149). The median PFS1 and PFS2 were 13 months [95% CI 10-16.5] and 4.4 months [95% CI 3-6.5] respectively. PFS2 was longer in patients discontinued because of clinical decision (6.5 months [95% CI 2.5-11.9]) or toxicity (5.8 months [95%CI 3.5-18]) compared to disease progression (2.9 months [95% CI 2.0-4.4]) (*P* = 0.021) and in those receiving a chemotherapy between the two ICPis (5.8 months [95%CI 4.1-10.5]) compared to those who did not (3.0 months [95% CI 2.0-4.4])(*P* = 0.002). Median OS1 was 3.3 years [95% CI 2.9-3.9] without differences according to the discontinuation reason (*P* =0.266). Median OS2 was 1.5 y [95%CI 1.0-2.1] and was longer in patients discontinuing the first ICPi due to toxicity (2.1y [95%CI 1.4-NR]) compared to disease progression (1.0y [95%CI 0.4-1.5]) or clinical decision (1.5y [95%CI 0.4-NR]) (*P* = 0.031). Neither OS1 nor OS2 were affected by treatments received between the two ICPis (*P* = 0.345 and *P* = 0.117 respectively). **Conclusion:** ICPi re-challenge might be a useful option mainly in patients discontinuing the first ICPi because of toxicity or clinical decision. Chemotherapy administration between the two ICPis might improve PFS under the second ICPi.

Keywords: Immune Checkpoint Inhibitors, rechallenge, NSCLC

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.06 IMMUNOTHERAPY RE-CHALLENGE AFTER NIVOLUMAB TREATMENT IN ADVANCED NON-SMALL CELL LUNG CANCER IN FRENCH REAL-WORLD SETTING

M. Giaj Levra[1], F.-E. Cotté[2], R. Corre[3], C. Calvet[2], B. Jouaneton[4], R. Jolivel[4], A.-F. Gaudin[2], V. Grumberg[5], J.-B. Assié[6], C. Chouaid[6]

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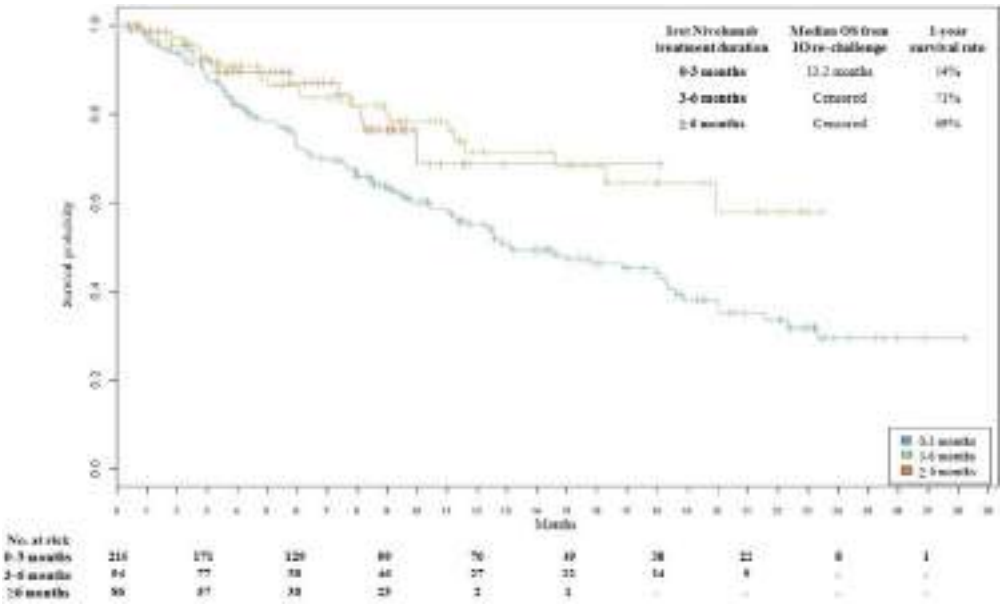
Background: Real-world evidence of nivolumab as treatment for advanced non-small cell lung cancer (aNSCLC) can complement evidence from clinical trials to optimize routine usage and personalization of care. Further, little is known about treatment options and outcomes after discontinuation of nivolumab. **Method:** Based on the National hospitals database (PMSI), we built a retrospective cohort of all NSCLC patients (ICD code: C34*) starting nivolumab in 2015-2016 and followed them until Dec 2017. Information on patients' baseline characteristics (demographics, comorbidities, treatment history) was retrieved. Nivolumab treatment was considered discontinued if ≥3 infusions were missed. Time to treatment discontinuation (TTD) and overall survival (OS) were estimated with Kaplan-Meier methodology. Re-challenged patients were analyzed according to their first nivolumab treatment duration i.e. <3; 3-6; ≥6 months. **Result:** We identified 10,452 NSCLC patients initiating nivolumab during the inclusion period (male: 71%; mean age; 63.8±9.6 years; squamous histology: 44%; cerebral metastasis: 17.4%; median aNSCLC history: 12.5 months; previous curative surgery: 15.6%; median time since first chemotherapy: 10.5 months; mean dose of nivolumab: 213±54mg). Median TTD and OS were 2.8 months and 11.6 months. One-year and 2-year OS rates were 48.8% and 27.4%. Overall, 5118 (53.4%) patients received subsequent systemic therapy after nivolumab discontinuation. Among them, 1517 patients (29.6%) were re-treated with anti-PD1 agents (nivolumab: 98.8%) either after a therapeutic break ('immunotherapy resumption group': n=1127; mTTD: 4.1 months; mOS: 14.9 months from second initiation) or after chemotherapy ('immunotherapy re-challenge group': n=390; mTTD: 3.0 months; mOS: 18.2 months from second initiation). The Figure presents OS curves of the 're-challenge group' according to first nivolumab treatment duration.



Conclusion: After nivolumab discontinuation, around 30% of patients received immunotherapy again, either as a resumption or as a re-challenge following non-immunotherapy treatment. The influence of the first nivolumab treatment duration on re-challenged patients' OS should be further investigated.

Keywords: immunotherapy; nivolumab; re-challenge

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.08 THE ROLE OF A CACHEXIA GRADING SYSTEM IN PATIENTS WITH NSCLC TREATED WITH IMMUNOTHERAPY: IMPLICATIONS FOR RESPONSE AND SURVIVAL

J. Turcott[1], A.F. Cardona[2], L. Ramírez-Tirado[1], Z.L. Zatarain Barrón[1], F. Barrón[1], L. Corrales[3], C. Martin[4], P.A. Barragán Castillo[5], D. Flores-Estrada[1], A. Ruiz-Patiño[6], O.G. Arrieta[1]

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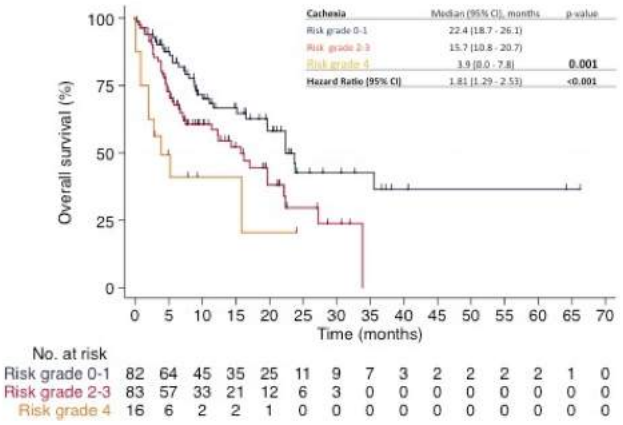
Background: The association between cancer-induced weight-loss (CIWL) and poor clinical outcomes is well established. However, many of these studies were performed in the chemotherapy era. Meanwhile, current standard of care for NSCLC patients has shifted towards the more efficacious immunotherapy agents (IO). IO has improved survival outcomes, nonetheless clinicians face the challenge of identifying who will derive substantial clinical benefit from these more costly agents. Response to IO is influenced by several patient-related factors, including microbiome, medications, and nutritional status. **Method:** In this study we sought to evaluate the effect of cachexia in survival of NSCLC patients undergoing treatment with IO. Included patients had advanced NSCLC (IIIB, IV), who received IO agents in any line of therapy, and had a good performance status. All the patients were evaluated by the nutritionist specialist and were graded according to a previously documented cachexia scale which takes into consideration body mass index (BMI) and weight loss in order to stratify patients into 5 risk categories (0 [pre-cachexia] - 4 [refractory cachexia]). Primary endpoint was overall survival (OS), secondary endpoints included objective response rate (ORR) and progression-free survival. **Result:** A total of 181 patients met the inclusion criteria and were included in the analysis. Among these 82 (45%) were classified in the first category (risk grade 0-1 [low risk]), 83 (46%) were classified in the second category (risk grade 2-3[intermediate risk]) and 9% were in the third category (risk grade 4 [high risk]). Patients classified as low-risk had a significantly longer OS compared to those with intermediate or high risk (22.4 months [95%CI: 18.7-26.1] vs. 15.7 [95%CI: 10.8-20.7] vs. 3.9 [0.0-7.8]; p<0.001; Hazard ratio: 1.81 [1.29-2.53]; p<0.001). In the multivariate analysis ORR, hemoglobin and risk category were independent factors associated with OS. Grade of cachexia was also significantly associated with ORR, with low-risk patients having a significantly higher ORR compared to intermediate and high-risk patients (36.6% vs. 17.3% vs. 25%; p=0.021). PFS was also influenced by risk category, with low risk patients having a longer PFS compared with intermediate and high-risk patients.



Conclusion: Cachexia is independently associated with worse OS in NSCLC patients who receive IO, while better nutritional status is related to higher ORR, highlighting a potential role for nutritional assessment in the selection of patients who are candidates for IO. Early assessment of nutritional status in these patients is imperative in order to timely diagnose and treat anorexia-cachexia and improve outcomes.

Keywords: cachexia, Immunotherapy, overall survival

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.09 IMPACT OF BODY MASS INDEX ON CLINICAL OUTCOMES OF IMMUNE CHECKPOINT BLOCKERS IN ADVANCED NON-SMALL CELL LUNG CANCER

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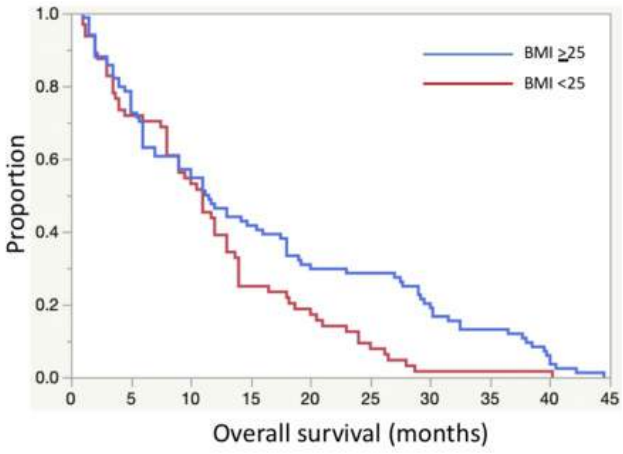
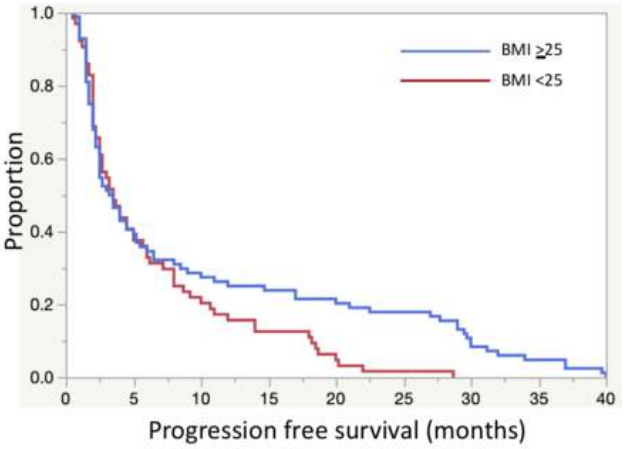
Background: Studies have suggested that obesity may have a paradoxical effect on the efficacy of immune check-point blockers (ICB). Higher Body Mass Index (BMI) has been associated with favorable outcomes with ICB. There is limited data on the impact of BMI on ICB efficacy in real-world patients with advanced non-small-cell lung cancer (NSCLC). We evaluated whether BMI is associated with survival outcomes in metastatic NSCLC patients treated with ICB. **Method:** We identified advanced NSCLC patients treated with anti-PD1/PD-L1 at our institution between 5/2015 to 1/2019. Data regarding BMI at the beginning of ICB treatment were collected. Patients with BMI ≥ 25 (overweight and obese) were assigned to high-BMI group and patients with BMI < 25 were assigned to low-BMI group. The primary outcome was overall survival (OS). Secondary outcomes were progression-free survival (PFS) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Cox proportional hazards model were used for statistical analysis. **Result:** 148 patients with NSCLC were eligible for inclusion. The median follow-up time was 12 months. Median age was 66 years. Majority of patients were female (52.1%), Caucasian (93%), had adenocarcinoma histology (66%), current or previous smokers (88%) and received Nivolumab (88%) in the 2nd or later line setting. The median number of treatment doses were 7. Median BMI of the patient population was 25.4 kg/m^2. 64/148 (43%) of patients were in the low-BMI group (BMI < 25) and 84/148 (57%) patients were included in the high-BMI group (BMI ≥ 25). Patients in high-BMI group had superior OS (HR=0.64, 95% CI 0.45-0.90; p=0.01) that was statistically significant. 1-year OS was 46.4% and 39.0% in the high-BMI and low-BMI group respectively. PFS was also greater in high-BMI group with a trend towards statistical significance (HR=0.73, 95% CI 0.51-1.03; p=0.07). 1-year PFS was 25.0% and 15.6% in the high-BMI and low-BMI group respectively. In multivariate analysis, OS benefit remained statistically significant after adjustment for clinical covariates (age, sex, performance status, number of previous lines of therapy, smoking status and brain metastasis). **Conclusion:** Our study provides independent validation of previously published results demonstrating an association of BMI with survival outcomes in NSCLC patients treated with ICB. The OS benefit in the high-BMI group is independent of classical prognostic factors. While the reasons underlying this relationship remains unknown, prospective studies are needed to confirm this association. Future clinical trials with ICB should consider stratification of patients based on BMI.





Keywords: immune checkpoint blockers, obesity, lung cancer

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
SUNDAY, SEPTEMBER 8 13:30–15:00

MA07.10 THE INFLUENCE OF SEX ON IMMUNOTHERAPY EFFICACY IN NON-SMALL CELL LUNG CANCER

S. Tuminello[1], R. Veluswamy[1], N. Alpert[1], J. Lazar[2], R. Flores[1], M. Van Gerwen[1]

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Background: Patient's sex impacts clinical outcomes for multiple cancers, including non-small cell lung cancer (NSCLC). A recent meta-analysis demonstrated sex may also impact response to novel immunotherapeutic agents, where men appear to derive greater benefit than women. However, the role of important clinical confounders of immunotherapy response that differ according to sex was not accounted for. The aim of this project was to investigate the effect of sex on immunotherapy benefit for NSCLC patients using a large, nationally representative database while adjusting for important clinical confounders. **Method:** Advanced metastatic NSCLC patients diagnosed between 2013-2015 were identified in the National Cancer Database (NCDB). A Cox Proportional Hazards model was used to assess the interaction between sex and immunotherapy treatment for overall survival. This model was also adjusted for histology, stage, age, race, tumor size, comorbidities and other treatment (i.e. chemotherapy, radiation). **Result:** Of 103,525 advanced NSCLC patients, 69,120 (67%) had adequate follow-up information for survival analysis. Of these, 37,423 (54.1%) were males and 31,697 (45.9%) females; 4,012 patients received immunotherapy as first-course treatment. In the adjusted model, both males (Hazard Ratio [HR]adj: 0.77, 95% Confidence Interval [CI] 0.73-0.81) and females (HRadj: 0.80, 95% CI 0.76-0.85) receiving immunotherapy had improved survival compared to those not receiving immunotherapy. The interaction between sex and immunotherapy was not significant (p=0.2539) after adjusting for clinical variables. Among the covariates, younger age, adenocarcinoma histology, Black race, smaller tumor size, lower comorbidity score and additional cancer treatment (either chemotherapy or radiation) were independently associated with better survival (p<0.0001 for all comparisons). **Conclusion:** Patient sex does not appear to affect the benefit of immunotherapy in advanced NSCLC patients after adjusting for potential clinical confounders. Other clinical factors may play a role in immunotherapy response and should be explored in future research.

Keywords: Immunotherapy, NSCLC

MA07 CLINICAL QUESTIONS AND POTENTIAL BLOOD MARKERS FOR IMMUNOTHERAPY
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MA07.11 SURVIVAL OUTCOMES BASED ON GENDER OF ADVANCED NONSMALL CELL LUNG CANCER PATIENTS TREATED WITH PEMBROLIZUMAB OR NIVOLUMAB IN EVERYDAY CLINICAL PRACTICE

D. Ksienski[1], E. Wai[1], N. Croteau[2], A. Freeman[1], L. Fiorino[1], A. Chan[3], D. Fenton[1], G. Geller[1], E. Brooks[1], Z. Poonja[1], S. Irons[1], M. Lesperance[2]

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Background: Women are underrepresented in clinical trials of PD1 Ab. We investigated the relationship between gender and overall survival (OS) in aNSCLC patients (pts) treated with PD1 Ab in a large Canadian provincial cohort. **Method:** All aNSCLC pts treated with nivolumab (NIV) or pembrolizumab (PEM) between 06/2015 and 11/2018 at BC Cancer were identified. Demographic, tumor, treatment details, and survival status were collected from chart review. Kaplan-Meier (KM) curves of OS from initiation of PD1 Ab were generated and compared by the log-rank test. **Result:** Of 527 pts analyzed (58.9% NIV, 36.1% PEM), 50.5% were female. Women were more likely to have Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0/1 at PD1 Ab initiation (72.9% vs. 64.8%, p=0.05), lower median Charlson Comorbidity Index score (CCI, 2.0 vs. 3.0, p=0.006), and tumors with non-squamous histology (83.5% vs. 69.7%, p<0.001) or Epidermal Growth Factor Receptor (EGFR) mutation (9.8% vs. 3.4%, p=0.006). No significant gender variation in age at diagnosis, smoking status, and programmed death ligand 1 tumor proportion score (PD-L1 TPS) was observed. In addition, there were no differences in type of PD1 Ab, line of treatment, duration of treatment, or treatment discontinuation due to immune related adverse events. With a median follow-up of 16.3 months by reverse KM method, 65% of pts had died. In the entire cohort, women had a longer median OS than men (10.2 vs. 8.1 months, p=0.029). In the subgroup of ECOG PS 2/3 pts, men had worse OS (3.9 vs. 6.5 months, p=0.034). Women ≥60 years of age at initiation of PD1 Ab demonstrated superior median OS to men (12.2 vs. 6.1 months, p=0.006). On multivariable analysis of NIV pts, male gender (HR=1.3, 95% CI 1.0-1.7, p=0.02), baseline ECOG PS 2/3 (HR=2.5, 95% CI=1.9-3.2 p<0.001), CCI score≥3 (HR=1.6, 95% CI=1.3-2.1, p<0.001), and EGFR/ALK aberration (HR=2.3, 95% CI 1.4-3.9, p<0.001) predicted for worse survival; for PEM pts, only ECOG PS 2/3 (HR=2.5, 95% CI 1.6-3.9, p<0.001) was associated with OS. **Conclusion:** In this large series with a significant proportion of women, females treated with PD1 Ab for aNSCLC lived longer than men (especially if ECOG PS 2/3 or age≥ 60 years.) Despite similarities in smoking status and PD-L1 TPS, gender divergence in outcome could be attributed to more favorable histology and baseline ECOG PS in females. Increased enrollment of women in PD1 Ab trials would facilitate evaluation of gender as a predictive variable.

Keywords: Gender, Immunotherapy, metastatic

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.01 ANALYSIS OF PD-L1 EXPRESSION ON CIRCULATING STROMAL AND TUMOR CELLS IN LUNG CANCER PATIENTS TREATED WITH CHEMORADIATION THERAPY AND ATEZOLIZUMAB

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Background: We have previously shown dynamic changes to PD-L1 expression during chemoradiotherapy (CRT) could be tracked by evaluating PD-L1 expression on circulating cells. How these changes relate to immunotherapy response is unknown. We prospectively monitored PD-L1 expression in 2 cell types found in circulation (Circulating tumor cells [CTCs] and Cancer Associated Macrophage-like Cells [CAMLs]) in locally advanced non-small cell lung cancer (LA-NSCLC) patients (pts) treated with atezolizumab and CRT. **Method:** Samples were taken from a completed phase II DETERRED trial (NCT02525757) where atezolizumab was added for one year after completing CRT (N=10) or concurrently and after CRT (N=30). Samples from 39 pts from the study were available for analysis. Baseline blood sample (7.5 ml) were drawn prior to start of CRT (T0), and a second sample was drawn ~1 month after completing CRT (T1), and a 3rd sample was drawn ~2 months after completing CRT (T2). Blood was processed by CellSieve™ microfilters; stained for cytokeratin/PDL1/CD45 to identify CTCs and CAMLs. PD-L1 intensity was measured and grouped by 4 scores: 0-negative, 1-low, 2-medium, & 3-high. Tumor IHC for PD-L1 levels from core biopsies was done with Dako 22c3 and was compared to T0 samples. PD-L1 levels from tumor and in circulating cells were used to evaluate PFS and OS. Significance was assessed by log-rank testing. **Result:** PD-L1 IHC was available for 85% of pts, and there was at least one cytokeratin positive cell (CTC or CAML) found in 100% of T0 samples. CTCs were found in 33% of T0, 24% of T1 & 43% T2. CAMLs were found in 92% of T0, 97% of T1, & 97% of T2 samples. No correlation was seen comparing tumor PD-L1 expression percentage and the T0 PD-L1 staining intensity on CTCs/CAMLs. Tumor PD-L1>1% was found in 58% and >50% in 24% of IHC samples, yet there was no correlation between tumor PD-L1 expression and PFS or OS. At T0, PD-L1 expression in CTCs/CAMLs was low (0-1) in 18 pts and high (2-3) in 15, but no relationship to PFS (HR=0.6, 95%CI 0.2-1.7, p=0.48) or OS (HR=1.7, 95%CI 0.5-6.4, p=0.66) was found. However, pts with high PD-L1 at T1 or T2, regardless of levels at T0, had a trend towards improved PFS (HR 2.5, 95%CI 0.7-8.6, p=0.13), and a significantly better OS (HR 14.2, 95%CI 2.4-81.8, p=0.003). Interestingly, of the 15 pts who had low PD-L1 at T0, 7 had induced PD-L1 expression at T1 or T2. All samples with induced PD-L1 expression had better PFS (HR 8.3, 95%CI 1.4-50.2, p=0.02) and OS (HR 8.7, 95%CI 1.2-64.0, p=0.03) compared to those who remained low. **Conclusion:** While baseline tumor or circulating cellular PD-L1 expression was not correlated with clinical outcomes, sequential monitoring of high PD-L1 expression in CTCs/CAMLs after CRT appeared to be associated with better clinical outcomes in pts who received consolidation atezolizumab after CRT, particularly in pts who had induced expression at follow up during the consolidation phase. Dynamic tracking of PD-L1 may serve as a predictive biomarker for immunotherapy effectiveness in LA-NSCLC after CRT.

Keywords: chemoradiotherapy, Immunotherapy, PD-L1

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.02 DURVALUMAB IMPACT IN THE TREATMENT STRATEGY OF STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): AN EORTC YOUNG INVESTIGATOR LUNG CANCER GROUP SURVEY

M. Giaj Levra[1], J. Benet[1], B. Hasan[2], T. Berghmans[3], A. Bruni[4], A.M. Dingemans[5], N. Giaj Levra[6], J. Edwards[7], C. Faivre-Finn[8], N. Girard[9], E. Gobbini[1,10], L. Greillier[11], L. Hendriks[5], S. Lantuejoul[12], A. Levy[13], S. Novello[14], M. O'Brien[15], M. Reck[16], A. Pochesci[2], J. Menis[17], B. Besse[18]

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Background: Stage III NSCLC represents a very heterogeneous population with extremely different treatment modalities including surgery, chemotherapy (CT) and radiotherapy (RT), mostly in combination. The results of the PACIFIC trial have now been reported in full including an overall survival (OS) benefit with durvalumab in addition to concomitant CT-RT. An electronic European survey was circulated to evaluate the impact of durvalumab in the staging and treatment strategy of stage III disease. **Method:** A Young Investigator EORTC Lung Cancer Group survey containing 31 questions, was distributed between 31/01/18 and 31/03/19 to EORTC LCG and several European thoracic oncology societies' members **Result:**

206 responses were analyzed (radiation oncologist: 50% [n=103], pulmonologist: 26.7% [n=55], medical oncologist: 22.3% [n=46]; 81.5% with >5 years experience in treating NSCLC). Italy (27.7%, n=57), Netherlands (22.8%, n=47), France (13.6%, n=28), and Spain (11.6%, n=24) contributed most. 83.5% (n=172) confirmed that they had access to durvalumab at the time of the survey. 97.6% (n=201) report that treatment decision is made by a multidisciplinary board. Regarding staging, 76.7% (n=158) support the need of a mediastinal pathological staging in case of suspect lymph-nodes, with a preference for EBUS/EUS (61.2%, n=126). 81.6% (n=168) treated more than half of patients with a concomitant CT-RT with the 1st cycle of chemotherapy in 39.7% (n=81). 95.1% consider durvalumab as practice changing, especially given the OS results (77.9%, n=152/195). 30% (n=119/395) will give patients concomitant CT-RT if PD-L1 >1%, and in borderline resectable cases 17.7% (n=70/395) will propose concomitant CT-RT instead of surgery. Durvalumab administration will be given regardless of PDL1 status in 13.1% (n=27) and 28.6% (n=59) would consider the possibility of a rebiopsy after CT-RT in case of negative PD-L1. 38.8% (n=80) foresee some problems with PD-L1 testing in this population due to availability of cytologic or small histologic samples. About 53.8% (n=105/195) normally will start durvalumab within 6 weeks after CT-RT and 48.5% (n=100) would also use durvalumab after sequential CT-RT **Conclusion:** Durvalumab results are changing the treatment approach to stage III unresectable (and maybe resectable) NSCLC and planned strict adherence to the patient population as recruited to the PACIFIC study, was not demonstrated. This survey was released after the EMA approval of durvalumab and PD-L1 status seems to play a role in the treatment strategies, but surprisingly almost half of the clinicians will use durvalumab after sequential CT-RT without safety or efficacy data.

Keywords: durvalumab, stage III NSCLC, treatment strategy

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.03 ADJUVANT PEMBROLIZUMAB IN N2 POSITIVE NSCLC TREATED WITH CONCURRENT CHEMORADIOTHERAPY FOLLOWED BY SURGERY: PHASE II, PROSPECTIVE STUDY

S. Park[1], H.A. Jung[1], J.H. Cho[2], J.-M. Sun[1], H.K. Kim[2], S.-H. Lee[1], Y.S. Choi[2], J.S. Ahn[1], J. Kim[2], K. Park[1], J.I. Zo[2], Y.M. Shim[2], M.-J. Ahn[1]

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Background: The standard treatment option for stage IIIA-N2 subgroup is still under discussion with controversies. We hypothesize that immune checkpoint inhibitor consolidation therapy could have an additional role in prolongation of the disease-free survival (DFS) for stage IIIA-N2 NSCLC treated with tri-modalities therapy. **Method:** This is a phase 2 study evaluating the clinical efficacy of pembrolizumab treatment after CCRT with curative resection in stage IIIA-N2 NSCLC pts (NCT03053856). Pathologically confirmed pts were treated with five cycles of CCRT, weekly paclitaxel (50mg/m^2) and cisplatin (25mg/m^2) combined with radiotherapy (total of 44Gy over 22 fractions) followed by curative resection. Adjuvant Pembrolizumab (200mg fixed dose) is applied every three weeks up to 2 years or until disease recurrence. The primary objective is disease-free survival of more than 20 months. The first patient was recruited in October 2017, and the data for this abstract was locked at 20th of January, 2019. **Result:** Total of 40 pts were screened, and 37 pts received treatment. Median age was 64 years (range 39-74), and twenty-three pts were male (62.2%). As a curative surgery, pts received lobectomy (n=34), bi-lobectomy (n=2), or pneumonectomy (n=1). Adenocarcinoma was predominant (n=27, 73.0%). After the neoadjuvant CCRT, down-staging were observed in nine pts (24.3%). The median follow-up duration was 10.6 months (range 3.1-17.2), and pts received a median of 11 cycles (range 1-22) of adjuvant pembrolizumab. DFS is not reached. Fourteen patients discontinued treatment due to disease progression (n=9), adverse events (n=4) and withdraw consent (n=1). There was a case of grade 4 pneumonitis and a case of grade 3 autoimmune hepatitis which lead to discontinuation of the treatment. Otherwise, grade 1-2 hypothyroidism (n=6), pneumonitis (n=5), skin rash (n=3) were observed. Patients with severe immune-related adverse event showed a significantly high percentage of Ki-67 + cells among CD8 T-cells in peripheral blood. **Conclusion:** This study is the first study to demonstrate the feasibility of adjuvant pembrolizumab monotherapy in stage IIIA-N2 patients. Updated clinical outcome will be presented at the conference.

Keywords: Adjuvant, N2 disease, Pembrolizumab

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.05 A MULTI-CENTER ANALYSIS OF RIGHT VS LEFT-SIDED PNEUMONECTOMY FOLLOWING INDUCTION THERAPY

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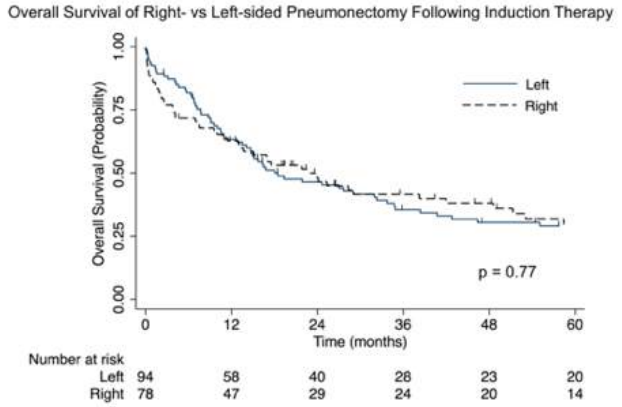
Background: Previous single-center studies of pneumonectomy following induction therapy for non-small-cell lung cancer (NSCLC) have found a significant perioperative risk associated with right-sided pneumonectomy. We examined the impact of laterality on long-term survival after induction therapy followed by pneumonectomy in a multi-institutional analysis. **Method:** Perioperative and long-term outcomes of patients with NSCLC who underwent pneumonectomy following induction chemotherapy with or without radiation from 2000-2016 across 3 institutions were evaluated using multivariable logistic regression, Cox proportional hazards modeling and propensity score-matched analysis. Patients who underwent a completion pneumonectomy or who had M1 disease were excluded from the analysis. **Result:** During the study period, 172 patients (right n = 78 [45%], left n = 94 [55%]) met inclusion criteria. Right-sided pneumonectomy was associated with a similar perioperative complication rate (38% [30/78] vs 27% [25/94], p=0.10), and 30-day (13% [10/78] vs 9% [8/94], p=0.36) and 90-day mortality (23% [18/78] vs 13% [12/94], p=0.08) when compared to left-sided pneumonectomy. In multivariable analysis, right-sided pneumonectomy was not found to be a predictor of higher perioperative complications (OR 0.85 [95% CI: 0.33-2.14], p=0.73) or 30-day (OR 2.06 [95% CI: 0.44-9.69], p=0.36) and 90-day mortality (OR 2.06 [95% CI: 0.54-7.88], p=0.29). Overall survival between right and left pneumonectomy was not significantly different in unadjusted (5-year survival 30% [95% CI: 19%-41%] vs 29% [95% CI: 20%-39%], log-rank p=0.77 [Figure]) or multivariable analysis (adjusted hazard ratio, 1.05 [95% CI: 0.63-1.76], p = 0.84). A propensity score-matched analysis of 108 patients balancing baseline characteristics—including pulmonary function, tumor size and stage—was also performed, and found no significant differences in perioperative complication rates (46% [25/54] vs 48% [26/54], p=0.85), 30-day (17% [9/54] vs 7% [4/54], p=0.14) and 90-day mortality (26% [14/54] vs 13% [7/54], p=0.09) between right versus left pneumonectomy, respectively. Overall survival was not significantly different between right- and left-sided pneumonectomy (5-year survival 33% [95% CI: 20%-47%] vs 28% [95% CI: 16%-41%], log-rank p=0.98).



Conclusion: In this multi-center analysis, right-sided pneumonectomy after induction therapy was not associated with significantly higher perioperative mortality rates or worse long-term survival when compared to a left-sided pneumonectomy.

Keywords: Non-Small Cell Lung Cancer, pneumonectomy, induction therapy

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.06 PERIOPERATIVE OUTCOMES OF LUNG CANCER PATIENTS WITH INTERSTITIAL PNEUMONIA

A. Kobayashi, Y. Okubo, M. Yotsukura, Y. Yoshida, K. Nakagawa, N. Motoi, S. Watanabe

National Cancer Center Hospital, Tokyo/Japan

Background: Interstitial lung disease is mostly found in elderly male smokers who also have relatively high risks of developing lung cancer. For these patients, modality to treat malignancy is limited to prevent acute exacerbation of interstitial pneumonia. We analyzed the perioperative outcomes of this group of patients with both interstitial pneumonitis and resectable lung cancer with curative intent. **Method:** We retrieved the characteristics and medical courses of consecutive patients who had undergone pulmonary resections from medical records. In this analysis, usual interstitial pneumonia (UIP) was characterized by the presence of basal predominant, subpleural reticular abnormalities with traction bronchiectasis and honeycomb cysts detected in bilateral lung field on chest computed tomography preoperatively. Pathological findings on surgical specimen were used confirmation of diagnosis. The incidence and outcomes of acute exacerbation within 30 days from operation were analysed. **Result:** From 2015 to 2017, there were 1,477 patients who underwent pulmonary resection for primary lung cancer at our institute. Among them there were 81 (5.5%) patients diagnosed as UIP by specific findings on chest computed tomography. Of 81 patients evaluated, 68 (84.0 %) were men, the median age was 73 years (range, 55-88). For Eastern Cooperative Oncology Group (ECOG) performance status, all 81 patients were categorized in status 0. Seventy-four patients (91.4%) underwent lobectomy, 1 (1.2%) bi-lobectomy, 2 (2.5%) segmentectomy and 4 (4.9%) wide wedge resections for primary lung cancer. The mean duration of surgery was 129 mins (range, 54-316), and mean value for blood loss was 36.5 ml (range, 0-396). A complete resection (R0) was achieved in 79 cases (97.5%). Postoperative complications were observed in 19 patients (23.5%) including prolonged air leakage (n=4, 4.9%), late onset of air leakage (n=3, 3.7%), surgical site infection, chylothorax and cerebral infarction. Nine patients (11.1%) manifested acute exacerbation of interstitial pneumonia within 30 days after surgery. There were 3 post-operative deaths (3.7%) within 30 days after surgery. Two deaths (2.5%) were due to acute exacerbation of interstitial pneumonia and 1 (1.2%) case of SAH on 1POD. **Conclusion:** Pulmonary resection for patients with interstitial lung disease led to 9 (11.1%) cases of acute exacerbation within 30 days from surgery. Mortality related to acute exacerbation was found only 2 cases (2.5%) at our hospital, which was tolerable postoperative outcome for pulmonary resection for lung cancer with curative intent.

Keywords: interstitial pneumonia, acute exacerbation, pulmonary resection

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.07 THE CONCORDANCE BETWEEN PATIENT REPORTED OUTCOMES AND CLINICIAN REPORTED OUTCOMES DURING RADIOTHERAPY IN LUNG CANCER PATIENTS

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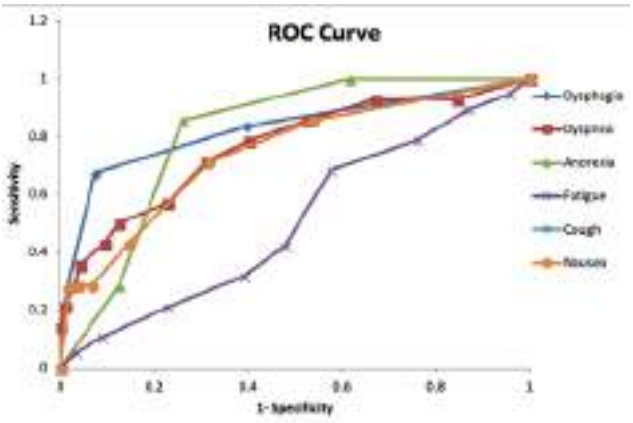
Background: Capturing information on toxicity in (non-)small cell lung cancer patients receiving radiotherapy or chemoradiotherapy, is crucial for optimal symptom management. Patient Reported Outcomes (PROs) have the potential to improve toxicity detection by adding direct information from the patient perspective. The aim of this study is therefore to determine the predictive and additional value of PROs on prospectively scored clinician reported toxicity. **Method:** An observational study was performed in lung cancer patients (n=111) treated with (chemo)radiation with curative intent. The EORTC QLQ-C30 and the EORTC LC-13 questionnaires were used to score PROs on a scale of 0-100 for a selection of commonly occurring toxicities (i.e. dysphagia, dyspnea, anorexia, fatigue, cough and nausea). Clinicians prospectively scored the maximum toxicity during, and at the end of treatment using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Receiver operating characteristic (ROC) curves were constructed to evaluate the performance (i.e. discrimination) of PROs on predicting clinician scored CTCAE toxicity (grade ≥2). Furthermore, cut-off points were determined from the ROC-curve on the basis of the best trade-off values between sensitivity and specificity (0,5). Validity of the model was assessed with the ability to predict the number of grade ≥2 toxicities (calibration). **Result:**



Assessment of predictive performance in our cohort demonstrated a good fit for anorexia (AUC: 0,810 95% CI 0,699 to 0,921) and dysphagia (AUC: 0,828 95% CI 0,743 to 0,914) with sensitivity scores of 85,7%, 67,4% and specificity scores of 74,0% and 92,6% respectively. Both dyspnoea (AUC: 0,765 95% CI 0,60 to 0,910) and nausea (AUC: 0,745, 95% CI 0,548 to 0,942) showed a fair fit with sensitivity score of 74,1% for both toxicities and specificity of 69,1% and 68,3% respectively. A poor fit was found for cough (AUC: 0,667 95% CI 0,495-0,839) with a sensitivity of 55,6% and specificity of 30,4%. The model failed to discriminate for fatigue (AUC: 0,507 95% CI 0,368-0,645). Calibration showed that clinician based CTCAE toxicities substantially underestimated all PRO-based toxicities. **Conclusion:** This study has identified that patient reported toxicities and clinician reported toxicities do not always concord. Only anorexia and dysphagia showed good agreement, while for the other toxicities, the agreement was only fair to poor. Furthermore, we showed that clinicians substancially underreport the existence of toxicities. This study adds to the growing body of evidence indicating the potential beneficial role of using PRO-based toxicity reporting in clinical cancer care for lung cancer.

Keywords: Patient Reported Outcomes, toxicity, Clinician report

MA08.09 RESULTS OF TRIMODALITY THERAPY FOR PATIENTS WITH CN2 LUNG CANCER DIAGNOSED BY VIDEO-ASSISTED MEDIASTINOSCOPIC LYMPHADENECTOMY (VAMLA)

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Background: After a properly performed transcervical lymphadenectomy, invasive restaging of the mediastinum is unnecessary because there is no material left for a new biopsy. Therefore, when video-assisted mediastinoscopic lymphadenectomy (VAMLA) is used at primary staging, the only parameters to select patients for lung resection after induction therapy are: the stability of the primary tumor and the absence of extrathoracic disease assessed by PET-CT. The aim of this study is to analyze the results of those patients with cN2 NSCLC diagnosed by VAMLA who underwent trimodality treatment in terms of feasibility and survival. **Method:** Prospective observational single-center study of 250 patients (206 men; median age, 65.7; range, 42-86) with NSCLC cN0-1 (by PET-CT) who underwent VAMLA from 01-2010 to 12-2017. Patients with cN2 diagnosed by VAMLA who underwent trimodality treatment (cisplatin-based chemotherapy concomitant with radical radiotherapy [mean 54Gy, range 40-70Gy] plus lung resection) were analyzed. Follow-up was completed in March 2019. Median follow-up for surviving patients was 39.5 months (range, 8-108). Survival analysis was performed by the Kaplan-Meier method; the log-rank test was used for comparisons. Patients who died within 90 days after resection were excluded from survival analyses. A p-value of less than 0.05 was considered significant. The IBM SPSS Statistics for Mac, version 20.0 was used. **Result:** The rate of unsuspected N2-3 disease in the whole series was 14.5% (35 patients). 28 patients out of 35 were considered for trimodality treatment. The results of restaging based on the PET-CT were: disease progression in 8 (28.5%) (mostly distant metastases), and stability of the primary tumor or partial response in 20 patients (71.5%). Of 20 patients without progression, 13 (46.5%) underwent lung resection; the remaining 7 were considered unfit for surgery. Three- and 5-year survival rates for those candidates for chemoradiotherapy (n=28) were: 91.7% and 80.2%, respectively, for patients in whom complete lung resection was achieved; 34.3% and 0%, respectively, for those considered unfit for surgery; and 19% and 0%, respectively, for those with progression after chemoradiotherapy ($p < 0.0001$)(Figure 1).

Conclusion: The use of VAMLA to select patients for trimodality treatment is feasible. Based on the results obtained (high rate of unsuspected cN2 diagnosed by VAMLA and prolonged survival of those patients in whom the trimodality treatment was accomplished), VAMLA should be included in the current staging algorithms, especially for those tumors with intermediate risk of N2 and normal mediastinum by PET-CT.

Keywords: Transcervical lymphadenectomy, trimodality treatment, N2 disease

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.10 EARLY AND LATE OUTCOMES AFTER SURGERY FOR PT4 NSCLC RECLASSIFIED BY AJCC 8TH EDITION CRITERIA

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Background: Classically, T4 non-small cell lung cancers (NSCLC) are tumors of any size that have features of local extension often precluding surgical resection or necessitating complex extended pulmonary surgery. However, the new AJCC 8thedition includes tumors greater than 7cm regardless of adjacent organ extension. The early perioperative outcomes from T4 resections must be contextualized to the increasingly heterogeneous classification offered by the new staging system. Our goal was to examine perioperative and long-term outcomes from pT4 resections based on the AJCC 7thedition versus those of the expanded criteria of the 8thedition. **Method:** This is a retrospective study of pT4 surgical resections at the Montreal General Hospital from 2011-2018. Data was analyzed using GraphPad Prism and SPSS. **Result:** We identified 158 patients with pT4 tumors based on AJCC-8: 40 by AJCC-7 criteria (Group1) and 118 with tumors >7cm considered pT4 in AJCC-8 (Group2). Demographics and clinical characteristics are detailed in Table 1. The incidence of major complications (grade 3 or 4) was similar in both cohorts (17.5% in Group1 and 13.6% in Group2; p=0.37), with 3.8% in-hospital mortality (7.5% in Group1 and 2.5% in Group2; p=0.16). Overall survival was 76% at 1 year, 44% at 3 years and 34% at 5 years. Median overall survival was 27 months and was similar between Group1 and Group2 (25.8 and 27.4 months, respectively p=0.7). Nevertheless, Group2 had better peri-operative survival than Group1: 99% vs 92% 90-day mortality (p=0.02) and 95% vs 83% 6-month mortality (p<0.01). Finally, Kaplan-Meier curves adjusted for predictors of survival with Cox regression analysis show early mortality in Group 1 with equalization of the curves at 1 year (Figure 1).

Table 1. Demographics and clinical characteristics.

	pT4 7th Edition (n=40)	Larger than 7cm[‡] (n=123)
Age		
Median (Range)	70.5 (56-83)	70 (51-86)
Sex		
Male	23 (57.5%)	60 (50.8%)
Female	17 (42.5%)	58 (49.2%)
Laterality of tumor		
Right	25 (62.5%)	67 (57.8%)
Left	15 (37.5%)	51 (42.2%)
Structures involved		
Mediastinum	17 (42.5%)	-
Separate tumor in an ipsilateral lobe	12 (30%)	-
Heart	5 (12.5%)	-
Great vessels	7 (17.5%)	-
Recurrent laryngeal nerve	2 (5%)	-
Trachea	1 (2.5%)	-
Esophagus	1 (2.5%)	-
Spine	1 (2.5%)	-
Histology		
Adenocarcinoma	17 (42.5%)	59 (50%)
Squamous cell carcinoma	17 (42.5%)	38 (32%)
Other	6 (15%)	21 (18%)
Lymph node status (pN stage)*		
N0	12 (30%)	78 (66%)
N1	14 (35%)	29 (25%)
N2	14 (35%)	11 (9%)
Synchronous metastasis at diagnosis*		
M1	6 (15%)	1 (0.08%)
Tumor size*		
Median size in cm (Range)	6.2 (1.5-17.5)	8.5 (7-26)
Lymphovascular invasion*		
Identified	18 (45%)	33 (28%)
Visceral pleural invasion*		
Identified	28 (70%)	59 (50%)
Focality*		
Unifocal	27 (67.5%)	104 (88.1%)
Multifocal	13 (32.5%)	14 (11.9%)
Operative approach		
Open	35 (87.5%)	93 (78.8%)
VATS	3 (7.5%)	17 (14.4%)
VATS converted to open	2 (5%)	8 (6.8%)
Type of resection* (>1 type of resection per patient possible)		
Pneumonectomy	15 (37.5%)	21 (17.8%)
Lobectomy (or bilobectomy)	18 (45%)	96 (81.4%)
Wedge resection	8 (20%)	13 (11%)
Segmentectomy	5 (12.5%)	3 (2.5%)
Resection margins		
Positive	7 (17.5%)	11 (9.3%)
Complications		
Major complication	7 (17.5%)	16 (13.6%)
In-hospital mortality	3 (7.5%)	3 (2.5%)
Treatment		
Neoadjuvant chemotherapy	3 (7.5%)	3 (2.5%)
Neoadjuvant radiotherapy*	3 (7.5%)	1 (0.08%)
Adjuvant chemotherapy	13 (32.5%)	45 (38.1%)
Adjuvant radiotherapy	9 (22.5%)	27 (22.9%)
Status at last follow-up		
No disesase	23 (57.5%)	82 (79.5%)
Disease	17 (42.5%)	36 (30.5%)
Recurrence at any point (local or distant)	10 (25%)	32 (27.1%)
Duration of follow-up		
Mean duration in months (range)	19.4 (0.13-68)	15.6 (0-89.3)

[‡]*Excludes pT4 7th Edition*
*p<0.05

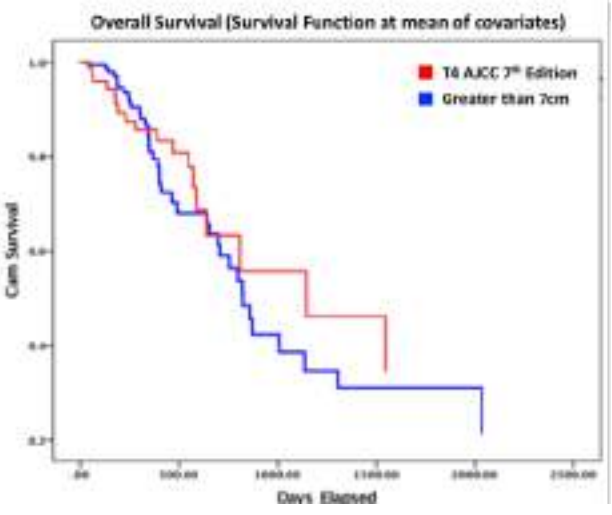

Figure 1. Overall survival of Group1 and Group2. Adjusted survival curves for Group1 (T4 AJCC 7th Edition; red curve) and Group 2 (Greater than 7cm; blue curve) generated using SPSS. Covariates in the Cox regression model included age, sex, laterality, histology, lymph node status, synchronous metastasis status, resection margins, tumor size, lymphovascular and visceral pleural invasion, surgical approach and treatment.

Conclusion: While long-term oncological outcomes are similar for pT4 >7cm to those of AJCC-7 pT4 patients, differences in perioperative outcomes point to the heterogeneity of the new AJCC-8 classification with regards to surgical management.

Keywords: T4 lung cancer, extended surgical resection, advanced lung cancer staging

MA08 PAWING THE WAY TO IMPROVE OUTCOMES IN STAGE III NSCLC
SUNDAY, SEPTEMBER 8 15:15–16:45

MA08.11 SLCG SCAT TRIAL: SURGICAL AUDIT TO LYMPH NODE ASSESSMENT BASED ON IASLC RECOMMENDATIONS

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Background: The Spanish Lung Cancer Group (SLCG) developed a multicenter trial in which completely resected pathological N positive NSCLC patients received different schemes of adjuvance based on level of tumoral BRCA expression (SCAT trial). We assess here surgical topics, with an in-depth analysis of quality of lymphadenectomy based on IASLC recommendations, evaluating their effect on survival. **Method:** Phase-III SLCG-SCAT trial included patients with completely resected (R0) NSCLC with pathological hilar and/or ipsilateral mediastinal lymph node (LN) involvement. Patients from SLCG-SCAT trial in which complete pathologic report with information about mediastinal lymph node dissection was available (including number of lymph nodes assessed and involved by tumor in each hilar and mediastinal region), were included for our study. We also analyzed data about estimated overall survival (OS) and disease-free survival (DFS). All patients underwent surgical resection in high-volume departments of thoracic surgery. **Result:** Lymph node assessment From the whole series (451 patients), in 33.7%, 17.7% and 49.9% of cases, regions 7, 10 and 11 respectively were not assessed. No lymph nodes were biopsied from region 8, 9 and 12 in 80%, 61.9% and 91.1% of cases, respectively. Region 10 was that with the higher number of lymph nodes resected (medium 4.64). From them, 27.9% were involved by tumor. Median assessed mediastinal regions was 4. In 21.1% of patients, lymph nodes from only one or two regions were obtained. In most of the patients (91.8%), one or two N1 regions were assessed. From 272 patients with N1 (no N2) involvement, 15.4% had no N2 regions biopsied, 20.2% had one N2 region evaluated and only 39.7% had three or more N2 regions assessed. On the other hand, from 179 patients with positive N2, 8.9% had no N1 regions biopsied and 54.7% had one. From 409 patients with at least one N2 lymph node resected, 120 (29.3%) shown the highest region involved. Number of mediastinal regions assessed and affected, and number of lymph nodes resected and affected were significantly higher in patients with N1 plus N2 disease than those with isolated N1 or N2 involvement. Survival Median follow-up was 52.3 months. Five-year OS was 55.7% (CI95% 50.8%-60.3%). Differences were found on OS regarding type of lymph node involvement (N1, N2 or both) (p=0.002). Five-year OS was 61.7% (CI95%:55.4%-67.4%), 51.5% (CI95%:39.2%-62.4%) and 42.3% (CI95%:32.1-52.2%) for patients with N1, N2 and N1+N2 disease, respectively. No differences were found in survival regarding total number of N1 or N2 regions evaluated. Both number of regions involved and number of lymph nodes with tumor were significantly related to worse prognosis. **Conclusion:** International recommendations for surgical lymph node assessment in NSCLC were not deemed for the design of the trial and were not followed in a high proportion of cases. Patterns of N1 and N2 involvement shown to impact prognosis. The design of trials assessing surgical series of patients undergoing complete resection requires the control of surgical procedures in order to avoid recruitment biases.

Keywords: Lymphadenectomy, Complete resection, Adjuvance

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.01 A PHASE I/II TRIAL OF DASATINIB AND OSIMERTINIB IN TKI NAÏVE PATIENTS WITH ADVANCED EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

C. Kim, S. Liu, J. Crawford, D. Subramaniam, G. Giaccone

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Background: EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy is the standard of care in patients with EGFR-mutant NSCLC. However, a fraction of patients do not respond to EGFR-TKI therapy or have short duration of response. In addition, virtually all patients develop resistance. In a preclinical study, we have shown that overexpression of Cripto-1, a member of the EGF–CFC family, contributes to the development of resistance to EGFR-TKI therapy through the Src pathway and that the combination of EGFR-TKI therapy and Src inhibition works synergistically. **Method:** This is an open-label, single-arm phase I/II trial of osimertinib and dasatinib, a Src inhibitor, in treatment-naïve patients with advanced EGFR-mutant NSCLC (NCT02954523). Patients with pleural or pericardial effusions were excluded. The primary endpoint of the phase I portion was to establish a safe and tolerable phase II dose of osimertinib and dasatinib. Dose escalation includes 2 dose levels (DLs) (DL1: osimertinib 80 mg QD, dasatinib 50 mg BID, DL2: osimertinib 80 mg QD, dasatinib 70 mg BID). 2 DLs below the starting dose level (DL-1: osimertinib 80 mg QD, dasatinib 70 mg QD; DL-2: osimertinib 80 mg QD, dasatinib 50 mg QD) could be explored if necessary. Adverse events (AEs) were assessed per CTCAE 4.03. **Result:** 10 patients (DL2: 3, DL1: 6, DL -1: 1) were enrolled. None of the patients enrolled at DL2 had dose limiting toxicities (DLTs) but given the frequent dose reductions required and toxicities beyond the DLT period, DL1 was further assessed. 3 (50%) of 6 patients at DL1 experienced a DLT (grade 3 headaches and body pain, grade 3 neutropenia, grade 3 rash, one each). One patient was enrolled at DL -1 and did not have a DLT. The most common treatment-related adverse events (TRAEs) included pleural effusion (n=9), diarrhea (n=8), rash (n=7), AST elevation (n=6), ALT elevation (n=6), most of which were grade 1 or 2. 4/4/1 patients had grade 1/2/3 pleural effusion, respectively. 7 (70%) patients had grade 3 TRAEs. No grade 4 or 5 toxicities were observed. Eight (80%) patients had a partial response (including 1 unconfirmed partial response) and 2 had stable disease. Median PFS was 27.2 months; median OS was not reached. The recommended phase II dose was determined as osimertinib 80 mg QD and dasatinib 70 mg QD. Pharmacokinetics (PK) analysis is being performed and will be presented. Due to slow accrual after approval of osimertinib in first-line, the trial was closed to enrollment. **Conclusion:** The combination of dasatinib and osimertinib demonstrated encouraging anticancer activity. Median PFS is longer than what is historically reported with osimertinib alone in first-line setting, although definitive conclusions cannot be drawn given the small sample size. The tolerability of the combination was limited by TRAEs, but they were generally manageable with dasatinib dose reductions and supportive measures.

Keywords: EGFR-mutant NSCLC, Resistance, Osimertinib dasatinib

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.02 IN VIVO, EX VIVO AND EARLY CLINICAL ACTIVITY OF EGFR MONOCLONAL ANTIBODY AND OSIMERTINIB IN EGFR EXON 20 INSERTION NSCLC

J. Riess[1], N. Floch[2], P. Mack[1], M. Martin[2], D. Vang[1], P. Smith[2], D. Cross[2], M. Cheng[3], J. Keck[3], S. Groshen[4], M. Rabin[5], S. Padda[6], G. Oxnard[5], J. Sands[5], K. Ramchandran[6], M. Koczywas[7], J. Moscow[8], P. Jänne[5], P. Lara[1], E. Newman[7], D. Gandara[1]

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Background: *EGFR* Exon 20 insertions (Ex20Ins) are the 3rd most common class of *EGFR* activating mutation, but patients with NSCLC harboring EGFR Ex20Ins lack effective approved EGFR-TKIs. Newer-

generation TKIs and combination strategies with EGFR-monoclonal antibodies (moAbs) may enhance activity against EGFR Ex20Ins. **Method:** Xenografts derived from CRISPR-modified H2073 cells with Ex20Ins (A763_Y764InsFQEA, D770_N771InsSVD or V769_D770InsASV) and Ex20Ins patient-derived xenografts (PDXs) (D770_N771InsSVD, A797_V769dupASV, D770_N771_InsG, H773_V774_InsNPH) were treated with vehicle, osimertinib, cetuximab, and osimertinib+cetuximab. Ex20Ins spheroid models (D770_N771InsSVD and M766_A767InsASV) were treated with cetuximab at fixed dose and increasing concentrations of osimertinib. Ex20Ins PDX (A763_Y764InsFQEA) was also treated with afatinib and erlotinib; Ex20Ins PDX (D770_N771InsSVD) was treated with these combinations plus afatinib+cetuximab. Immunoblotting for pharmacodynamic studies of on-target and downstream proteins, phospho-proteins and apoptosis markers were performed at relevant timepoints for D770_N771InsSVD PDX and CRISPR model. A phase 1 clinical trial with a dose expansion cohort in Stage IV EGFR Ex20Ins NSCLC is currently open to accrual at osimertinib 80 mg qd and the EGFR-moAb necitumumab 800 mg IV D1 and D8 of 21D cycle with response assessment by RECIST 1.1 (NCT02496663). **Result:** The combination of osimertinib and cetuximab achieved significant tumor growth inhibition compared to osimertinib alone across PDX and CRISPR cell line xenograft models (p=0.05), except for the A763_Y764InsFQEA PDX model where osimertinib alone and osimertinib+cetuximab were equivalently effective (both p<0.001 compared to control). Spheroid models for D770_N771InsSVD and M766_A767InsASV showed significantly increased cytotoxicity from the addition of cetuximab across multiple doses of osimertinib. Osimertinib+cetuximab was superior to erlotinib, cetuximab, afatinib and afatinib+cetuximab in a D770_N771InsSVD PDX model (p<0.001). In this model, inhibition of p-EGFR, p-ERK, p-HER2 and increased caspase 3 cleavage were noted, consistent with significant tumor growth inhibition. In the phase 1 EGFR Ex20Ins expansion cohort of necitumumab in combination with osimertinib, 6/18 patients enrolled with 4 patients evaluable for response; 2 patients achieved a partial response and median PFS was 5.3 months. **Conclusion:** *In vivo* and *ex vivo* modeling in CRISPR cell line xenografts, PDXs and organoids demonstrated preclinical activity of dual EGFR blockade with osimertinib and EGFR monoclonal antibody in the 5 most common EGFR Ex20Ins representing a frequency of ~60% of detectable EGFR Ex20Ins in clinical practice. Osimertinib alone was as active as osimertinib plus cetuximab in A763_Y764InsFQEA, consistent with known sensitivity of this proximal insertion to single-agent EGFR-TKI. In a phase 1 study, osimertinib and the EGFR moAb necitumumab demonstrates preliminary clinically activity in EGFR Ex20Ins NSCLC.

Keywords: EGFR exon 20 insertion, Developmental Therapeutics

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.03 IDENTIFICATION OF MECHANISMS OF ACQUIRED RESISTANCE TO POZIOTINIB IN EGFR EXON 20 MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

Y. Elamin[1], J. Robichaux[1], B. Carter[2], M. Altan[2], D. Gibbons[2], F. Fossella[2], G. Simon[3], V. Lam[3], G. Blumenschein Jr[2], A. Tsao[1], J. Kurie[2], F. Mott[3], M. Negrao[2], L. Hu[1], J. He[1], M. Nilsson[1], B. Roeck[4], Z. Yang[4], V. Papadimitrakopoulou[3], J. Heymach[2]

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Background: Insertions/mutations in exon 20 of EGFR occur in ~2% Insertions/mutations in exon 20 of EGFR occur in ~2% of all lung adenocarcinomas. These alterations are characterized by primary resistance to approved tyrosine kinase inhibitors (TKIs) with response rates of <12%. We have shown that exon 20 insertions restrict the size of the drug-binding pocket, limiting binding of large inhibitors. However, poziotinib can circumvent these steric changes and is a potent inhibitor of EGFR exon 20 mutants. In our investigator-initiated phase 2 trial of EGFR exon 20 mutant NSCLC, poziotinib was associated with a best objective response rate of 55% (Heymach et al, 19th WCLC). Herein, we use preclinical models and clinical samples from our phase 2 study to identify mechanisms of acquired poziotinib resistance (NCT03066206). **Method:** EGFR exon 20 insertion (D770insNPG) genetically engineered mice (GEM) were treated with poziotinib until progression. Upon progression, tumor DNA and protein were analyzed using whole exome sequencing (WES) and reverse phase protein assay (RPPA). Mandatory and optional biopsies were obtained at baseline and progression, respectively, from patients treated in our phase 2 trial of poziotinib in EGFR exon 20 mutant NSCLC. Serial cfDNA was collected at baseline, 8 weeks of therapy, and on progression. Patient samples were analyzed using targeted next generation sequencing or WES. **Result:** Poziotinib acquired-resistance GEM tumors acquired mutations in ErbB4, KRAS, and other genes which represent potential targetable bypass pathways. Resistant GEM tumors displayed increased activation of MAPK, AKT, ERK and MEK compared to sensitive tumors, suggesting that poziotinib acquired resistance is associated with reactivation of the MAPK/PI3K pathways. We enrolled 50 EGFR exon 20 mutant patients in our phase 2 trial. Analysis of matched pre-poziotinib and on-progression samples from 20 responding patients revealed acquired EGFR tyrosine kinase domain point mutations in 4 patients (T790M (2), V774A (1), D770A, (1)). Ba/F3 cells co-expressing EGFR exon 20 insertion (S768supSVD) and T790M were resistant to poziotinib, suggesting that T790M is a poziotinib resistance driver. Potential acquired EGFR-independent resistance mechanisms identified in patients to date include PIK3CA E545K (1), MAP2K2 S94L (1), MET amplification (1), EGFR amplification (2), and CDK6 amplification (2). **Conclusion:** Parallel to acquired resistance mechanisms seen in classical EGFR mutation, acquired resistance to poziotinib can be mediated through EGFR-dependent mechanisms, notably T790M and other EGFR tyrosine kinase domain point mutations. EGFR-independent resistance mechanisms include activation of bypass pathways. Preclinical validation of resistance mechanisms and additional analysis of patient samples will be presented at the meeting.

Keywords: EGFR exon 20 insertion, Targeted therapy

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.05 GENOMIC CORRELATES OF DIFFERENTIAL RESPONSE TO EGFR-DIRECTED TYROSINE KINASE INHIBITORS

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Background: Oncogenic mutations in *EGFR* are powerful biomarkers of response to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). However, there remains significant heterogeneity in duration of response to therapy and overall survival, and the molecular determinants of this differential response have been incompletely characterized. **Method:** We identified NSCLC patients at our institution with sensitizing oncogenic *EGFR* mutations who had been treated with EGFR TKI(s) and who had at least one tumor specimen profiled via targeted next generation sequencing (OncoPanel). Duration of therapy (DOT) on first-line EGFR TKI and overall survival (OS) were assessed. Mutations associated with differential benefit to therapy were identified by comparing mutation rates in outliers with DOT or OS ≥75th percentile vs ≤25th percentile. Fisher's exact test was used to calculate statistical significance, and the Benjamini-Hochberg method was used to correct for false discovery rate (FDR). Time to event outcomes were assessed with the Kaplan-Meier method. **Result:** We identified 270 patients for inclusion in our cohort. 70% were female (190/270), 60% were never smokers (163/270), and median age was 62 (range 29-93). Sensitizing EGFR mutations were predominantly exon 19 deletion (51%, 138/270) or L858R (38%, 103/270). 94% of patients were treated with first-line erlotinib (253/270), and 30% received second-line osimertinib (82/270). The median DOT on first-line TKI was 12 months (range 0-72 months) and median OS was 28 months (range 1-133 months). Pre-treatment sequencing was available for 188 patients, 65 of whom also had documented assessment of resistance mechanism (T790M 78%, other 22%). Pre-existing concurrent *TP53* mutations were associated with shorter DOT (median 10 vs 16 mo, p=0.0017), but there was no significant difference in OS (median 25 vs 36 mo, p=0.2) and no association with resistance mechanism (p=0.674). In

addition to *TP53*, *BCOR* and *SMARCA4* mutations were enriched in patients with shorter DOT, whereas *MTOR* mutations were enriched in patients with DOT in the top quartile, though these analyses did not pass FDR correction. Pre-treatment *SMARCA4* mutations were more frequent in patients with survival in the bottom quartile (Fisher's p=0.01), and were associated with decreased OS (median 32 vs 12 mo, log-rank p<0.0001). **Conclusion:** Genomic features may contribute to differential outcomes in patients with EGFR-mutated NSCLC. In addition to *TP53* mutations, pre-treatment *SMARCA4* mutations may associate with worse outcomes in these patients.

Keywords: EGFR, genomic landscape, Response predictor

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.06 ADAPTIVE MECHANISMS OF RESISTANCE TO TARGETED THERAPY IN EGFR MUTANT BRAIN METASTASIS

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Background: A subset of non-small cell lung cancers (NSCLCs) can be effectively treated with EGFR tyrosine kinase inhibitors (TKIs). However, a significant proportion of patients with brain metastasis progress after front-line treatment, underscoring the central nervous system (CNS) as a unique sanctuary site for persistent disease. Herein, we performed an integrated examination of the cellular, pharmacological, and molecular causes of resistance to targeted therapies in brain metastases. **Method:** The efficacy of osimertinib, a brain penetrant third generation TKI, was studied in mice using EGFR mutant NSCLC models derived from cell lines or patient biopsies. Animals with multi-organ metastases were treated continuously until disease progression was detected in the brain parenchyma. We also developed an *in situ* transcriptomic approach, referred to as Brain Metastasis Xenograft-RNA Sequencing (BMX-seq), to distinguish the transcriptome of tumor versus stroma *in vivo*. Molecular and biological responses were integrated with pharmacological analysis of loco-regional distribution of osimertinib in and around brain lesions. **Result:** In EGFR mutant models with multi-organ metastases, extra-cranial tumors could be effectively controlled, while brain metastases eventually progress despite strong osimertinib penetrance into the normal and tumor bearing CNS. Importantly, tumor cells isolated from progressing brain metastases did not exhibit resistance *in vitro*. However, these cells exhibited an enhanced resistant capacity when transplanted into the brain, demonstrating that this resistant phenotype is selected for and that exposure to the brain is a requirement for drug resistance *in vivo*. BMX-seq reveals that the stroma of drug resistant brain metastasis is characterized by activation of innate pro-inflammatory pathways. Reciprocally, we identified stromal induced activation of cytoskeletal and interferon response genes in drug resistant tumor cells. Interestingly, several of these genes are induced *in situ* independently of drug treatment, suggesting that the brain metastatic niche can precondition tumor cells for ensuing drug resistance. Finally, we demonstrate that inhibiting mediators of interferon and cystoskeletal signaling increases the sensitivity of brain metastasis to osimertinib *in vivo*. **Conclusion:** Although advances have been made in the brain penetrating abilities of targeted therapies, acquired resistance in this unique TME still develops. Our results suggest that adaptive molecular interactions within the brain TME preconditions metastatic cells for TKI resistance and that targeting such pathways in combination with osimertinib should be explored to treat NSCLC patients suffering from or at risk for brain relapse.

Keywords: brain metastasis, Drug resistance, Osimertinib

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.07 ACTIVITY OF LAROTRECTINIB IN TRK FUSION LUNG CANCER

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Background: Tropomyosin receptor kinase (TRK) fusions involving *NTRK1*, *NTRK2*, and *NTRK3* occur in a range of tumor types. Larotrectinib, the first FDA-approved highly selective TRK inhibitor, has demonstrated an overall response rate (ORR) of 75% by independent central review across a broad spectrum of tumors that harbor *NTRK* gene fusions (Drilon et al., *NEJM* 2018;378:731–9). Here, we report updated data on the patients with lung cancer who have been treated with larotrectinib. **Method:** Patients with non-small cell lung cancer (NSCLC) in two clinical trials (NCT02122913 and NCT02576431) with TRK fusion cancer were included in this analysis. Larotrectinib (100 mg BID) was administered on a continuous 28-day schedule until withdrawal, unacceptable toxicity, or disease progression. Response was assessed by investigator (INV) and independent review committee (IRC) per RECIST v1.1. **Result:** As of July 30, 2018, 11 patients with metastatic lung adenocarcinoma were enrolled. Median age was 52 years (range 25–76 years). Eight patients had fusions involving *NTRK1* and diverse fusion partners: *EPS15* (n=2), *TPM3* (n=2), *IRF2BP2* (n=2), *TPR* (n=1), and *SQSTM1* (n=1). Three patients had fusions involving *NTRK3* (fusion partner: *SQSTM1* [n=2] and *ETV6* [n=1]). Ten patients had prior systemic therapy (five patients had three or more prior therapies) with best responses on last prior therapy being one partial response, four with stable disease, three progressive disease, and three unknown or unevaluable. Seven patients were evaluable for response to larotrectinib. INV and IRC assessment were in agreement, with one complete response, four partial responses (including one patient with central nervous system [CNS] metastases), and two with stable disease (ORR 71%). Results from four patients not evaluable at the July 30, 2018 data cut-off due to insufficient follow-up are expected in April 2019 and will be presented at the meeting. The median time to response was 1.8 months. One patient with brain metastases had an intracranial near complete response (–95% reduction) to larotrectinib, as well as an extracranial response. The duration of response by IRC ranged from 7.4^{+} months to 25.8^{+} months; the median duration of response was not reached. One patient continued receiving treatment post-progression. Two patients discontinued treatment due to disease progression and one withdrew without cause. Larotrectinib was well tolerated, with treatment-related adverse events being predominantly grade 1–2. **Conclusion:** Larotrectinib is highly active in advanced lung cancer patients harboring *NTRK* gene fusions, including those with CNS metastases, with a favorable safety profile. These results support the use of larotrectinib in *NTRK* fusion NSCLC.

Keywords: TRK fusion, Lung cancer, Larotrectinib

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.09 LONG-TERM OUTCOMES TO TEPOTINIB PLUS GEFITINIB IN PATIENTS WITH *EGFR*-MUTANT NSCLC AND MET DYSREGULATION: 18MONTH FOLLOW-UP

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Background: In *EGFR*-mutant NSCLC, *MET* amplification may cause resistance to EGFR tyrosine kinase inhibitors (TKIs). In a Phase Ib/II study in EGFR TKI-resistant patients with *EGFR*-mutant MET+ NSCLC, progression-free survival (PFS) and objective response rate (ORR) after ≥6 months of follow-up were improved with tepotinib (a highly selective MET TKI) plus gefitinib, compared with chemotherapy, particularly in patients with *MET* amplification. Here we present data at ≥18 months of follow-up. **Method:** Asian patients with advanced, EGFR+, T790M-, MET+ NSCLC with resistance to prior EGFR TKIs were randomized to receive oral tepotinib 500 mg/day+gefitinib 250 mg/day or ≤6 cycles of cisplatin/carboplatin+pemetrexed chemotherapy±pemetrexed maintenance until confirmed progression, unacceptable toxicity, or withdrawal. Primary endpoint was investigator-assessed PFS. Secondary endpoints included ORR, overall survival (OS) and safety. Subgroup analyses were preplanned in MET IHC3+ and *MET* amplification populations (NCT01982955). **Result:** Low recruitment halted full enrolment with 55 of 156 planned patients enrolled. As of 12-Dec-2018, median (range) duration of treatment with tepotinib+gefitinib was 21.4 (4.6, 110.9) weeks, with 3 patients still receiving treatment; and with pemetrexed was 18.0 (3.0, 60.4) weeks. 15 patients (62.5%) received ≥4 cisplatin/carboplatin cycles. Better outcomes were reported with tepotinib+gefitinib vs chemotherapy (Table), particularly in patients with MET IHC3+ (PFS: HR 0.35 [90% CI 0.17–0.74], OS: 0.32 [0.14–0.75]) or *MET* amplification (PFS: HR 0.13 [90% CI 0.04–0.43], OS: 0.08 [0.01–0.51]). Drug-related grade ≥3 adverse events (AEs) occurred in 17 (54.8%) patients receiving tepotinib+gefitinib and 12 (52.2%) patients receiving chemotherapy. Any-cause AEs leading to discontinuation occurred in 3 (9.7%) patients receiving tepotinib+gefitinib and 1 (4.3%) receiving chemotherapy. Dose reductions due to AEs were reported in 5 (16.1%) vs 4 (17.4%) patients. **Conclusion:** Tepotinib+gefitinib has durable antitumor activity in patients with *EGFR*-mutant NSCLC with MET IHC3+ or *MET* amplification, and was generally well tolerated. *MET* amplification will be further explored as a biomarker for tepotinib.

Table: Summary of efficacy data

Population		Tepotinib + gefitinib	Chemotherapy	HR/OR (90% CI)
Overall MET+*	Patients, n	31	24	
	mPFS, months (90% CI)	4.9 (3.9, 6.9)	4.4 (4.2, 6.8)	0.67 (0.35, 1.28)
	mOS, months (90% CI)	17.3 (12.1, 37.3)	18.7 (15.9, 20.7)	0.67 (0.33, 1.37)
	ORR, n (%) [90% CI]	14 (45.2) [29.7, 61.3]	8 (33.3) [17.8, 52.1]	1.99 (0.56, 6.87)
MET IHC3+	Patients, n	19	15	
	mPFS, months (90% CI)	8.3 (4.1, 21.2)	4.4 (4.1, 6.8)	0.35 (0.17, 0.74)
	mOS, months (90% CI)	37.3 (24.2, 37.3)	17.9 (12.0, 20.7)	0.32 (0.14, 0.78)
	ORR, n (%) [90% CI]	13 (68.4) [47.0, 85.3]	5 (33.3) [14.2, 57.7]	4.33 (1.03, 18.33)
MET amplification†	Patients, n	12	7	
	mPFS, months (90% CI)	21.2 (8.3, NE)	4.2 (1.4, 7.0)	0.13 (0.04, 0.43)
	mOS, months (90% CI)	37.3 (NE, NE)	13.1 (3.3, NE)	0.08 (0.01, 0.51)
	ORR, n (%) [90% CI]	8 (66.7) [39.1, 87.7]	3 (42.9) [12.9, 77.5]	2.67 (0.37, 19.56)

CEP-7, centromere protein 7; CI, confidence interval; EGFR, epidermal growth factor receptor; GCN, gene copy number; HR, hazard ratio; IHC, immunohistochemistry; IRC, independent review committee; ITT, intention to treat; MET, mesenchymal-epithelial transition factor; NE, not estimable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival All efficacy outcomes are investigator-assessed by RECIST v1.1. *IHC2+/IHC3+/gene amplification. †*MET* amplification is defined as GCN ≥5 and/or *MET/CEP-7* ratio ≥2. 17 of 19 patients with *MET* amplification have MET overexpression (IHC3+).

Keywords: Tepotinib, MET amplification, NSCLC

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.10 COMPREHENSIVE ANALYSIS OF SECONDARY MUTATION AS RESISTANCE MECHANISM TO SEVEN MET-TKIS FOR MET EXON 14 SKIPPING IN VITRO

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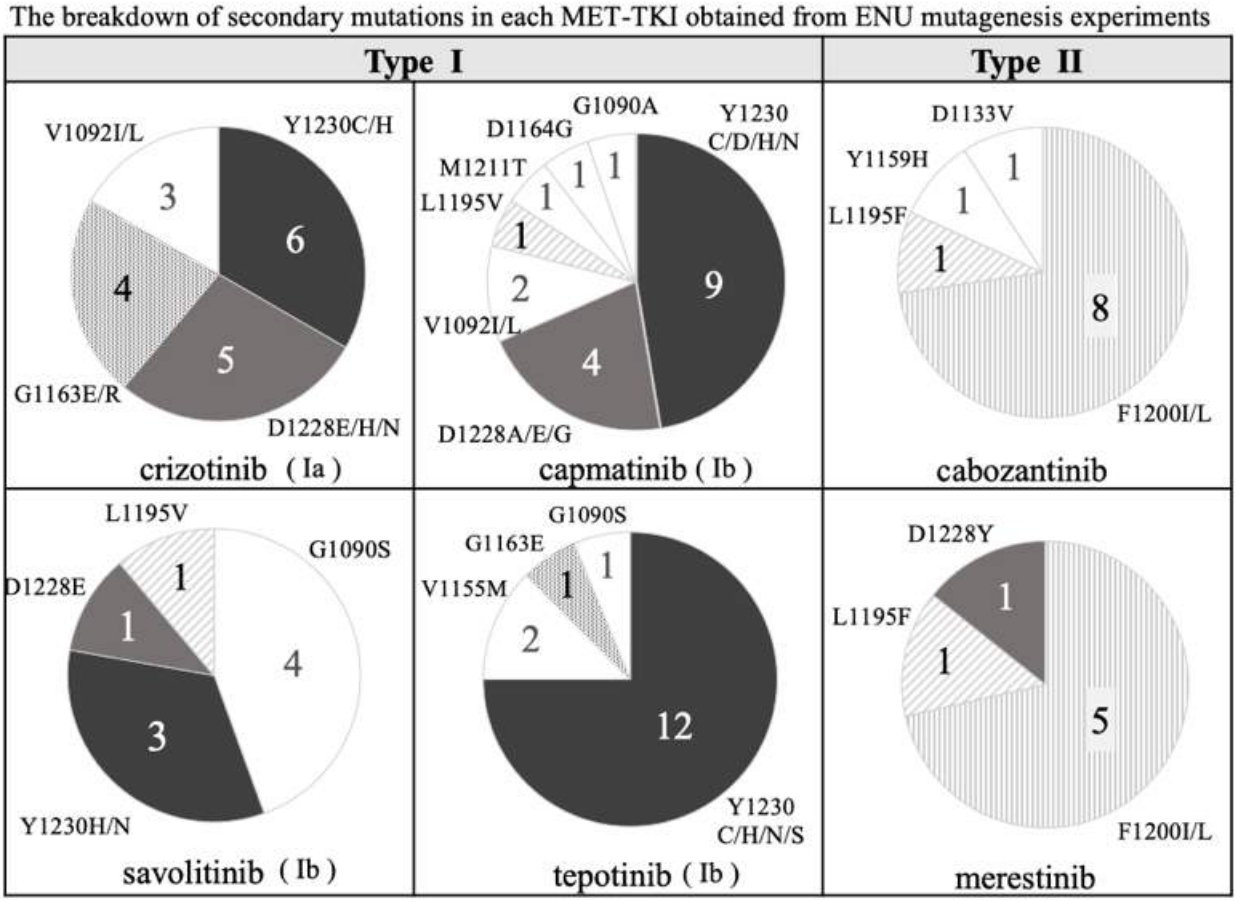
Background: MET exon 14 skipping mutation have been attracting attentions of thoracic oncologists as a new target of therapy for lung cancer. The efficacy of MET-TKI has been reported, while these tumors, almost always acquire resistance, as in the case of other oncogene-addicted lung cancers. However, its resistance mechanisms are not fully understood. **Method:** MET exon14 skipping mutation was introduced to Ba/F3 cell retrovirally. Using N-ethyl-N-nitrosourea mutagenesis, we derived resistant clones to seven MET-TKIs and searched for secondary MET mutations. We evaluated their sensitivities to following different TKIs. Type Ia, crizotinib; Type Ib, capmatinib, tepotinib and savolitinib; Type II, cabozantinib, merestinib and glesatinib. **Result:** We sequenced 201 resistant clones and could obtain 80 clones which had secondary mutations in the MET tyrosine kinase domain. A total of 26 different missense mutations occurring at 12 codons were identified. Of them, D1228 and Y1230 in the activation loop were common sites for type I TKIs that bind to active kinase form (DFG-in), while L1195 and F1200 were those for type II TKIs that bind to inactive form (DFG-out). In general, resistant mutations against type I were sensitive to type II, and vice versa.



Conclusion: We identified mutation sites specific for TKI types as resistance mechanisms and complementary activities between type I and type II inhibitors against those mutations. These finding should provide relevant clinical implication for treating patients with lung cancer harboring MET exon 14 skipping.

Keywords: MET exon14 skipping, Targeted therapy, resistance mechanism

MA09 EGFR & MET
SUNDAY, SEPTEMBER 8 15:15–16:45

MA09.11 MECHANISMS OF RESISTANCE TO MET TYROSINE KINASE INHIBITORS IN PATIENTS WITH MET EXON 14 MUTANT NON-SMALL CELL LUNG CANCER

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Background: Type I and II MET tyrosine kinase inhibitors (TKIs) are under development for patients with *MET* exon 14 mutant non-small cell lung cancer (NSCLC). Understanding the mechanisms driving resistance to MET TKIs is critical to design novel treatment strategies for this molecular subtype of NSCLC. **Method:** Among patients with MET exon 14 mutant NSCLC treated with MET TKIs, pre- and post-TKI tumor tissue specimens and plasma samples were analyzed using next-generation sequencing (NGS) to explore genomic mechanisms of resistance upon disease progression. **Result:** Between April 2014 to March 2019, 38 patients were treated with MET TKIs. Among these, paired samples from 15 individuals were evaluable for this study. Patients were treated with MET TKIs in the first-line (N=7; 46.7%), second-line (N=5; 33.3%), third-line (N=1; 6.7%) and fourth-line (N=2: 13.3%) setting. Eight patients were treated with one type I MET TKI and 7 patients received ≥2 MET TKIs. On target mechanisms of resistance were identified in 5 patients (33.3%), through secondary mutations in the *MET* tyrosine kinase domain (N=4) and *MET* amplification (N=1). Single MET kinase domain mutations D1228H/N were detected in 2 patients progressing on treatment with a type I MET TKI. In two cases, tumor tissue revealed only one resistance mutation (case #1 with Y1230H; case #2 with H1094Y), whereas paired plasma analysis demonstrated ≥3 resistance mutations in ctDNA (case #1 with G1163R, D1228N, Y1230H/S; case #2 with H1094Y, L1195F/V), reflecting the emergence of polyclonal on-target resistance. Off-target mechanisms of acquired resistance were identified in 7 patients treated with Type I MET TKI (46.7%) and involved amplification of *EGFR* (N=2), *EGFR/HER2* (N=1), *EGFR/HER3* (N=1), *KRAS* (N=1), *EGFR/KRAS/BRAF* (N=1), *CCND1* (N=1). In 2 cases with bypass activation, sequential treatment with type II MET TKIs did not confer benefit. A concurrent *NF1* mutation was present at baseline in a patient with primary resistance to MET TKI (6.7%). In 2 patients (13.3%), no genomic mechanisms of resistance were identified. **Conclusion:** The landscape of resistance mechanisms to MET TKIs in NSCLC includes single and polyclonal secondary kinase domain mutations and bypass track activation by amplification of key oncogenes involving the ErbB/HER family of tyrosine kinase receptors and the MAPK signaling pathway. Given the complexity of resistance, therapeutic efforts to prevent acquired resistance in MET exon 14 mutant NSCLC should be developed.

Keywords: MET exon 14, resistance, Tyrosine Kinase inhibitors

MA10.01 INVASIVE ADENOCARCINOMA IN SCREEN DETECTED PURE GROUND-GLASS NODULES (GGN)

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Background: A major criticism of lung cancer screening initiatives is their propensity to instigate enhanced surveillance and over-treatment of otherwise indolent disease, including adenocarcinoma-in-situ (AIS). These nodules present radiographically as GGN. There are wide variations in the recommendations for surveillance (repeat imaging), diagnosis (biopsy) and therapeutic intervention (resection) for these lesions. To further our understanding of the optimal management of screen detected GGN, we used data from two screening studies in Canada with up to 17 years of follow-up to determine the proportion of persistent GGN that are invasive adenocarcinomas. **Method:** Two lung cancer screening studies data sets were reviewed: the BC Lung Health Study (BCLHS) with 1365 participants and the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) with 2537 participants. BCLHS enrolled ever smokers 45-74 years of age with >30-year smoking history. The median follow-up in this cohort was 12 years (0.1-17.6) The PanCan study screened participants age 50-75 years with a PLCOm2008 6-year lung cancer risk > 2%. The median follow-up was 5.5 years (3.2-6.1). The nodules were followed until they resolved, demonstrated stability for >2 yrs or were surgically resected. All pure GGO resected were re-reviewed and classified by two pulmonary pathologists according to the revised 2015 World Health Organization classification of lung tumours. Cancers were staged using the 8th edition of the AJCC/UICC cancer staging manual. **Result:** A total of 18,589 nodules in 3902 participants were reviewed. 2392 (13% of all nodules) were classified as pure GGN. 1073 of the 2392 were > 5mm at the baseline scan. Of these 1073 GGN, 156 (15%) resolved, 879 (82%) remained pure GGN, 38 (3.5%) became part-solid or solid. 32(3%) of the GGN from 29 patients that demonstrated growth were resected. The median size prior to resection was 16 mm (range 7 to 33 mm). The histopathology distribution included: 19 invasive adenocarcinomas, 7 minimally invasive adenocarcinomas, 6 adenocarcinoma-in-situ. The TNM stage distribution and average size of the GGN on the CT prior to resection are listed in Table 1. Sixty-one percent of the invasive cancers (Stage IA1 to IIIA) were less than 20 mm. Eleven percent of the invasive adenocarcinomas had lymph node metastasis.

Stage	N=	Mean (mm)	Range (mm)
0	6	12	10-13
1A1mi	7	14	9-25
IA1	3	9	7-10
IA2	9	16	11-20
IA3	4	25	21-26
IB	1	33	33
IIB	1	23	23
IIIA	1	18	18

Conclusion: A high proportion of pure GGN that demonstrate growth are invasive cancers. The majority were < 20mm in size when they were resected. This has significant implication in the development of recommendations to manage screen detected GGN.

Keywords: Screening, GGN, nodule management

MA10.02 DEEP LEARNING WITH RADIOMICS MAY PREDICT HIGH-GRADE LUNG ADENOCARCINOMA BASED ON HISTOLOGICAL PATTERNS IN GROUND GLASS OPACITY LESIONS

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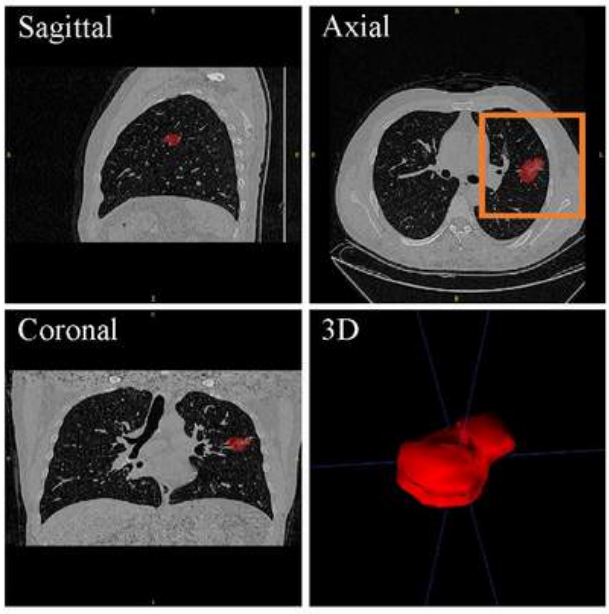
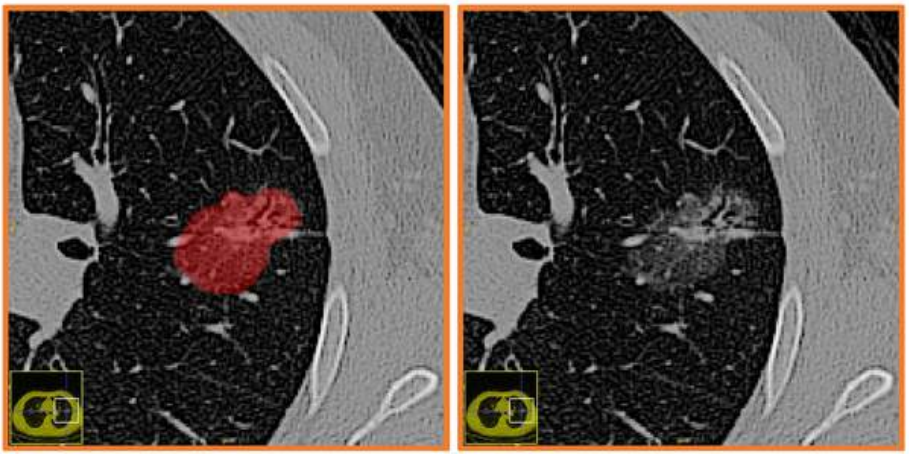
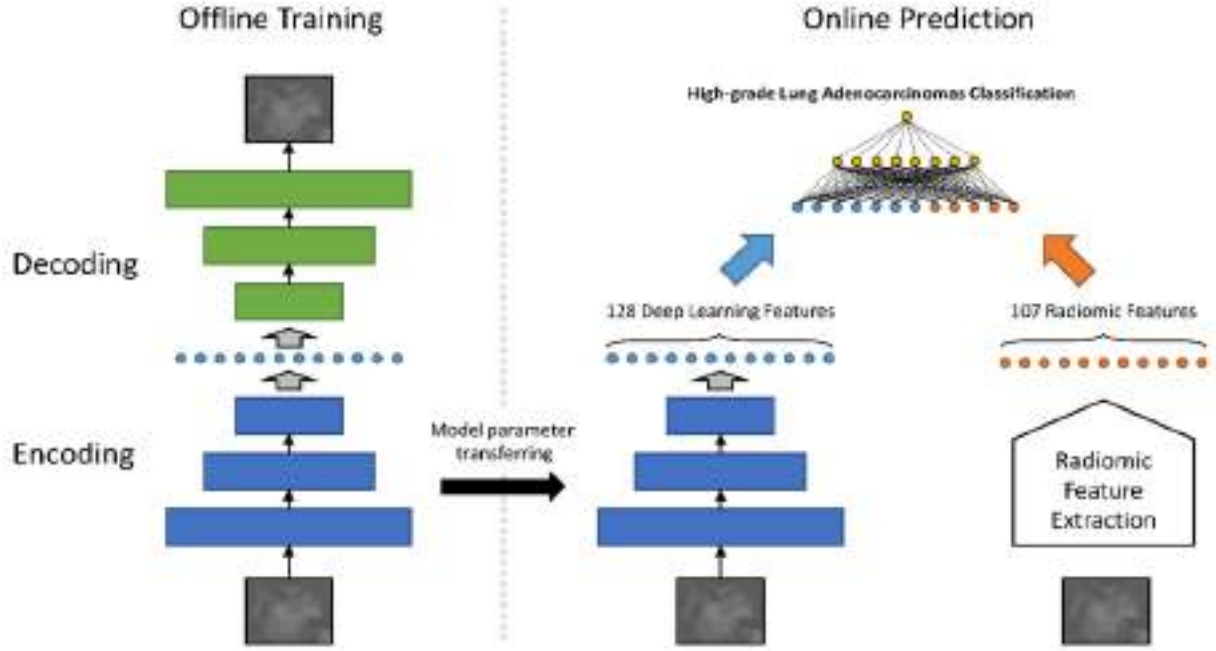
Background: Adenocarcinoma (ADC) is the most common histological subtype of lung cancers in non small cell lung cancer (NSCLC) in which ground glass opacifications (GGOs) found on computed tomography (CT) scans are the most common lesions. These lesions are usually treated with limited lung resection. However, the presence of a micropapillary or solid component is identified as an independent predictor of prognosis, indicating a more extensive resection. The accurate classification of subtypes still remains difficult in radiology or in frozen pathological analysis, even with the help of classical radiomics. The purpose of our study is to explore imaging phenotyping using a novel method combining radiomics with deep learning (RDL) to predict high-grade patterns within lung ADC. **Method:** Included in this study were 111 patients differentiated as having GGOs and pathologically confirmed ADC. Four different methods were compared to classify the GGOs for the prediction of the pathological subtypes of high-grade lung ADCs, including classic machine learning, radiomics, deep learning method, and a proposed novel method referred as RDL. A four-fold cross-validation approach was used to evaluate the performance of such methods. **Result:** We analyzed 32 patients with high-grade patterns and 79 without such patterns. The proposed RDL has achieved an overall accuracy of 0.888, which significantly outperforms classic machine learning, radiomics, and deep learning alone (p< 0.001, paired t-test).







Conclusion: High-grade lung ADC based on histologic pattern spectrum in GGO lesions might be predicted by a novel framework combining radiomics with deep learning, which reveals a significant advantage over traditional methods.

Keywords: ground glass opacifications, deep learning, NSCLC

MA10.03 QUANTITATIVE COMPUTED TOMOGRAPHY (CT) BASED TEXTURE ANALYSIS; COULD WE PREDICT THE FUTURE GROWTH OF THE PURE GROUND GLASS NODULES?

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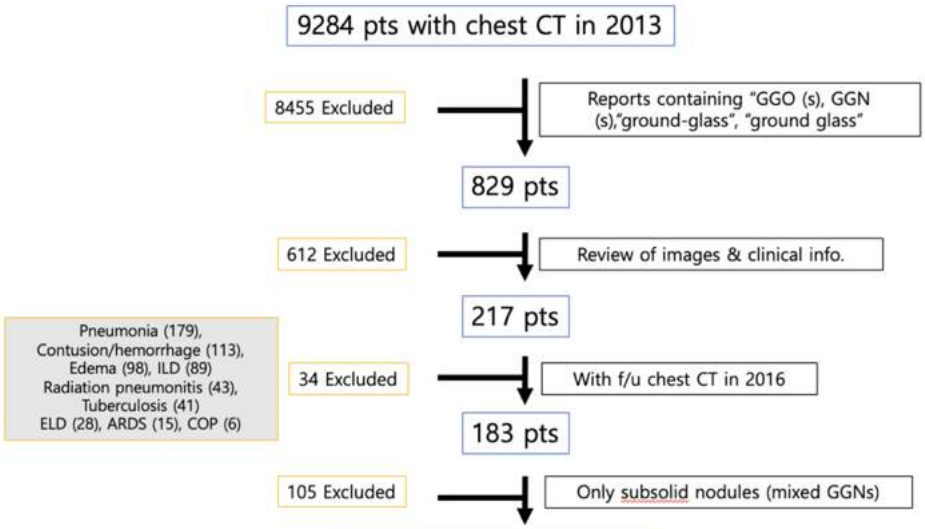
Background: To evaluate whether the quantitative computed tomography based texture analysis (QTA) could predict the future growth of the pure ground glass opacity nodule (GGN) or not. **Method:** We retrieved CT images of 9284 patients who underwent chest CT in 2013 from the picture archiving and communication system (PACS). We queried the database of PACS to filter reports of chest CT containing one of these key words, as follows; "ground-glass", ground glass", or "GGO(s)". 78 patients were finally included [5 patients (5GGNs) who underwent operation due to growth of GGN during follow-up and 73 patients who had 3-year-follow-up CT]. Total 90 GGNs from 78 patients were analyzed by QTA. The parameters of QTA were mean HU value, standard deviation (SD), entropy, mean positive pixels (MPP), skewness, and kurtosis. QTA was performed with image filtration step to remove photon noise, filtration technique enhanced features of different sizes based on the spatial scale filter (SSF) value varying from fine-texture (SSF2), medium-texture (SSF3), and coarse-texture (SSF4). We focused on the change of volume% of GGNs [(follow-up volume of GGN/ initial volume of GGN)*100%], and assessed the differences of QTA parameters' value according to the change of volume % for three cut-off levels (150%, 170%, and 200%); group 1a (≤130%), group 1b (>130%);group 2a (≤150%), group 2b (>150%);group 3a (≤170%), group 3b (>170%). **Result:**



P value / CO	Entropy			
	SSF0	SSF2	SSF3	SSF4
130	0.1701	0.2121	0.2015	0.2142
150	0.0770	0.0495	0.0487	0.0535
170	0.0271	0.0167	0.0144	0.0187

P value / CO	Mean HU value				Standard deviation			
	SSF0	SSF2	SSF3	SSF4	SSF0	SSF2	SSF3	SSF4
130	0.9649	0.8639	0.6628	0.5404	0.8950	0.8977	0.6378	0.6439
150	0.4558	0.8229	0.9549	0.8994	0.6326	0.5914	0.8327	0.5529
170	0.3932	0.3624	0.6673	0.9153	0.3274	0.7941	0.4279	0.1864

P value / CO	Mean positive pixels				Skewness				Kurtosis			
	SSF0	SSF2	SSF3	SSF4	SSF0	SSF2	SSF3	SSF4	SSF0	SSF2	SSF3	SSF4
130	0.4754	0.8942	0.7990	0.5707	0.3924	0.7389	0.6689	0.2597	0.7771	0.2902	0.6219	0.9580
150	0.8215	0.6456	0.9662	0.9378	0.4807	0.9386	0.9018	0.4717	0.2994	0.2386	0.2234	0.3589
170	0.4884	0.5170	0.7161	0.9782	0.3798	0.6618	0.9429	0.9122	0.2891	0.4968	0.4802	0.1366

Only entropy was a variable that showed statistically significant difference between group 3a and 3b with all the filtrations (SSF2, 3, 4) applied or without filtration (SSF0). The mean, SD, MPP, kurtosis and skewness, showed no significant difference according to the cut-off value of volume % change (130%, 150%). There was no significant difference in QTA parameters in group2a vs 2b, group3a vs 3b. **Conclusion:** The initial entropy parameter of texture analysis for GGNs may have the potential to predict the GGNs growth.

Keywords: Pure ground glass nodule, Texture analysis, Radiomics

MA10.05 BREATH ANALYSIS: NEW KEY-CHALLENGES FOR EARLY DETECTION OF LUNG AND PLEURAL NEOPLASMS

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Background: The growing interest about breath analysis relies on the need of tools to get an early diagnosis of respiratory pathologies with high mortality rate such as lung cancer (LC) and malignant pleural mesothelioma (MPM). Nowadays the key-challenge of the scientific community is the search for non-invasive diagnostic biomarkers able to identify patients at risk of developing cancer or with early stage cancer. A diagnostic progress would be crucial to improve the survival outcome of these neoplasms, generally detected at an advanced stage. The analysis of Volatile Organic Compounds (VOCs) pattern in human breath for early detection and follow-up of diseases such as cancer is low-cost, non-invasive and promising alternative to traditional exams (i.e., colonoscopy, biopsy). **Method:** This study is based on the development and validation of a methodological approach aimed to the identification of VOCs breath pattern to discriminate between patients affected by both LC and MPM, and healthy controls (CTRL). A total of 80 breath samples from 36 patients with LC, 14 patients with MPM and 30 CTRL have been collected into inert Tedlar bags, transferred to sorbent tubes (biomonitoring, Markes) and analysed by TD-GC/MS (TD Markes Unity 2 - GC Agilent 7890/MS Agilent 5975). **Result:** Non parametric test as Wilcoxon/Kruskal Wallis tests (R version 3.5.1) allowed to identify the most weighting variables in discrimination between LC, MPM and HC breath samples. On the basis of p-values lower than 0.05 (selection between CTRL and LC, and between CTRL and MPM) and current knowledge on metabolic processes, a multivariate statistics (Principal Components Analyses (PCA) -PAST 3.20) has been applied on breath samples, considering only selected variables. The preliminary statistical elaboration by PCA of data collected from the analysis of LC and CTRL samples have shown two principal components: PC1 characterized by higher loadings of benzoic acid, methylcyclohexane and hexanal, and PC2 characterized by high loadings for dimethyldecane, pentane and pentanal. Similar results were obtained by PCA applied to MPM and CTRL breath samples considering 2-methylpentane, cyclopentane, hexane and 2-butanone as discriminant variables. **Conclusion:** PCA was able to discriminate between LC and CTRL and between MPM and CTRL breath samples. Leave-one-out cross-validation method was applied to calculate the prediction accuracy obtaining good sensitivity (88%), accuracy (86%) and specificity (92%). Further investigation about breath analysis is strongly warranted, due to the need of biomarkers potentially useful both for the screening of high-risk subjects and for the early diagnosis of lung and pleural neoplasms.

Keywords: Breath analysis, Lung cancer, pleural mesothelioma

MA10.06 RANDOMIZED CLINICAL TRIAL WITH COMPUTER ASSISTED DIAGNOSIS (CAD) VERSUS RADIOLOGIST AS FIRST READER OF LUNG SCREENING LDCT

R. Yuan[1], J. Mayo[2], I. Streit[3], S. Atkar-Khattra[3], R. Myers[3], J. Yee[2], S. Lam[3]

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MA10.07 INTEGRATIVE ANALYSIS OF EPISTASIS INVOLVING ONCOGENESIS-RELATED GENES IN LUNG CANCER RISK DEVELOPMENT

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Background: Our previous study identified significant genetic interactions within oncogenesis-related genes in lung cancer risk development. More genetic interactions may exist between oncogenesis-related genes and outside regions in the genome. A functional annotation and pathway analysis of the identified epistasis-related genes will advance our understanding about the complicated biological mechanisms underlying lung tumorigenesis. **Method:** The genotypes from two independent lung cancer GWAS studies including a total of 23,351 lung cancer patients and 19,657 health controls with European ancestry were collected for the analysis. Pairwise epistasis was conducted between 27,722 SNPs, from 2,027 oncogenesis-related genes, and 317,624 SNPs from the rest of the genome. A two-stage study design including discovery and replication studies, and stringent Bonferroni correction for multiple statistical analysis were applied in the analysis, Additional genotyping and gene expression data from 409 independent individuals with Caucasian ancestry were used to evaluate the effect of identified epistasis on gene expression levels. The epistasis-involved genes, were submitted to DAVID, Reactome, and GeneMANIA for gene functional annotation and pathway analysis. **Result:** Significant genetic interactions were identified between SNPs in gene pairs ATR-GALNT18 (Interaction OR=0.76, p value=7.98x10-13) and MET-DPF3 (Interaction OR=0.76, p value=1.62x10-12) in lung adenocarcinoma; and PICALM-PDZRN4 (Interaction OR=1.47, p value=1.67x10-12) in lung squamous carcinoma. None of these genes have been identified from previous main effect association studies in lung cancer. Further eQTL gene expression analysis revealed the significant association in expression levels between joint genotypes at rs637304:rs285581 and the PICALM gene expression (p=0.009). A total of 12 unique genes, from six significant interactions, including those from within oncogenesis-related genes and between oncogenesis-related genes and outside variants, were submitted to functional annotation and pathway analysis. Three of them (ATR, MET and FHIT) are shown to be related with lung cancer, and six of them (RAD51B, FHIT, CALNT18, RGL1, SYNE1 and TSPAN8) are involved in tobacco-use disorders. The top 10 pathways include TP53 regulates transcription of DNA repair genes (FDR=1.67x10-2), homologous DNA pairing and strand exchange (FDR=2.57x10-2), and Meiotic synapsis (3.08x10-2), etc. GeneMANIA predicted one gene network harboring all the 12 candidate genes, supporting the epistasis at 3 genes pairs and indirect interactions at 3 gene pairs. **Conclusion:** We identified novel genes involved in lung cancer risk development by interacting with other genetic variants. The study provides evidence that epistasis explains part of the missing heritability in lung cancer; and complex gene network and pathways contribute to lung carcinogenesis.

Keywords: Epistasis, gene network and pathway, Lung cancer

MA10.09 EVALUATION OF THE CLINICAL UTILITY OF THE PANCAN, EU-NELSON AND LUNG-RADS PROTOCOLS FOR MANAGEMENT OF SCREEN DETECTED LUNG NODULES AT BASELINE

R. Myers[1], J. Mayo[2], M. Tammemägi[3], S. Atkar-Khattra[4], R. Yuan[5], J. Yee[6], J. English[2], K. Grant[1], A. Lee[1], A. Mcguire[1], A. Mcwilliams[7], F. Brims[7], L. Mo[7], S. Lam[4]

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MA10 EMERGING TECHNOLOGIES FOR LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8 15:15–16:45

MA10.10 UPTAKE IN LUNG CANCER SCREENING – DOES CT LOCATION MATTER? A PILOT STUDY COMPARISON OF A MOBILE AND HOSPITAL BASED CT SCANNER

E. Bartlett[1], S. Kemp[1], S. Desai[1], S. Mirsadraee[1], C. Ridge[1], J. Morjaria[1], P. Shah[1], K. Morris[2], J. Derbyshire[2], M. Chen[2], C. Peacock[1], N. Ivashniova[1], M. Martins[1], J. Addis[1], S. Padley[1], A. Devaraj[1]

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Background: Community based lung cancer screening has been proposed as a method of increasing uptake for lung cancer screening by reducing barriers to participation. We report baseline statistics for a lung cancer screening pilot study in which patients were scanned on either a community based mobile CT unit or on a University Hospital based fixed-site CT scanner. **Method:** Ever smokers aged 60-75 registered at 17 participating general practitioner practices (GP) in West London were invited for a lung health check at either a mobile unit situated in a supermarket car park or in a hospital site. The location offered was based upon proximity to the participant's home address. On attendance a lung health check, assessing lung cancer risk, was undertaken. Participants with a LLP_{v2} score of ≥2.0% and/or $PLCO_{M2012}$ score of ≥1.51% were offered a same day low dose CT (LDCT) scan. Uptake, attendance and non-attendance (DNA) rates were compared using Chi-squared (χ^2) test. **Result:** 8366 potentially eligible participants were invited for a lung health check appointment; 5135 (61.4%) to the hospital site, and 3231 (38.6%) to the mobile site. 1749/8366 (20.9%) participants responded (males n=954/1749 (54.5%)). 1047/5135 (20.4%) were booked an appointment at the hospital site and 702/3231 (21.7%) at the mobile site (p=0.14). No difference was observed in lung cancer risk between participants at the two sites. Patients at the mobile site were more likely to be ex-smokers (p=0.048). The DNA rate at the hospital site was 96/1047 (9.2%) and at the mobile site was 48/702 (6.8%) (p=0.08). On attendance, 63 patients were ineligible for screening; 52/1749 (3.0%) did not meet the entry criteria and 11/1749 (0.6%) were acutely unwell. Therefore 1542 patients attended and had a risk score calculated and of these 1145/1542 (74.3%) underwent CT. Median [range] risk scores for scanned patients were 1.97 [0-25.34] for $PLCO_{M2012}$ and 4.71 [0.94-35.92] for LLP_{v2}. Lung cancer was confirmed in 17/1145 (1.5%) participants at baseline. A further 151/1145 (13.2%) participants will undergo interval CT for indeterminate nodules. **Conclusion:** There was a small but non-significant increase in participant response rates for the community based mobile site compared to the hospital site CT scanner, but no difference in DNA rates. While community based mobile scanners may provide valuable additional capacity to lung screening programmes, the magnitude of any benefit to participant uptake needs to be balanced against the additional complexity of setting up these stand-alone facilities. Further work is ongoing to understand the interaction between CT location and other factors that influence recruitment, with a view to using effective methods to increase uptake at all sites for future screening invitations.

Keywords: Screening, Uptake, Mobile

MA10 EMERGING TECHNOLOGIES FOR LUNG CANCER DETECTION
SUNDAY, SEPTEMBER 8 15:15–16:45

MA10.11 SENSITIVITY AND OPTIMAL CLINICOPATHOLOGICAL FEATURES OF GENETIC TARGETED LIQUID BIOPSY IN PN0M0 LUNG ADENOCARCINOMA

M. Ito[1], Y. Miyata[1], S. Hirano[1], F. Irisuna[1], N. Kishi[1], Y. Tsutani[1], R. Rosell[2], M. Okada[1]

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Background: Liquid biopsy for diagnosis of early-stage lung cancer is still challenging. The optimal marker and methodology has not been established. In Asia, almost 40-50% of lung adenocarcinomas harbor the *EGFR* mutation and L858R is a representative of a somatic *EGFR* mutation. We evaluated the usefulness of the *EGFR* somatic mutation in liquid biopsy using droplet digital PCR (ddPCR), which is a sensitivity device to detect several types of genetic mutations. **Method:** We examined weather L858R could be detected from preoperative ctDNA by ddPCR. Cases without *EGFR* mutation (wild type) were utilized as negative control. All involved cases underwent surgical resection after preoperative HRCT and PET-CT. Serum for ctDNA extraction was collected before the operation. L858R in the primary site was confirmed by resected surgical specimen. Clinicopathological features (e.g.: whole and invasive tumor size on HRCT, SUV max on PET-CT, histological subtype) were also explored for an optimal liquid biopsy candidate. **Result:** Forty-five pN0M0 lung adenocarcinoma patients harboring L858R were enrolled. Twenty-one and 24 cases showed part-solid and pure solid appearance on HRCT, respectively. Median whole and invasive tumor size on HRCT was 21 and 19 mm, respectively. 91.1% (41/45) cases were clinical stage IA1-IB and 97.8% (44/45) cases were pathological stage IA1-IB. In wild type cases, positive droplet for L858R was almost completely undetectable. Whereas, L858R was significantly detected in 7 *EGFR* mutant cases (sensitivity is 15.56%, 7/45). Among 7 positive cases, 6 cases showed pure solid appearance in preoperative HRCT. Except for pure solid appearance, there was no significant features related to the positive result. If cases are limited to pure solid appearance, 25.0% (6/24) of cases could be diagnosed by liquid biopsy. Even small-sized tumors (1.1 cm in diameter) or tumors with slight accumulation on PET-CT (SUV max 0.5) could be detected if it showed pure solid appearance on HRCT. **Conclusion:** L858R can be a definitive marker for liquid biopsy using ddPCR in pN0M0 lung adenocarcinoma. 15.56% (7/45) of cases were diagnosed in pN0M0 cases. Limited to pure solid tumor, 25.0% (6/24) could be detected. Liquid biopsy can be a useful diagnostic option, especially for tumors with pure solid appearance.

Keywords: EGFR, liquid biopsy, adenocarcinoma

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.01 MULTIFACTORIAL MODEL TO PREDICT RESPONSE TO PD-(L)1 BLOCKADE IN PATIENTS WITH HIGH PD-L1 METASTATIC NON-SMALL CELL LUNG CANCER

K. Arbour[1], M. Oprescu[2], J. Hakim[2], H. Rizvi[1], M. Leiserson[3], M. Ginsburg[1], A. Plodkowski[1], J. Sauter[1], I. Preeshagul[1], S. Gillett[2], P. Rosenfield[2], L. Mackey[2], M. Dudik[4], M. Hellmann[1]

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Background: High PD-L1 expression (≥50%) is a routine biomarker but is incompletely predictive, with response rates to PD-1 monotherapy only 35-45% in patients with lung cancer. Beyond PD-L1, additional individual pre-treatment variables, including clinical (smoking history, BMI), genomic (TMB, STK11, EGFR), and laboratory features (baseline dNLR), individually associate with response but have not been comprehensively examined in combination. We hypothesized that a multifactorial model incorporating routinely available clinical, pathologic, and genomic variables could improve prediction of response in high PD-L1 patients receiving first line anti-PD-(L)1 monotherapy. **Method:** 190 patients from MSKCC with advanced, PD-L1 high NSCLC (PD-L1 ≥50%) treated with PD-1 or PD-L1 inhibitor were identified and separated into training (n=134, 70%) and validation cohorts (n=56, 30%). In addition to PD-L1 expression, 39 variables were collected, including histology, clinical (age, gender, performance status, smoking, clinical trial vs standard of care treatment), molecular (TMB, EGFR, KRAS, STK11, KEAP1, TP53, ALK, ROS1, BRAF), and baseline CBC (including dNLR). Radiologic response assessments were performed according to RECIST 1.1. To distinguish responders vs. non-responders, a logistic regression classifier with an elastic net penalty was used to restrict the number of variables considered and to optimize generalizability to independent cohorts. The parameters of the model were optimized using only the training cohort and its performance was measured on the validation cohort. **Result:** In PD-L1 high NSCLC patients treated with PD-(L)1 blockade, the ORR was 43%. In the training cohort, 5 features (PD-L1 expression, current smoking status, lymphocyte count, platelets, total WBC) associated with response. Three features (EGFR mutation, STK11 mutation, standard of care treatment) associated with lack of response. TMB was not predictive within this selected PD-L1 high cohort. In the training cohort, the eight identified features

were used to develop a multifactorial model which improved BOR prediction (AUC 0.83) compared to PD-L1 alone (AUC 0.65), p=0.02. Improved performance of the model was confirmed in the validation cohort (AUC 0.66 for multifactorial model vs. AUC 0.52 for PD-L1 alone). **Conclusion:** Among patients with high PD-L1 expression, multiple clinical, molecular, and baseline laboratory features impact response to PD-(L)1 monotherapy. The addition of these routinely available variables to PD-L1 in a multifactorial model improves prediction of response to PD-(L)1 blockade in patients with high PD-L1. This approach may help further stratify patients within the PD-L1 high population and identify which patients are likely to benefit from PD-(L)1 monotherapy vs those who should consider chemotherapy + immunotherapy.

Keywords: Non-Small Cell Lung Cancer, PD-1 inhibitor, High PD-L1 expression

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.02 KEYNOTE-042 CHINA STUDY: FIRST-LINE PEMBROLIZUMAB VS CHEMOTHERAPY IN CHINESE PATIENTS WITH ADVANCED NSCLC WITH PD-L1 TPS ≥1%

Y.-L. Wu[1], L. Zhang[2], Y. Fan[3], J. Zhou[4], L. Zhang[5], Q. Zhou[1], W. Li[6], C. Hu[7], G. Chen[8], X. Zhang[9], C. Zhou[10], T. Dang[11], J. Penrod[11], D. Kush[11], Y. Qin[12], B. Li[12], T. Mok[13]

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Background: In the global, open-label KEYNOTE-042 study (NCT02220894), pembrolizumab significantly improved OS vs chemotherapy in PD-L1–positive locally advanced/metastatic NSCLC without targetable *EGFR/ALK* aberrations (HRs: TPS ≥50%, 0.69; ≥20%, 0.77; and ≥1%, 0.81). We present the very first results for Chinese patients enrolled in the KEYNOTE-042 global and China extension (NCT03850444) studies. **Method:** The global and extension studies were designed identically. Patients were randomized 1:1 (stratified by ECOG PS 0/1, squamous/nonsquamous histology, and TPS ≥50%/1-49%) to up to 35 cycles of pembrolizumab 200 mg Q3W or up to 6 cycles of paclitaxel/pemetrexed + carboplatin with optional pemetrexed maintenance (nonsquamous only). Primary endpoints were OS in patients with PD-L1 TPS ≥50%, ≥20%, and ≥1%. No alpha was allocated to the China extension analysis. Overall, ~350 patients from China will be enrolled including 140 patients with TPS ≥50%, to determine the OS effect of pembrolizumab and consistency across outcomes in Chinese patients. **Result:** As of September 4, 2018, 262 Chinese patients with PD-L1–positive (TPS ≥1%) NSCLC were enrolled (global, n=92; China extension, n=170) and randomized to pembrolizumab (n=128) or chemotherapy (n=134). 146 patients (55.7%) had PD-L1 TPS ≥50%; 204 (77.9%) had PD-L1 TPS ≥20%. After median (range) follow-up of 11.3 (0.1-23.2) months, 32 patients (25.0%) were still receiving pembrolizumab and 6 (4.8%) were receiving pemetrexed maintenance. Pembrolizumab improved OS vs chemotherapy in patients with PD-L1 TPS ≥50%, ≥20%, and ≥1% (Table). Among patients who received ≥1 dose of pembrolizumab (n=128) or chemotherapy (n=125), grade 3–5 drug-related AEs occurred in 17% vs 68%, respectively.

Overall Survival				
		n	Median (95% CI), mo	HR (95% CI)
PD-L1 TPS ≥50%	Pembrolizumab	72	20.0 (15.5–NR)	0.62 (0.38–1.00)
	Chemotherapy	74	14.0 (10.0–17.9)	
PD-L1 TPS ≥20%	Pembrolizumab	101	20.0 (17.4–NR)	0.62 (0.41–0.95)
	Chemotherapy	103	13.7 (10.1–17.9)	
PD-L1 TPS ≥1%	Pembrolizumab	128	20.0 (17.4–NR)	0.65 (0.45–0.94)
	Chemotherapy	134	13.7 (10.1–17.9)	
PD-L1 TPS 1–49%[a]	Pembrolizumab	56	19.9 (11.9–NR)	0.69 (0.40–1.20)
	Chemotherapy	60	10.7 (8.3–20.9)	

NR, not reached. [a]Exploratory analysis.

Conclusion: Pembrolizumab monotherapy improved OS with a favorable safety profile vs platinum-based chemotherapy as first-line therapy in Chinese patients with locally advanced/metastatic NSCLC without sensitizing *EGFR/ALK* aberrations and a PD-L1 TPS ≥1%. Findings are consistent with the global study primary endpoints, supporting first-line use of pembrolizumab for PD-L1–expressing advanced/metastatic NSCLC in China.

Keywords: PD-L1, Pembrolizumab, Chemotherapy

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.03 PEMBROLIZUMAB PLUS DOCETAXEL INCREASES PROGRESSION-FREE SURVIVAL COMPARED WITH DOCETAXEL ALONE IN PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

O.G. Arrieta[1], F. Barrón[2], A. Carmona[2], L. Ramírez-Tirado[1], Z.L. Zatarain Barrón[1], A.F. Cardona[3], Y. Bautista[4], F. Aldaco[5], M. Lazaro[6], R. Baez[7], R. Gerson[8], C. Blanco[8]

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Background: Immunotherapy is now the standard of care for non-small cell lung cancer patients without actionable mutations, due to a clear survival benefit in large phase III trials, further this benefit can be translated into the first-line setting, alone or in combination with chemotherapy. Nonetheless, due to several circumstances many patients do not receive immunotherapy as first-line. The effect of the combination therapy with pembrolizumab plus docetaxel in previously-treated NSCLC patients has not been prospectively assessed. **Method:** In this phase II clinical trial, we evaluated the effect of a combination therapy with pembrolizumab plus Docetaxel (PD) compared with Docetaxel (D) for the treatment of advanced NSCLC patients who had progressed to previous lines of therapy. Primary endpoint was overall response rate (ORR); secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety profile. **Result:** Eighty patients met the inclusion criteria and were enrolled in the study, among which 78 were randomized 1:1. Forty patients were allocated to receive PD, while thirty-eight were allocated to receive D. Baseline characteristics, including sex, age, tobacco index, performance status and EGFR mutation were well-balanced between both arms of the trial. We found a statistically significant difference in terms of ORR (42.5% vs. 15.8%; OR: 3.9 [95%CI: 1.34-11.5]; p=0.01), in patients receiving PD compared with D alone. Further, patients receiving PD had a significantly longer PFS compared with those receiving D monotherapy (9.5 months [95%CI: 4.2-NR] vs. 3.9 [95%CI: 3.2-5.7]; HR: 0.24 [95%CI:

0.13-0.46]; p<0.001). In the multivariate analysis the therapeutic intervention was an independently associated factor with better PFS (Figure). In terms of safety, a total of 22.5% vs. 5.3% of patients experienced any-grade pneumonitis in the PD and D arm of the trial respectively (p=0.048), while 27.5% vs. 16% experienced any-grade hypothyroidism (p=0.20). No new safety signals were identified. **Conclusion:** Patients who receive the combination therapy have a significantly increased ORR and PFS, with a significant decrease in the hazard of progressing. This work was performed through a grant from MSD (Investigator Initiated Study). The sponsor did not have any role in the acquisition or interpretation of the data.

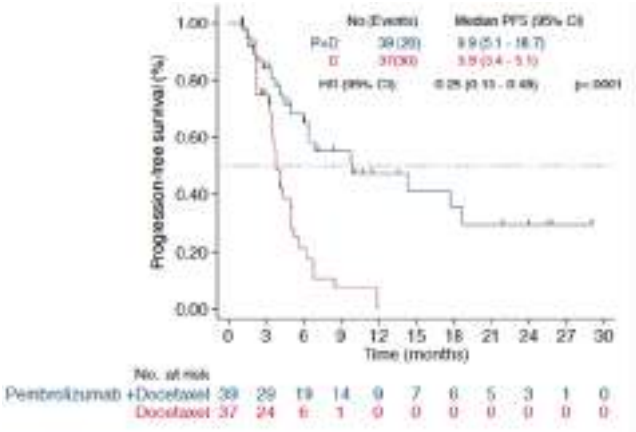

Figure. Kaplan-Meier curve for the progression-free survival of patients in the experimental (P+D) vs. the control (D) arm of the trial.

Keywords: Pembrolizumab, Docetaxel, combination therapy

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.04 PLATINUM DOUBLET + DURVALUMAB +/- TREMELIMUMAB IN PATIENTS WITH ADVANCED NSCLC: A CCTG PHASE IB STUDY - IND.226

R. Juergens[1], P. Ellis[1], D. Tu[2], D. Hao[3], S. Laurie[4], M. Mates[5], G. Goss[4], J. Goffin[1], P. Bradbury[6], M. Tehfe[7], C. Kollmansberger[8], P. Brown-Walker[2], M. Smoragiewicz[2], M. Tsao[6], L. Seymour[2]

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Background: Studies of single agent immune checkpoint inhibitors with platinum-based chemotherapy in non-small cell lung cancer (NSCLC) have demonstrated survival benefit over chemotherapy alone. The primary objective of this multi-centre study was to evaluate the safety and tolerability of durvalumab (Du), a PD-L1 inhibitor, +/- tremelimumab (Tr), a CTLA-4 inhibitor, with one of four standard platinum-doublet regimens (pemetrexed (pem), gemcitabine, etoposide (each with cisplatin or carboplatin) or nab-paclitaxel (with carboplatin)), in order to establish a recommended phase II dose (R2PD) for each combination. This abstract updates the results in the NSCLC cohort in this study. **Method:** Patients (pts), regardless of tumour PD-L1 status, were enrolled into one of six dose levels (Table 1). Dose escalation was according to a Rolling Six type design. Concurrent enrollment of cohorts was allowed.

Table 1

Dose level	DURVALUMAB Dose concurrent with chemotherapy*	TREMELIMUMAB Dose concurrent with platinum chemotherapy	DURVALUMAB Dose after chemotherapy completion	TREMELIMUMAB Dose after platinum chemotherapy completion
4	1500 mg q3 weeks	75 mg q3 weeks up to 4 doses	1500 mg q4 weeks	75 mg to complete up to a maximum TOTAL of 5 doses
3	1125 mg q3 weeks	56 mg q3 weeks up to 4 doses	1125 mg q3 weeks**	56 mg to complete up to a maximum TOTAL of 6 doses
2b	15 mg/kg q3 weeks	3 mg/kg single concurrent dose	20 mg/kg q4 weeks	3 mg/kg q8 weeks up to 2 doses
2a	15 mg/kg q3 weeks	1 mg/kg q6 weeks up to 3 doses	20 mg/kg q4 weeks	1 mg/kg q8 weeks up to 2 doses
1	15 mg/kg q3 weeks	1 mg/kg single concurrent dose	20 mg/kg q4 weeks	1 mg/kg q8 weeks up to 2 doses
0	15 mg/kg q3 weeks	None	20 mg/kg q4 weeks	None

*Chemotherapy regimens included (all 21 day cycles):
pemetrexed (500mg/m2) day 1 + cisplatin (75 mg/m2) or carboplatin (AUC = 6) day 1 +/- pemetrexed maintenance
gemcitabine (1250mg/m2) days 1 and 8 + cisplatin (75 mg/m2) or carboplatin (AUC = 5) day 1
nab-paclitaxel (100 mg/m2) days 1, 8 & 15 + carboplatin (AUC = 6) day 1
** q4 week schedule was allowed after discussion with CCTG after completion of the tremelimumab doses

Result: Seventy-three pts (median age=63 (range 34-80); 52% female; 77% non-squamous) were enrolled. The majority of drug-related adverse events (AEs) were grade 1 or 2. Most AEs were related to chemotherapy; other AEs were chemotherapy or immune-related (renal, hepatic, skin and pulmonary toxicity). AEs that were considered related to Du or Tr (immune related AEs (irAEs)) were mainly grade 1 or 2. The most common irAEs were fatigue (64%), rash/itch (42%), diarrhea/colitis (34%), anorexia (22%), thyroid dysfunction (19%), and nausea/vomiting (21/12%). The most common grade 3 or 4 irAEs were diarrhea/colitis (11%), fatigue (10%), and rash (5%). No treatment related grade 5 toxicities were reported. Twenty pts (27%) discontinued treatment due to an AE. Twelve pts (16%) discontinued treatment for toxicity related to D+/-T. Objective response rate (ORR) was 50.7% (95% CI = 38.7-62.6%). Median progression free survival (mPFS) was 6.5 months (95% CI = 5.5-9.4). Median overall survival (mOS) was 19.8 months (95% CI = 14.8-not yet reached). ORR was similar for all levels of PD-L1 staining including PD-L1 negative patients. ORR for pts with EGFR mutations (N=5) was similar to the ORR of wild type pts. Exploratory analyses suggest mPFS and mOS were longer in patients who experienced irAEs. **Conclusion:** In this PD-L1 unselected patient population, Du and Tr can be safely combined with full doses of platinum-doublet chemotherapy. The ORR, mPFS and mOS are similar to results reported from other immunotherapy + chemotherapy combination trials. A randomized trial, CCTG BR.34, is evaluating the incremental benefit of adding platinum doublet to Du+Tr.

Keywords: durvalumab, tremelimumab, Chemotherapy

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.06 A PII STUDY OF TORIPALIMAB, A PD-1 MAB, IN COMBINATION WITH CHEMOTHERAPY IN EGFR+ ADVANCED NSCLC PATIENTS FAILED TO PRIOR EGFR TKI THERAPIES

J. Zhang[1], C. Zhou[2], Y. Zhao[3], X. Mu[4], J. Zhou[5], Z. Bao[6], Y. Fan[7], Y. Xu[7], Y. Shu[8], R. Guo[9], X. Liu[10], H. Wang[10], H. Zhang[11], L. Deng[12], N. Ma[12], J. He[13], Y. Zhang[14], M. Chen[15], Y. Jiang[15]

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Background: EGFR TKI is the standard 1st line therapy for the patients with advanced NSCLC harboring EGFR mutations. While PD-1 checkpoint blockade has become an integral component of disease management for EGFR wild type NSCLC patients at various settings, platinum-based chemotherapy is still the standard of care for EGFR mutated NSCLC pts who progressed after EGFR targeting therapy. Early attempts to combine EGFR TKI with checkpoint blockade had resulted in exacerbated immune related toxicity in the lung. Here we aimed to prospectively evaluate toripalimab, a humanized PD-1 mAb approved for 2nd line treatment of melanoma, in combination with chemotherapy to treat EGFR mutated NSCLC patients failed to EGFR TKI therapies. **Method:** This is a phase II, multicenter, open-label, single-arm study for pts with *EGFR* activating mutations who have failed prior EGFR-TKI therapies without *T790M* mutation or failed osimertinib treatment. Pts were treated with 240mg or 360mg fixed dose toripalimab once every 3 weeks in combination with carboplatin and pemetrexed for up to 6 cycles, followed by toripalimab plus pemetrexed maintenance therapy until disease progression or intolerable toxicity. Primary endpoint was objective response rate as assessed by investigator per RECIST v1.1 once every 6 weeks. **Result:**

Forty pts were enrolled from Apr 25, 2018 to March 22, 2019 with 52.5% female patients and a median age of 57. 57.5% pts harbored *EGFR* exon19 deletion while 42.5% pts had exon21 L858R mutation. Only 1 pt had T790M mutation who progressed after osimertinib treatment. As of Apr 3 2019, among 31 evaluable pts, 17 partial response and 12 stable disease were observed for a 54.8% ORR (95% CI, 36.0% to 72.7%) and a 93.5% DCR (95% CI, 78.6% to 99.2%). Median PFS was 7.6 months, while median DOR was not reached. Treatment emergent adverse events (TEAE) occurred in 86.5% of the pts, grade 3 or higher events occured in 51.4% of patients including one death. Most common AE included leukopenia, neutropenia, thrombocytopenia, anemia, nausea, and loss of appetite. Treatment discontinuation due to AE occurred in 10.8% of the pts. **Conclusion:** Anti-PD-1 mAb, toripalimab in combination with carboplatin and pemetrexed has shown a promising anti-tumor efficacy with a tolerable safety profile for advanced NSCLC patients with *EGFR* mutated who progressed after EGFR TKI therapies. Pts will be continuously monitored for safety and efficacy readouts (DOR, PFS and OS). A phase III registration study will be initiated in May 2019. (Clinical trial information: NCT03513666)

Keywords: non-small-cell lung cancer, PD-1 mAb, T790M negative

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.07 EFFICACY OF IMMUNE-CHECKPOINT INHIBITORS AND EGFR-TKIS IN NSCLC PATIENTS WITH HIGH PD-L1 EXPRESSION

K. Masuda, H. Horinouchi, M. Tanaka, R. Higashiyama, Y. Shinno, J. Sato, T. Yoshida, Y. Matsumoto, Y. Goto, S. Kanda, N. Yamamoto, Y. Ohe

National Cancer Center Hospital, Tokyo/Japan

Background: Recently, several studies have demonstrated that patients with non-small cell lung carcinoma (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations show poor clinical outcomes in response to treatment with anti-programmed cell death-1 (PD-1) inhibitors. Conversely, EGFR tyrosine kinase inhibitors (EGFR-TKIs) are not effective in NSCLC showing high programmed death ligand 1 (PD-L1) expression levels. In this study, we retrospectively investigated the relationship between high PD-L1 expression and the efficacy of PD-1 inhibitors and EGFR-TKIs in patients with NSCLC. **Method:** The subjects of this study were patients with NSCLC who had received treatment with PD-1 inhibitors at the National Cancer Center Hospital between March 2017 and December 2018. The PD-L1 expression in the tumor cells was divided into two groups based on the tumor proportion score (TPS): <50% (low) and ≥50% (high). **Result:** Of the 414 patients treated with PD-1 inhibitors, the 263 patients in whom the PD-L1 expression levels could be evaluated were considered as being eligible for inclusion in this study. Among the 153 patients with high PD-L1 expression, we assessed the efficacy of PD-1 inhibitors according to the EGFR mutation status. The objective response rate (ORR) was 29.4% (95% confidence interval [CI], 1.3 to 53.1) in the EGFR-mutated patients and 43.4% (95% CI, 35.4 to 51.8) in the EGFR wild-type patients. The median progression-free survival (PFS) was 5.3 months (95% CI, 1.3 to 12.4) in the EGFR-mutated patients and 8.3 months (95% CI, 6.0 to 11.7) in the EGFR wild-type patients (hazard Ratio [HR] = 0.62; 95% CI, 0.62 to 1.14). A total of 33 patients received EGFR-TKI therapy. We assessed the efficacy of EGFR-TKIs according to the PD-L1 expression level. The ORR was 50.0% (95% CI, 28.0 to 72.0) in the high PD-L1 expression group and 52.9% (95% CI, 31.0 to 73.8) in the low PD-L1 expression group. The median PFS was 18.8 months (95% CI, 2.8 to 35.7) in the high PD-L1 expression group and 12.7 months (95% CI, 7.2 to 20.9) in the low PD-L1 expression group (HR = 0.83; 95% CI, 0.38 to 1.81).

	PD-L1 High EGFR+	PD-L1 High EGFR−	PD-L1 Low EGFR+	PD-L1 Low EGFR−
Total N	17	136	18	92
Median age, years (range)	62 (47–85)	62 (33–87)	64.5 (37–83)	62 (33–83)
Sex (n) Female Male	7 10	36 100	15 3	25 67
ECOG PS (n) 0, 1 2	14 3	125 11	16 2	81 11
Smoking history (n) Nev-er-smoker Smoker	7 10	21 115	12 6	13 79
EGFR mutation status (n) Ex 19 del L858R Others	7 6 4		13 2 3	
ICI agent used (n) Pembrolizumab Nivolumab	11 6	105 31	4 14	21 71
Line of ICI therapy (n) First-line Second-line Third-line or more	2 3 12	85 42 9	5 64 23	0 2 16
Efficasy ORR (%) PD-1 inhibitors EGFR-TKIs PFS (months) PD-1 inhibitors EGFR-TKIs	29.4 50.0 5.3 18.8	43.4 8.3	0 52.9 1.6 12.7	16.3 3.8

Conclusion: Even in a population of NSCLC patients showing high PD-L1 expression, the efficacy of PD-1 inhibitors tended to be lower in the EGFR-mutated patients as compared to the EGFR wild-type patients. In regard to EGFR-mutated patients with a PD-L1 TPS of ≥50%, our findings suggested that high PD-L1 expression might not predict a poor efficacy of EGFR-TKIs.

Keywords: high programmed death ligand 1 expression, Epidermal growth factor receptor, immune checkpoint inhibitor

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.09 INCREASED FREQUENCY OF BYSTANDER T CELLS IN THE LUNGS IS ASSOCIATED WITH RECURRENCE IN LOCALIZED NON-SMALL CELL LUNG CANCER

A. Reuben[1], J. Zhang[2], R. Gittelman[3], S.-H. Chiou[4], J. Li[2], J. Fujimoto[2], C. Behrens[2], F. Kheradmand[5], C.-W. Chow[2], C. Bernatchez[6], A.K. Eterovic[1], S. Benzeno[3], M. Vignali[3], X. Xifeng Wu[1], Y. Ye[1], T. Cascone[6], R. Herbst[7], S. Swisher[6], H. Kadara[6], C. Moran[1], J. Zhang[2], P. Scheet[1], A. Vaporciyan[8], B. Sepesi[6], D. Gibbons[6], H. Robins[3], P. Hwu[6], J. Heymach[6], P. Sharma[1], J. Allison[1], J. Lee[6], M. Davis[4], I. Wistuba[6], P.A. Futreal[2], J. Zhang[1]

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Background: Non-small cell lung cancer (NSCLC) exhibits a high mutational burden. As a result, patients afflicted by this tumor type experience greater responses to immune checkpoint blockade. This is largely due to the ability of T cells to destroy tumor cells on the basis of antigens recognized by their T cell receptor (TCR). However, the lungs are exposed to carcinogens and pathogens which can also trigger a T cell response distinct from cancer. Therefore, a better understanding of the T cell repertoire in the lungs is needed to improve upon the success of current immunotherapies in NSCLC. **Method:** We obtained peripheral blood, tumors, and adjacent uninvolved lungs from a cohort of 236 early stage NSCLC patients. Whole exome sequencing, RNA microarray, immunohistochemistry (CD3, CD4, CD8, CD57, CD68, FoxP3, CD45RO, GzmB, PD-1, and PD-L1) and T cell repertoire sequencing were performed in NSCLC patients and lungs from organ donors and COPD patients. Antigen specificity was predicted using the Grouping of Lymphocyte Interactions by Paratope Hotspot (GLIPH) algorithm. Single cell TCR and RNA sequencing as well as sequencing of the virome are underway. **Result:** Clonality was associated with CD8 T cells (r=0.31; p=0.0003), GzmB (r=0.29; p=0.001) and IFN-γ (r=0.52; p<0.0001) production as well as with tumor mutational burden (r=0.19; p=0.015), HLA-B (r=0.29; p=0.0005) and β2-m expression (r=0.20; p=0.018). Patients with classical EGFR mutations exhibited lower T cell clonality (p=0.003) even after adjustment for TMB, highlighting the impact of this driver mutation on the T cell response. Surprisingly, clonality was higher in the adjacent uninvolved lung than tumor (p<0.0001), suggesting an active antigenic response outside the tumor. Comparison of the composition of the T cell repertoire between the uninvolved lung and tumor revealed 57% of the top 100 T cells in the tumor were also found in the adjacent normal lung, highlighting certain parallels in the ongoing antigenic responses. Deeper analysis suggested that shared T cells may have been reactive against mutations shared between the normal lung and tumor (r=0.23, p=0.028) or viruses (p<0.0001). Accordingly, patients with a more reactive T cell repertoire outside the tumor (i.e. bystanders) exhibited shorter disease-free survival (p=0.036) suggesting these responses against shared mutations and/or viruses may detract from the anti-tumor T cell response. **Conclusion:** Our findings highlight the importance of understanding the specificity of the T cell repertoire in the lungs in patients with NSCLC treated with immunotherapy. As a high proportion of bystander T cells appear to reside in the lungs, their reactivation could contribute to the impaired responses and/or increased toxicity observed in certain patients with NSCLC treated with immunotherapy.

Keywords: Tumor Immunology, T cells, NSCLC

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.10 PERIPHERAL T CELL REPERTOIRE EVOLUTION IN RESECTABLE NSCLC TREATED WITH NEOADJUVANT PD-1 BLOCKADE

J. Zhang[1], Z. Ji[2], J. Caushi[1], M. El Asmar[1], V. Anagnostou[1], T. Cottrell[1], H.Y. Chan[1], H. Guo[1], T. Merghoub[3], J. Chaft[3], J. Wolchok[3], J. Reuss[1], K. Marrone[1], J. Naidoo[1], E. Gabrielson[1], J. Taube[1], J. Brahmer[1], V. Velculescu[2], N. Zhao[2], M. Hellmann[3], P. Forde[1], D. Pardoll[1], S. Yegnasubramanian[1], H. Ji[2], K. Smith[1]

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Background: Neoadjuvant PD-1 blockade has emerged as a promising treatment for resectable NSCLC. The neoadjuvant setting provides a unique opportunity to examine temporal-spatial dynamics of the T cell repertoire in the peripheral and tumoral compartments in response to PD-1 blockade. **Method:** T-cell receptor (TCR) repertoire dynamics and composition were assessed in matched tumor, normal lung, and longitudinal peripheral blood from 20 NSCLC patients treated with neoadjuvant nivolumab (NCT02259621) and were correlated with major pathologic response (MPR, ≤10% viable tumor in resected specimen) at the time of resection. Treatment-induced dynamics of activated T cell clonotypes were additionally evaluated using TCR sequencing (TCRseq) of flow-sorted PD-1+ T cell populations. To focus on the phenotype of on-treatment intratumoral T cell clones that were recruited from the periphery, combined single-cell RNAseq/TCRseq was performed on post-treatment tumors of 6 patients (3 MPR and 3 non-MPR). **Result:** MPR was associated with a more clonal intratumoral TCR repertoire and greater clonotypic sharing between pre-treatment blood and post-treatment tumor bed relative to non-MPR. Peripheral repertoire remodeling in response to anti-PD-1 treatment correlated with increased tumor infiltration. Specifically, in patients with MPR, the post-treatment tumor bed was enriched with T cell clones that were peripherally expanded between 2-4 weeks after PD-1 blockade. Clonotypic tracking of the peripherally expanded clones revealed persistence of those clones in the periphery 1+ years following surgical resection and cessation of PD-1 blockade. Single-cell RNAseq/TCRseq analyses revealed distinct phenotypes of peripherally expanded TIL for patients with MPR, with upregulated gene programs associated with cytotoxicity and cytoprotective effects against oxidative stress. Long-term peripherally-persistent TILs had significant upregulation of genes including GZMK, DUSP2, NKG7, 4-1BB and down-regulation of CTLA-4, CXCL13 and PDCD1 as compared to short-lived clones. **Conclusion:** Our findings support the notion that neoadjuvant checkpoint blockade expands anti-tumor T cell clones in the periphery that can accumulate in tumor bed, facilitate tumor regression, and promote clonotypic persistence in the periphery. Importantly, our data demonstrate the systemic effect of neoadjuvant PD-1 blockade and indicate that the periphery may be an underappreciated originating compartment of effective anti-tumor immunity.

Keywords: Neoadjuvant PD-1 blockade, Resectable NSCLC, T cell repertoire

MA11 IMMUNOTHERAPY IN SPECIAL POPULATIONS AND PREDICTIVE MARKERS
MONDAY, SEPTEMBER 9 14:00–15:30

MA11.11 STK11/LKB1 GENOMIC ALTERATIONS ARE ASSOCIATED WITH INFERIOR CLINICAL OUTCOMES WITH CHEMO-IMMUNOTHERAPY IN NON-SQUAMOUS NSCLC

F. Skoulidis[1], K. Arbour[2], M. Hellmann[2], P. Patil[3], M. Marmarelis[4], D. Owen[5], M. Awad[6], J. Murray[7], B. Levy[8], J. Hellyer[9], J. Gainor[10], T. Stewart[11], S. Goldberg[12], A. Dimou[13], C. Bestvina[14], A. Cummings[15], Y. Elamin[1], V. Lam[16], J. Zhang[16], C. Shu[17], J. Riess[18], C. Blakely[19], C. Pecot[20], L. Mezquita[21], F. Tabbò[22], A. Sacher[23], M. Scheffler[24], B. Ricciuti[6], D. Venkatraman[25], H. Rizvi[2], C. Liu[2], R. Johnston[2], Y. Ni[3], J. Azok[3], M. Kier[26], S. Katz[27], K. Davies[28], J. Segal[29], L. Ritterhouse[29], H. Shaish[17], L. Lacroix[30], R. Memmott[31], J. Madrigal[15], J. Goldman[15], S. Lau[32], J. Killam[11], Z. Walther[11], B. Carter[1], M. Woodcock[20], J. Roth[33], S. Swisher[33], N. Leighl[32], S. Digumarthy[10], M. Mooradian[10], J. Rotow[19], J. Wolf[34], G. Scagliotti[35], D. Planchard[30], B. Besse[36], T. Bivona[37], D. Gandara[18], E. Garon[38], N. Rizvi[17], D.R. Camidge[39], K. Schalper[40], R. Herbst[40], A. Shaw[10], J. Neal[41], H. Wakelee[42], J. Brahmer[43], P. Jänne[44], D. Carbone[5], C. Aggarwal[4], N. Pennell[3], C. Rudin[2], V. Papadimitrakopoulou[45], J. Heymach[16]

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Background: Addition of pembrolizumab (P) to platinum-doublet chemotherapy [carboplatin (or cisplatin) and pemetrexed (CP)] prolongs overall survival and is a standard of care (SOC) for the 1st line treatment of metastatic *EGFR/ALK* wild-type (wt) non-squamous non-small cell lung cancer (mnsNSCLC). Despite widespread use of the CPP regimen, molecular determinants of clinical benefit from the addition of P to CP remain poorly defined. We previously identified genomic alterations in *STK11/LKB1* as a major driver of primary resistance to PD-1/PD-L1 blockade in mnsNSCLC. Here, we present updated data on the impact of *STK11/LKB1* alterations on clinical outcomes with CPP chemo-immunotherapy from a large retrospective multi-institution international study. **Method:** 620 pts with mnsNSCLC and tumor genomic profiling encompassing *STK11/LKB1* from 21 academic institutions in the US and Europe were included in this study. Clinical outcomes were collected for two distinct patient cohorts: a) 468 pts treated with first-line CPP (or >1st line following FDA-approved TKIs) that were alive for 14 days thereafter and b) 152 *STK11/LKB1*-mt pts that received CP prior to regulatory approval of CPP. **Result:** Among 468 CPP-treated pts, *STK11/LKB1* genomic alterations (N=118) were associated with significantly shorter PFS (mPFS 5.0m vs 6.8m, HR 1.45, 95% CI 1.11 to 1.91; P=0.007) and shorter OS (mOS 10.6m vs 16.7m, HR 1.46, 95% CI 1.04 to 2.07; P=0.031) compared with *STK11/LKB1*-wt tumors (N=350). The likelihood of disease progression as BOR to CPP differed significantly between the two groups (29.5% vs 17%, P= 0.006). Similar results were obtained when limiting the analysis to *EGFR* and *ALK*-wt tumors (N=435) (mPFS 5.0m vs 6.9m, HR 1.48, 95% CI 1.12-1.95, P=0.006 and mOS 10.6m vs 16.7m, HR 1.45, 95% CI 1.02-2.05, P=0.036). Importantly, in pts with *STK11/LKB1*-mt mnsNSCLC, addition of pembrolizumab to CP did not result in significant improvement of PFS (mPFS 5.0m vs 3.9m, HR 0.82, 95% CI 0.63 to 1.07, P=0.14) or OS (mOS 10.6m vs 9.1m, HR 0.93, 95% CI 0.67 to 1.30, P=0.69) compared to CP alone. **Conclusion:** In mnsNSCLC, *STK11/LKB1* alterations define a subgroup of pts with inferior clinical outcomes with CPP and lack of benefit from the addition of pembrolizumab to CP chemotherapy. Novel therapeutic strategies are required to establish effective antitumor immunity in *STK11/LKB1*-mutant NSCLC.

Keywords: STK11/LKB1, chemo-immunotherapy, pembrolizumab

MA12 NEW FRONTIERS FROM PATHOLOGY TO GENOMICS
MONDAY, SEPTEMBER 9 14:00–15:30

MA12.01 REDEFINING MALIGNANT PLEURAL MESOTHELIOMA TYPES AS A CONTINUUM UNCOVERS IMMUNE-VASCULAR INTERACTIONS

N. Alcala[1], L. Mangiante[1], N. Le Stang[2], C. Gustafson[3], S. Boyault[4], F. Damiola[2], K. Alcala[1], J. Mazieres[5], J.-Y. Blay[2], S. Lantuejoul[6], R. Bueno[3], C. Caux[4], N. Girard[7], J. Mckay[1], M. Foll[8], F. Galateau Sallé[2], L. Fernandez-Cuesta[1]

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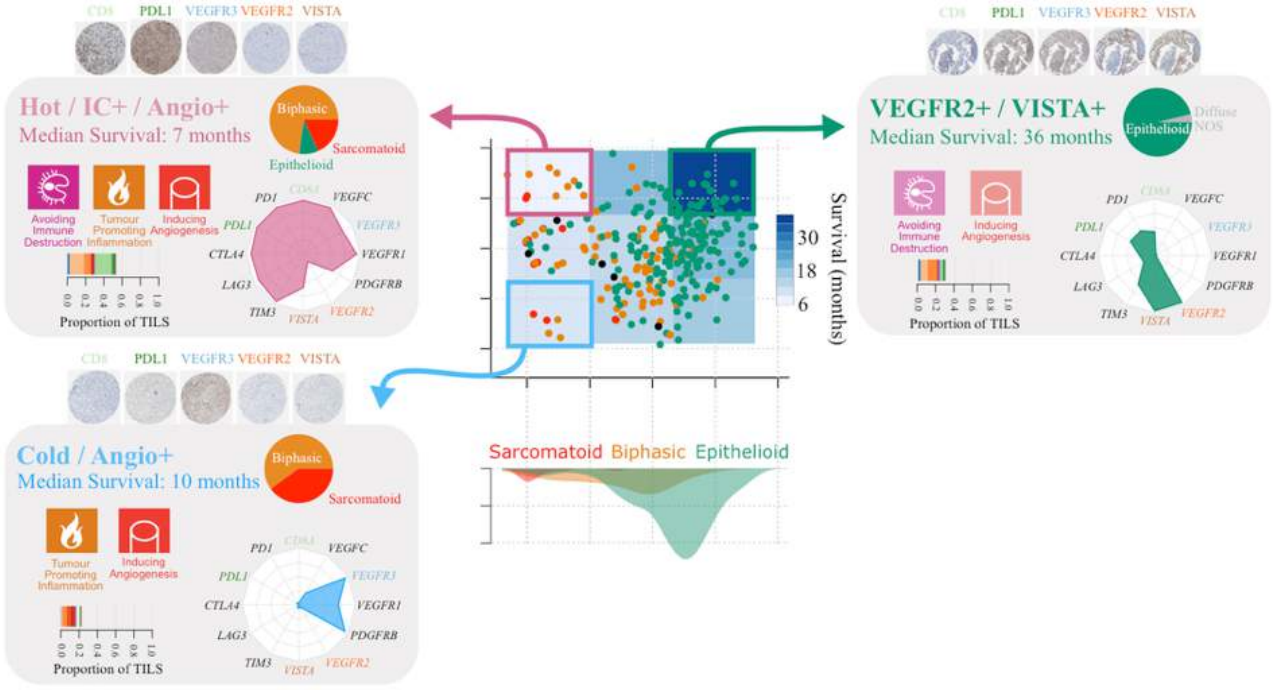
Background: Malignant Pleural Mesothelioma (MPM) is a deadly disease. The current histopathologycal classification recognises three major types (epithelioid, biphasic, and sarcomatoid) with different prognosis, but showes high interobserver variability. This classification also has a role in the clinical decision-making although, ultimately, MPM becomes refractory to all conventional treatment modalities, and alternative therapeutic options have been evaluated with limited success. **Method:** We have performed unsupervised analyses of publicly available RNA-seq data of 284 MPM tumours[1,2] with no assumption of discreteness. We have performed an orthogonal validation in a subset of 187 samples, and we have replicated the findings in an independent series of 77 MPM from the French MESOBANK. **Result:** A continuum of molecular profiles appeared to explain the prognosis of this disease better than discrete models based on the histopathological classification or on expression data. We identified the immune and vascular pathways as major sources of molecular variation, with strong differences in the expression of immune checkpoints and pro-angiogenic genes across samples; the extrema of this continuum had very specific molecular profiles: a "hot" bad-prognosis profile (median survival of 7 months), with high lymphocyte infiltration, and high expression of immune checkpoints and pro-angiogenic genes; a "cold" bad-prognosis profile (median survival of 10 months), with low lymphocyte infiltration and high expression of pro-angiogenic genes; and a better-prognosis profile (VEGFR2+/VISTA+, median survival of 36 months), with high expression of the immune checkpoint *VISTA* and the pro-angiogenic *VEGFR2* gene. We selected five genes belonging to the immune and vascular pathways (*CD8A, PDL1, VEGFR3, VEGFR2*, and *VISTA*), which expression was enough to capture the three molecular profiles, to validate the expression of these genes at the protein level by immunohistochemistry on a subset of 187 samples from the discovery cohort, and to replicate the molecular profiles as well as their prognostic value in an independent series of 77 MPMs.



Conclusion: In this study we found that the prognosis of MPM is best explained by a continuous model, which extremes show characteristic molecular profiles with specific expression patterns of genes involved in the angiogenesis and immune response[3]. These data may inform future classifications of MPM and provides insights that may assist the clinical management of this disease. [1]Bueno *et al., Nat Genet* 2016; [2]Hmeljak *et al., Cancer Discov* 2018; [3]Alcala *et al.,* under review in *Cancer Res*; NA and LM equally contributed to this work; MF, FGS, and LFC jointly supervised this work

Keywords: malignant pleural mesothelioma, angiogenesis and immune checkpoints, genomics data

MA12 NEW FRONTIERS FROM PATHOLOGY TO GENOMICS
MONDAY, SEPTEMBER 9 14:00–15:30

MA12.02 GROWTH PATTERNS IN EPITHELIOID MALIGNANT PLEURAL MESOTHELIOMA: A CLINICOPATHOLOGICAL REVIEW OF 614 CASES OVER 15 YEARS

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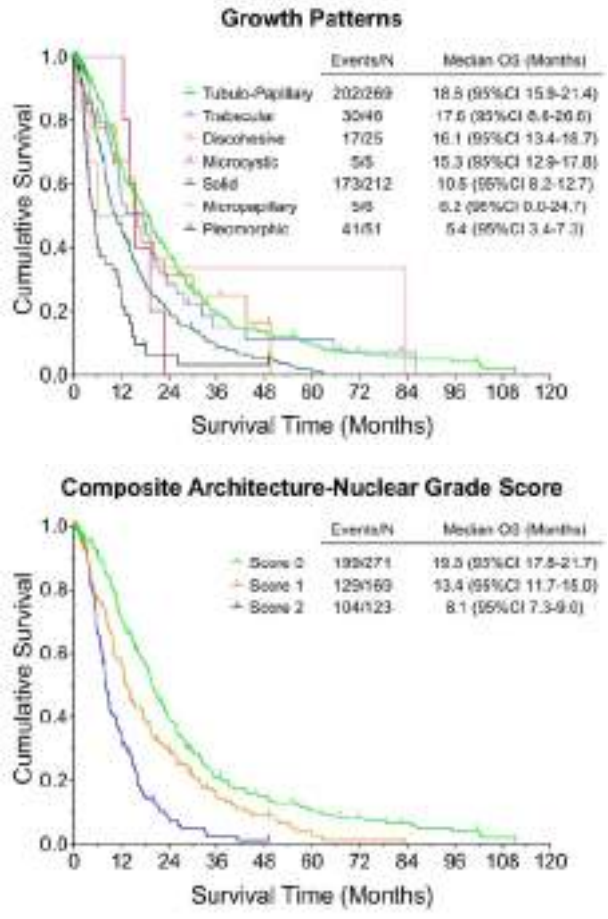
Background: Nuclear grading system has been validated as a powerful prognostic tool for epithelioid malignant pleural mesothelioma (MPM) whilst growth patterns had demonstrated prognostic value in earlier studies. We aim to externally validate the previous findings and evaluate the utility of a composite architecture-nuclear grade scoring system. **Method:** We retrospectively reviewed 614 consecutive cases of epithelioid MPM diagnosed at our institution over a 15-year period. Clinicopathological information including predominant growth pattern (Solid, Tubulo-papillary, Trabecular, Micropapillary, Microcystic, Discohesive, Pleomorphic) and 2-tier nuclear grade were retrieved from an institutional mesothelioma database. The tumours were categorised into High Grade (Solid, Micropapillary, Score=1) and Low Grade (All others, Score=0). A composite score (0-2) was generated based on growth pattern and 2-tier nuclear grade (0-1). Survival analysis was performed using Kaplan-Meier method. **Result:** Pleomorphic epithelioid MPM was associated with the worst median overall survival (5.4 months), followed by micropapillary- (6.2 months), solid- (10.5 months), microcystic- (15.3 months), discohesive- (16.1 months), trabecular- (17.6 months) and tubulo-papillary- (18.6 months) patterns. The composite scoring system further improved stratification of overall survival based on 2-tier nuclear grade (19.8 vs. 13.4 vs. 8.1 months, p<0.001).



Conclusion: Epithelioid MPM growth patterns predicted survival in our cohort. Composite architecture-nuclear grade scoring system further improved prognostic stratification.

Keywords: malignant pleural mesothelioma, Growth pattern, Scoring system

MINI ORAL SESSIONS

MA12.03 PARP INHIBITOR SENSITIVITY DOES NOT DEPEND ON BAP1 BUT IS ENHANCED BY TEMOZOLOMIDE IN MGMT DEFICIENT HUMAN MESOTHELIOMA CELLS

D. Rathkey[1], M. Khanal[1], J. Murai[1], J. Zhang[1], Q. Jiang[1], B. Morrow[1], C. Evans[2], R. Chari[2], M. Sengupta[1], A. Thomas[1], Y. Pommier[1], R. Hassan[1]

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Background: BRCA1 associated protein 1 (*BAP1*), a nuclear deubiquitinase involved in DNA double-strand (DSB) break repair by homologous recombination (HR), is frequently mutated in mesotheliomas. Because poly (ADP-ribose) polymerase inhibitors (PARPIs) target PARP1 and PARP2 and induce synthetic lethality in *BRCA1/2* mutant cancers deficient in HR, we evaluated whether *BAP1* inactivating mutations confer sensitivity to PARPIs in mesotheliomas. **Method:** Ten patient-derived mesothelioma cell lines were generated and characterized for *BAP1* mutation status, protein expression and function. Cellular sensitivity to two clinical PARPIs, olaparib and talazoparib were tested as single agents, and in combination with temozolomide. *BAP1*-deleted mesothelioma cellular models were generated by CRISPR/Cas9 and assessed for sensitivity to PARPIs. Because Schlafen 11 (SLFN11) and O^6-methylguanine methyltransferase (MGMT) also drive response to temozolomide and PARPIs, we tested their expression and relationship with drug response. **Result:** *BAP1* inactivating mutations were present in eight of ten cell lines, with two harboring homozygous deletion. Cell lines exhibiting BAP1 expression also showed deubiquitinase activity (DUB). IC_{50} of olaparib and talazoparib plot classified them into sensitive or resistant population irrespective of BAP1 status (Figure 1). Although *BAP1* knockout led to the loss of DUB activity, it did not increase the sensitivity of the cell ines to PARPI. Interestingly, cellular sensitivity to PARPI was increased by temozolomide in MGMT-negative and SLFN11-positive cell lines (Table 1).

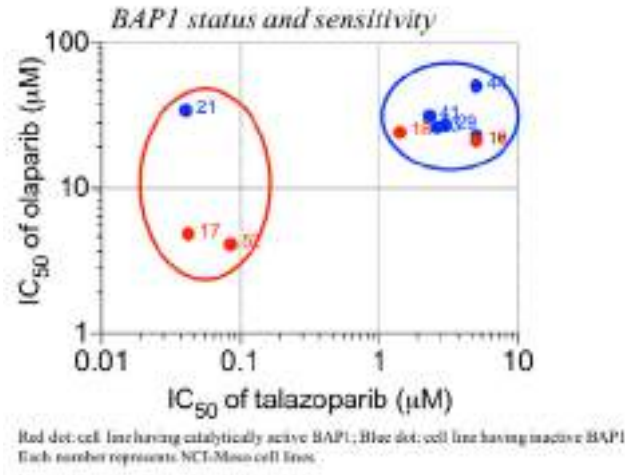

Figure 1. IC_{50} of olaparib vs talazoparib – based plot shows a separation of sensitive (red oval) and resistant (blue oval) cell line clusters independent of BAP1 activity.

	Protein expression (immunoblotting)				
	MGMT	SLFN11	Talazoparib (IC_{50}, μM)	TMZ (IC_{50}, μM)	Synergism
Sensitive cell lines					
NCI-Meso17	-	+	0.042	>250	+
NCI-Meso21	-	+	0.039	>250	+
Resistant cell lines					
NCI-Meso16	+	-	>5	>250	-
NCI-Meso19	+	-	>5	>250	-*
NCI-Meso29	+	+	3.0	>250	-*
NCI-Meso63	+	+	2.6	>250	-*

*Chou-Talay analysis has shown a strong synergistic effect. However the fraction affected is less than 0.5 indicating that the drugs do not make a meaningful combination, we therefore consider it as a negative synergism in our study.
* Synergism observed only in higher concentration ratio compared to sensitive cell lines

Table 1. Summary reflecting combination study between talazoparib and temozolomide in different cell lines having varying MGMT and SLFN11 expression status.

Conclusion: BAP1 status does not determine cellular sensitivity to PARPIs in patient-derived mesothelioma cell lines. In MGMT-deficient and SLFN11-positive cells, combination of PARPI and temozolomide is synergistic.

Keywords: BAP1, MGMT, PARP Inhibitor

MA12.05 GENOMIC ANALYSIS OF LONG TERM MALIGNANT PLEURA MESOTHELIOMA PATIENTS TREATED WITH PALLIATIVE CHEMOTHERAPY

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Background: Malignant Pleural Mesothelioma (MPM) is an aggressive tumor related to asbestos exposure with a median survival of 9 months from diagnosis. The aim of this study was to evaluate correlation between genetic mutations and survival in patients who received only palliative chemotherapy. **Method:** From 2005 to 2015, 720 patients underwent a surgical pleural biopsy and were diagnosed with malignant pleural mesothelioma. Among these, 27 patients survived longer than 30 months (long survival) from diagnosis and 113 survived less than 30 months. The pleural biopsy of the long term survival patients were reviewed and 12 FFPE samples were considered suitable and matched with 12 FFPE biopsy samples from patients who survived less than 12 months. **Result:** The DNA of 24 patients was sequenced. One sample did not reach quality to be further considered and was excluded. The mean age of total population was 71.6±8.8 and 15 patients were males (table 1). Eleven patients had a mean overall survival of 5.5 months while 12 patients lived more than 30 months. The mutational analysis identified a total of 428 alterations of which 148, classified as somatic and functional, were further considered. Among these, 85% were missense variants, 8% were variants causing a stop gain, 6% were splice variants. UQCRC1 was significantly associated with a reduced survival of MPM patients (p=0.027); figure 1. Positive trend of correlation was observed between mutations in ACTR1 and CUL1 and short MPM survival. By contrast, no significant correlation was observed between gene mutations and long survival. Figure 1.

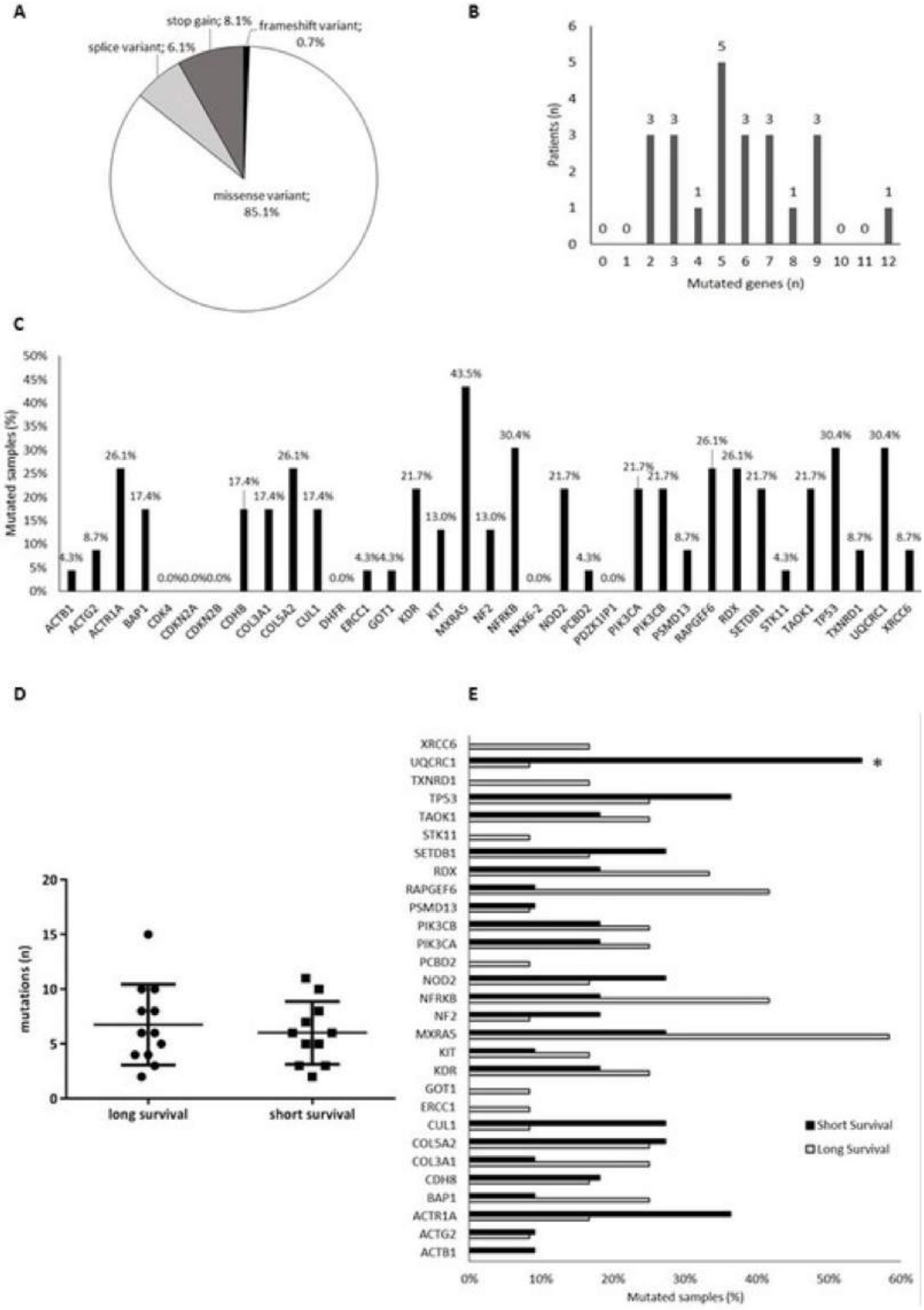

Table 1. patient characteristics.

Variable	Long survival n=12 (%)	Short Survival n=11 (%)	P value
Age (median)	67	72	0.216
Sex			0.193
Female	6 (50)	2 (18.2)	
Male	6 (50)	9 (81.8)	
Side			0.684
Right	7 (58.3)	5 (45.5)	
Left	5 (41.7)	6 (54.5)	

Conclusion: This is the first study that focusing on MPM patients not suitable for multimodality treatment investigated differences in mutational profile between short and long survivors. Our results suggest a possible role of mitochondria metabolism in mesothelioma aggressiveness.

Keywords: malignant pleural mesothelioma, genetic mutations, palliative chemotherapy

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MA12.06 PATIENT-DERIVED ORGANOTYPIC TUMOR SPHEROIDS (PDOTS) FACILITATE THERAPEUTIC SCREENING FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: While genotype directed therapies are an essential aspect of personalized medicine in non-small cell lung cancer (NSCLC), this modality is not currently an option in mesothelioma. Instead there is a need for improved functional testing via predictive platforms that can help identify the susceptibility of patient tumors to drug therapies. Here, we demonstrate the use of a novel *ex vivo* functional system utilizing 3D microfluidic culture and patient-derived organotypic tumor spheroids (PDOTS) as a platform to study the tumor microenvironment and predict tumor responses to treatment in mesothelioma. **Method:** We evaluated 31 mesothelioma patient specimens under an IRB approved protocol. PDOTS of mesothelioma were generated as previously described (Larios et al. AACR. 2017; Jenkins et al. Cancer Discovery. 2017). Samples were treated with standard chemotherapy (pemetrexed and cisplatin combined) as well as immunotherapy (ipilimumab and pembrolizumab combined) and live/dead quantification was conducted using dual labeling de-convolution fluorescence microscopy. Positive responses *ex vivo* included samples with significant cell death to control while positive *in vivo* responses were based on radiologic lack of tumor recurrence using the response evaluation criteria in solid tumors (RECIST, version 1.1) to assess for disease progression. **Result:** We found that in treatment naïve specimens prolonged ischemic times were associated with decreased tissue viability (ischemia >25 minutes resulted in decrease of live cells from an average of 81% to 56%), lower tumor yield (< 50% tumor content), and decreased generation of spheroids (< 20 spheroids/well). Specimens with prior treatment were consistently associated with low tissue viability irrespective of ischemic times. Of the 31 specimens studied, 10 samples met viability and tumor content standards to undergo further treatment with standard chemotherapy and immunotherapy, and 5 of those samples were tracked to available patient-treatment response data. Ultimately, comparison of *ex vivo* and *in vivo* treatment responses demonstrated that 4 of 5 samples treated with standard chemotherapy had concordant responses to those of patients who received the same or similar post-operative therapy. Notably, our discordant sample exhibited large variation in standard deviations due to technical variability. **Conclusion:** Here we demonstrate that analysis of *ex vivo* mesothelioma tissue correlates to *in vivo* responses. These results suggest that PDOTS can serve as a predictive platform for therapies. Further work streamlining human tissue collection and optimizing factors that affect formation of PDOTS prior to *ex vivo* treatment analysis should be further investigated.

Keywords: Mesothelioma, Tumor spheroids, Drug screening

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MA12.07 INTEGRATIVE TRANSCRIPTOME ANALYSIS OF MALIGNANT PLEURAL MESOTHELIOMA REVEALS A CLINICALLY-RELEVANT IMMUNE-BASED CLASSIFICATION

A. Alay[1,2], D. Cordero[1,2,3], E. Aliagas[1,2], S. Hijazo-Pechero[1,2], V. Moreno[1,2,3,4], R. Palmero Sánchez[1,2], J.C. Ruffinelli[1,2], R. Ramos[5], I. Macia[5], X. Solé[1,2,3], E. Nadal[4,6,7]

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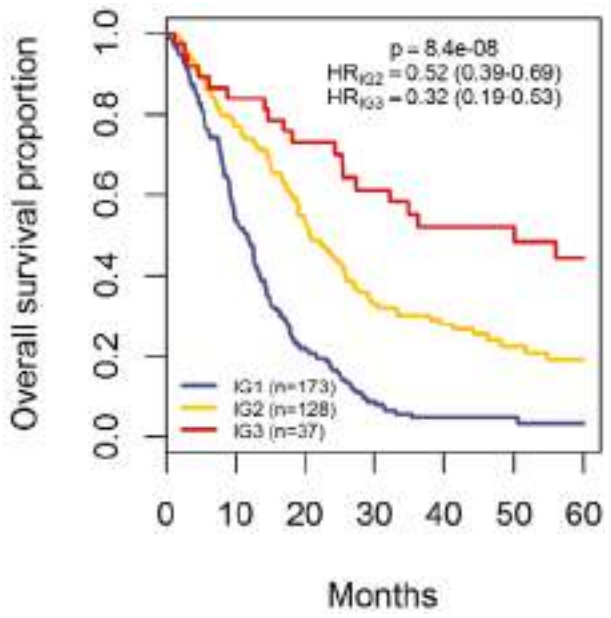
Background: Malignant pleural mesothelioma (MPM) is a rare and aggressive neoplasia affecting the lining of the lungs. Immune checkpoint inhibitors in MPM have not been extremely successful, likely due to a poor identification of suitable candidate patients for the therapy. The aims of this study were: to identify immune fractions associated with clinical outcome and classify MPM samples based on their immune contexture; to characterize the immune-based groups at the genomic and transcriptomic levels; and to identify potential therapeutic strategies for each group. **Method:** Seven gene-expression datasets of MPM were used to assess the immune microenvironment of 516 samples. The abundance of 20 immune fractions in each sample was inferred using Gene Set Variation Analysis. Identification of clinically-relevant fractions was performed with Cox Proportional-Hazards Models adjusted for age, stage, sex, and tumor histology. **Result:** T-Helper 2 (TH2, HR=2.14, $p=1.5x10^{-4}$) and cytotoxic T cells (CTC; HR=0.57, $p=9.1x10^{-3}$) were found to be consistently associated with overall survival in multiple datasets. Three immune clusters (IG) were subsequently defined based on TH2 and CTC immune infiltration levels: IG1 (54.5% of samples) was characterized by high TH2 and low CTC levels, IG2 (37%) had either low or high levels of both fractions, and IG3 (8.5%) was defined by low TH2 and high CTC levels. This classification was associated with overall survival independently of tumor histology, with an improving survival from IG1 to IG3 (HR_{IG2}=0.52 (0.39–0.69); HR_{IG3}=0.32 (0.19–0.53); $p=8.4x10^{-8}$).



IG3 was significantly enriched in epithelioid tumors (90% IG3 vs. 62% IG1, p=0.001) and patients were younger compared to the other groups (60 years IG3 vs. 66 years IG1, p=0.021). These groups showed differential molecular profiles, with IG1 enriched for CDKN2A

and IFN-related genes deletions. At the transcriptional level, IG1 samples showed upregulation of proliferation and DNA repair-related gene-sets, while IG3 samples presented upregulation of immune and inflammation-related pathways. Finally, integration of gene expression with functional signatures of *in vitro* drug response showed that IG3 patients are more likely to respond to immune checkpoint inhibitors, while IG1 patients could be more sensitive to PARP inhibitors. **Conclusion:** Analysis of publicly available MPM transcriptome data reveals three major immune-based groups, based on TH2 and CTC composition. These clusters are associated with distinct genomic profiles and clinical outcome. Further validation of this classification is warranted in an independent cohort of MPM.

Keywords: malignant pleural mesothelioma, cancer immune fractions, transcriptome profiling

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MA12.09 CHECKPOINT INHIBITORS SYNERGIZE WITH DENDRITIC CELL-THERAPY IN PRE-CLINICAL MODELS AND MESOTHELIOMA PATIENTS

R. Belderbos, F. Dammeijer, M. Gulijk, M. Lukkes, D. Dumoulin, R. Cornelissen, J. Aerts

Erasmus University Medical Center, Rotterdam/Netherlands

Background: Malignant Pleural Mesothelioma (MPM) is a lethal, treatment resistant neoplasm. Checkpoint inhibitors (CI) have shown promising clinical effects in a minority of patients. It is hypothesized that low response rates to CI are correlated to low numbers of tumor-infiltrating T-cells in MPM patients. Dendritic cell (DC) therapy instigates an immune response and activates tumor-specific T-cells. DC therapy has proven to be effective in pre-clinical models and in a subset of MPM patients. Upregulation of PD-L1 and PD-1 co-inhibitory checkpoints may suppress DC-therapy induced anti-tumor immune response and limit clinical efficacy. To investigate this, we conducted a preclinical and clinical study to evaluate the clinical and immunological effects of DC therapy combined with CI. **Method:** Immune competent CBA/J mice were orthotopically injected with a syngeneic mesothelioma cell line. Mice were treated with DC-therapy alone or in combination anti-PD-L1 antibodies at high tumor load when DC-monotherapy was found to be ineffective. Peripheral blood and tumors were obtained for flow cytometric analysis and survival was monitored.

In a clinical setting, nine patients that received DC therapy were sequentially treated with CI. Progression free survival (PFS) was determined from start of CI, using the modified RECIST criteria. **Result:** Tumors of mice treated with DC-therapy exhibited a three-fold increase in CD8+ T-cell infiltration which was paralleled by heightened expression of PD-L1 on tumor cells (r^2=0.69, *p=0.0015*). Whereas both anti-PD-L1 and DC-monotherapies were ineffective in prolonging survival in our model, combination immunotherapy did (median OS: 24 vs 35 days, *p=0.0063)*. Immune monitoring analyses demonstrated a synergistic increase in proliferation and activation of circulating T-cell following combination therapy. In the clinical trial 3 patients had partial response, 5 patients had stable disease and 1 patient had progressive disease. Median PFS was 5,2 months and median OS was 17,5 months. Currently 3 patients are still alive and two patients are still progression free. There were no grade 3/4 adverse events. PD-L1 expression in tumor biopsies was increased after DC therapy in two of the three responders to CI. **Conclusion:** In a murine model the synergy between DC therapy and CI was proven and efficacy was driven by activation of CD4+ and CD8+ positive cells. In humans, CI after DC therapy is safe and feasible. Disease control was seen in 8 out of 9 patients treated with CI after DC therapy. DC therapy induces tumor-specific CD8+ T-cell proliferation which is correlated to PD-L1 expression on tumor cells and possibly synergizes with CI treatment.

Keywords: malignant pleural mesothelioma, Immunotherapy, dendritic cell-based therapy

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MA12.10 NOVEL GERMLINE MUTATIONS IN DNA-DAMAGE REPAIR AND DNA REPLICATION IDENTIFIED IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM)

R. Guo, M. Duboff, M. Kris, M. Ladanyi, D. Mandelker, M. Zauderer

Memorial Sloan Kettering Cancer Center, New York/United States of America

Background: Recent efforts to characterize the germline genetic landscape of MPM have uncovered a surprising prevalence of pathogenic variants in DNA-damage sensing and repair genes. Increasingly, next-generation sequencing has helped bring new insight into critical mutations or pathways involved in the development of MPM. Additionally, observations from these studies could direct new screening, prevention, and therapeutic approaches for patients and families. **Method:** With IRB approval, we performed deidentified analysis on 87 additional cancer-predisposing genes on our NGS platform among patients with MPM previously consented to a BAP1 germline testing protocol. Additionally, germline variants in an additional 380 genes associated with somatic alterations in cancer, but not associated with hereditary cancer predisposition, were screened for loss of function variant or pathogenic entries in ClinVar. All variants were reviewed according to the American College of Medical Genetics and Genomics and Association for Molecular Pathology consensus guidelines. Founder mutations were excluded. Clinicopathologic information was also collected. Comparisons were done using Fisher's exact test. P values <0.05 were considered significant. **Result:** Of 88 patients with MPM analyzed, 11% (10/88) had pathogenic variants. Clinical characteristics such as age, sex, histology, and self-reported asbestos exposure, were similar between patients with and without pathogenic variants (Table 1). Pathogenic variants previously unreported in mesothelioma were identified: MSH3 1/88 (1%; 95% CI: 0-7%), BARD1 1/88 (1%; 95% CI: 0-7%), and RECQL4 2/88 (2%; 95% CI: 0-8%). We also identified pathogenic variants previously associated with mesothelioma: BAP1 in 3/88 (3%; 95% CI: 1-10%), BRCA2 1/88 (1%; 95% CI: 0-7%), and MRE11A 1/88 (1%; 95% CI: 0-7%). One patient had a potentially pathogenic alteration in SHQ1, which has not been associated with a heightened susceptibility to cancer. Patients with germline pathogenic variants were more likely to have more than 2 first-degree family members with cancer compared to those without germline mutations (40% vs 13%; p = 0.049). **Conclusion:** While the overall incidence of germline mutations identified is similar to prior reports, we identified germline pathogenic alterations in three DNA damage repair and replication genes not previously reported in mesothelioma. Furthermore, we describe a novel germline alteration in SHQ1, which has not been reported with hereditary cancer predisposition. Whether these variants increase the risk of mesothelioma is still under investigation, but given the high rate of germline pathogenic variant in individuals with pleural mesothelioma, germline testing for hereditary cancer susceptibility should be considered in all patients with MPM.

Table 1. Patient Demographics and Clinical Characteristics

	Patients with Germline Mutation (n=10)	Patients without Germline Mutation (n=78)
Sex[§]		
Female	4 (40%)	25 (32%)
Male	6 (60%)	53 (68%)
Self-Declared Ethnicity[§]		
Non-Hispanic White	9 (90%)	68 (87%)
Asian	1 (10%)	3 (4%)
Hispanic	0	5 (6%)
Black	0	2 (3%)
Age at Diagnosis		
Median	71.5	69
Range	33 - 85	30 - 88
Histology[§]		
Epithelioid	8 (80%)	62 (79%)
Sarcomatoid	2 (20%)	0
Mixed	0	11 (14%)
Not specified	0	5 (6%)
Clinical Stage at Diagnosis[§]		
Stage I	4 (40%)	28 (36%)
Stage II	0	2 (3%)
Stage III	3 (30%)	37 (47%)
Stage IV	3 (30%)	11 (14%)
Self-Reported Asbestos Exposure[§]		
Definite/Probable	5 (50%)	48 (62%)
None	0	12 (15%)
Unknown	5 (50%)	18 (23%)
Smoking History[§]		
Current	0 (0%)	1 (1%)
Former	4 (40%)	47 (60%)
Never	6 (60%)	30 (38%)
Relatives with Cancer		
First-degree relative	9 (90%)	52 (67%)
>2 first-degree relatives	4 (40%)	10 (13%)
Second-degree relative	3 (30%)	34 (44%)
None	1 (10%)	16 (20%)

[§]Percentages were rounded, so may not add up to 100%.

Keywords: Mesothelioma, Next-generation sequencing, Germline mutation

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MA12.11 ANTI-TUMOR EFFICACY OF MESOTHELIN TARGETED IMMUNOTOXIN LMB-100 PLUS PEMBROLIZUMAB IN MESOTHELIOMA PATIENTS AND MOUSE MODELS

Q. Jiang, A. Ghafoor, D. Rathkey, I. Mian, J. Zhang, B. Morrow, I. Pastan, R. Hassan

National Institutes of Health, Bethesda/United States of America

Background: LMB-100 is an immunotoxin targeting mesothelin (MSLN) that is highly expressed in malignant mesothelioma and lung adenocarcinoma. Given the clinical efficacy of immune checkpoint inhibitors in these cancers, we aimed to evaluate if LMB-100 in combination with αPD-1 antibody will result in greater anti-tumor efficacy. **Method:** Patients who were treated on a phase I clinical trial of LMB-100 and then received pembrolizumab were evaluated for anti-tumor response and overall survival. We also evaluated LMB-100/αPD-1 combination efficacy in humanized mouse model transplanted with the tumor cells derived from the mesothelioma patient who achieved complete response and healthy donor's PBMCs. Immune gene expression in pre- and post- LMB-100-treated mesothelioma patient tumor biopsies was detected with NanoString. To further understand the mechanisms of anti-tumor efficacy of LMB-100 plus αPD-1 therapy,we established a human MSLN expressing lung adenocarcinoma syngeneic mouse model with mouse lung adenocarcinoma cell line 531LN2 stably transfected with a vector encoding hMSLN. Using NanoString gene expression assay and flow cytometry, we analyzed drug induced cancer immune responses in 531LN2-hMSLN tumors. Finally, to understand the role of $CD8^+$ T cells in the anti-tumor effects, we depleted $CD8^+$ T cells in LMB-100 plus anti-PD-1 treated 531LN2-hMSLN bearing mice. **Result:** Nine mesothelioma patients received pembrolizumab, off-protocol, within 3-4 weeks post LMB-100 treatment. Two patients had disease progression before they could be evaluated for tumor response. Out of the 7 patients who were evaluable for response, 4 had durable objective tumor response including 1 complete and 3 partial responses with progression free survival of 104.3+, 49.6, 49.2 and 37.7 weeks. The overall survival of patients with response was 30.2+, 27.7, 23.8+, and 13.8 months from the start of LMB-100 treatments. The immune cell type signature scores including $CD45^+$, $CD8^+$ T cells, exhausted $CD8^+$ T cells, dendritic cells and macrophages were increased in 4 of 6 patients post LMB-100 treatments. The enhanced anti-tumor effects with LMB-100/αPD1 combination were also observed in the PBMC humanized mouse model transplanted with the tumor cells derived the patient with complete response. In the 531LN2-hMSLN mouse syngeneic model, tumor growth was significantly inhibited by LMB-100/αPD-1 treatments than either monotherapy and overall survival was improved in the combination treated mice. The median tumor volume was 865mm^3, 420mm^3, 277mm^3, and 65mm^3 in untreated, LMB-100-treated, αPD-1-treated, and combination treated groups respectively on day 34 post tumor inoculation ($p<0.001$). We observed increased expression of genes related to $CD8^+$T cells and antigen presentation in tumors treated with LMB-100/αPD-1 compared to either agent alone. Flow cytometry confirmed the $CD8^+$T cells increase in LMB-100 /αPD-1 treated 531LN2-hMSLN tumor. Depletion of $CD8^+$T cells significantly negated the anti-tumor benefits in LMB-100/αPD-1-treated mice. **Conclusion:** Pembrolizumab following LMB-100 is associated with durable tumor response in mesothelioma patients as well as pre-clinical models of mesothelioma and lung cancer. This combination is currently being evaluated in a prospective clinical trial in patients with mesothelioma (clinicaltrials.gov # NCT03644550).

Keywords: mesothelioma, LMB-100, PD-1

MA13 GOING BACK TO THE ROOTS!
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MA13.01 ASSOCIATIONS BETWEEN BASELINE SERUM BIOMARKER LEVELS AND CACHEXIA/PRE-CACHEXIA IN PRETREATED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

G. Lobato[1], M.J. Fidler[2], J. Fialkoff[1], M. Multani[1], C. Wakefield[1], S. Basu[2], M. Batus[2], P. Bonomi[2], J. Borgia[1]

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Background: We previously reported associations of pretreatment serum biomarkers with clinical outcomes in a cohort of advanced NSCLC patients that progressed on front-line therapy. This study aims to elucidate mechanisms underlying cancer cachexia/ pre-cachexia by evaluating relationships between baseline serum biomarker values and sequential changes in body weight, body mass index (BMI), and neutrophil/lymphocyte ratio (NLR) in NSCLC patients. **Method:** We used Luminex immunobead assays to survey 101 protein biomarkers in sera from advanced NSCLC (n=138) collected prior to their salvage regimen. Serial parameters associated with cancer cachexia included body weight, BMI, and NLR. Outcome variables (progression-free survival (PFS) and overall survival (OS)) were extracted with full IRB-approval. Biomarkers were evaluated as continuous variables with the cachexia surrogates using Pearson correlations, whereas associations of PFS and OS were accomplished with the Cox PH test. **Result:** High baseline values of BMI and low baseline NLR were associated with both OS and PFS (each p<0.05), though weight failed to reach significance. PFS and OS were similarly associated with percent changes (relative to baseline) in weight (p<0.01), BMI (p<0.01), and NLR (p<0.001). Thirteen biomarkers were found to be associated (p<0.05) with baseline BMI values, including positive correlations with leptin, sol. VEGFR2, and c-peptide and inverse correlations with adiponectin, ferritin, ghrelin, IGFBP-1 and IL-8; fifteen biomarkers were associated with baseline NLR (all p<0.05), including positive correlations with visfatin, insulin, and serum amyloid A and inverse correlations with IGF-II. Fifteen biomarkers were found to be associated (p<0.05) in common with percent weight and BMI changes, including positive correlations with IGFBP-3 and inverse correlations with insulin, FGF-2, TNF-alpha, and resistin. Only prolactin and placental growth factor were found to be associated (p<0.05) with percent change in NLR. **Conclusion:** A series of circulating protein biomarkers primarily connected with metabolic regulation and systemic inflammation/ acute phase response were found to be associated with cachexia/ pre-cachexia in NSCLC patients. Additional cohorts are currently being tested to verify these findings.

Keywords: serum biomarkers, NSCLC, weight loss

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.02 INCIDENCE OF VENOUS THROMBOEMBOLISM AT THE TIME OF LUNG CANCER DIAGNOSIS: A MULTICENTER, PROSPECTIVE OBSERVATIONAL TRIAL (RISING-VTE/NEJ037)

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Background: Venous thromboembolism (VTE) is a most well-known kind of cancer associated thrombosis, and a common complication of malignancy. However, little is known about the incidence of VTE at the time of lung cancer diagnosis. This information is important for clinicians and patients to inform their decision-making about cancer treatment. **Method:** The Rising-VTE/NEJ037 study was a multicenter, prospective, observational study with 40 participating Japanese institutions. It included 1,021 patients diagnosed with lung cancer unsuitable for radical resection or radiation between June 2016 and August 2018. The incidence of VTE and characteristics of patients diagnosed with VTE based on contrast-enhanced computed tomography or ultrasonography of the leg are described. Diagnosis of VTE was confirmed via central review by two radiologists. **Result:** Baseline data was available for 1,013 patients. The median age was 71 years (range 30-94). Eighty-six percent of patients had non-small cell lung cancer and 13.5% had small cell lung cancer. Histological types included adenocarcinoma (N=645, 63.7%), squamous cell carcinoma (N=180, 17.8%), small-cell lung cancer (N=137, 13.5%) and others (N=42, 4.1%). There were 59 patients (5.8%) diagnosed with VTE, of whom 53.9% had deep vein thrombosis (DVT), 28.7% had pulmonary embolism (PE) and 24.6% had both DVT and PE. Most patients with VTE had adenocarcinomas (89.1%). **Conclusion:** The incidence of VTE in this study seems to be higher than in the clinical setting, suggesting that screening may be desirable. Adenocarcinoma of the lung seems to be a risk factor for VTE that we should consider more carefully. The primary endpoint of this trial is the rate of symptomatic or asymptomatic recurrence or newly diagnosed VTE during 2 years after registration. Follow-up is ongoing, with a report of final findings planned for 2021. Clinical trial information: UMIN000020194. Funding: Daiichi Sankyo Company.

Keywords: venous thronboembolism, deep vein thrombosis, plumonary embolism

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.03 RETROSPECTIVE STUDY OF INTRATHECAL THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH LEPTOMENINGEAL CARCINOMATOSIS

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Background: Leptomeningeal carcinomatosis (LMC) is a devastating cancer-related neurological complication with poor prognosis. In *EGFR*-mutant (mut) NSCLC patients (pts), osimertinib achieves high penetration into cerebral-spinal fluid (CSF) and promising efficacy. However, for *EGFR*-mut *T790M*-negative pts treated with prior 1st- and 2nd-generation tyrosine kinase inhibitors (TKI) and for driver negative NSCLC pts, a combination of intrathecal therapy (IT) and systemic therapy (ST) seems to be an appropriate approach. Our purpose is to explore the clinical outcome of IT combined with ST among NSCLC with LMC depending on *EGFR* status. **Method:** NSCLC pts with LMC treated with IT in our institution between 2010 and 2018 were retrospectively studied. After LMC diagnosis, intrathecal methotrexate (scheduled: 12mg twice weekly for 4 weeks, then 12mg weekly for 4 weeks) was given in combination with ST. A Kaplan-Meier survival analysis was performed for overall survival (OS) and progression free survival (PFS). **Result:** A total of 39 pts were included. Patient's clinical characteristics are summarized in table 1. *EGFR* status was 17 mut (del19: 11pts); 11 wild-type (wt) and 11 unknown (unk). LMC and NSCLC diagnosis were more likely to be synchronous in *EGFR* wt compared with *EGFR* mut. The median follow-up from LCM diagnosis was 10.2 months. At the time of this analysis, only 6 pts were alive. Thirty-two pts received ST in combination with IT, 18 (46%) pts chemotherapy (6wt/ 3mut/ 9unk), while 14 (36%) pts an *EGFR* TKI (1wt/ 13mut). Clinical response (improvement of neurological symptoms and/or KPS) was seen in 11 (65%) *EGFR* mut pts vs 2 (18%) wt pts (p=0.033). Median OS and PFS for the whole cohort were 23 weeks (95%CI, 8.1 to 37.9) and 10 weeks (95%CI, 7.1 to 12.8) respectively. Median OS was higher for *EGFR* mut pts compared to wt pts, 38 weeks (95%IC 13.6-62.4) and 19 weeks (95%IC, 4.06-33.9) respectively, however this difference was not statistically significant (p=0.36) probably due to lack of statistical power.

EGFR status	EGFR Mut n=17	EGFR Wt n=11	EGFR Unk n=11	Total n=39	p-value
Age (mean), years	54	59	58	57	0.300(*)
Gender, n (%)					
Female	13 (76%)	4 (36%)	1 (9%)	18 (46%)	
Male	4 (24%)	7 (64%)	10 (91%)	21 (54%)	0.002(#)
Smoking history, n (%)					
Never smoker	11 (65%)	3 (27%)	0 (0%)	14 (36%)	
Former smoker	3 (18%)	4 (36.5%)	2 (18%)	9 (23%)	
Current smoker	3 (17%)	4 (36.5%)	9 (82%)	16 (41%)	0.003(#)
Histologic type, n (%)					
Adenocarcinoma	16 (94%)	10 (91%)	5 (45%)	31 (79%)	
Squamous cell carcinoma	1 (6%)	0 (0%)	6 (54%)	7 (18%)	
Others	0 (0%)	1 (9%)	0 (0%)	1 (3%)	0.003(#)
Stage, n (%)					
I-III	1 (6%)	3 (27%)	2 (18%)	6 (15%)	
IV	16 (94%)	8 (73%)	9 (82%)	33 (85%)	0.295(#)
KPS at LMC diagnosis, n (%)					
0-1	6 (35%)	3 (27%)	3 (27%)	12 (31%)	
>1	5 (30%)	7 (64%)	7 (64%)	19 (49%)	
Non available	6 (35%)	1 (9%)	1 (9%)	8 (20%)	0.221(#)
LMC at tumor diagnosis, n (%)					
Yes	0 (0%)	6 (54.5%)	5 (45.5%)	11(28%)	
No	17(100%)	5 (45.5%)	6 (54.5%)	28 (72%)	0.002(#)
First CSF cytology, n (%)					
Postive	10 (58%)	8 (73%)	5 (45.5%)	23 (59%)	
Negative/non available	7 (42%)	3 (27%)	6(54.5%)	16 (41%)	0.319(#)
MRI at LMC diagnosis, n (%)					
Postive	10 (58%)	5 (45.5%)	5 (56%)	20 (54%)	
Negative/undetermined	7 (41%)	6 (54.5%)	4 (44%)	17 (46%)	0.782(#)
BM at LMC diagnosis, n (%)					
Yes	8 (47%)	3 (28%)	2 (18%)	13 (33%)	
No	9 (53%)	8 (73%)	9 (82%)	26 (67%)	0.252(#)
Systemic disease status at LMC diagnosis, n (%)					
Stable/Response	8 (47%)	2 (18%)	2 (18%)	12 (31%)	
Progression	9 (53%)	4 (36.5%)	4 (36.5%)	17 (43.5%)	
Non available	0 (0%)	5 (45.5%)	5 (45.5%)	10 (25.5%)	0.027(#)
Previous systemic lines, n (%)					
None	0 (0%)	7 (64%)	6 (54.5%)	13 (33%)	
1	9 (53%)	3 (27%)	5 (45.5%)	17 (44%)	
≥2	8 (47%)	1 (9%)	0 (0%)	9 (23%)	0.001(#)

Table 1. Patients' clinical characteristics KPS: Karnofsky performance status, BM: Brain metastases, * ANOVA test, # Chi-square test

Conclusion: Methotrexate-based IT given concurrently with systemic TKI may confer a higher clinical benefit and a trend toward OS benefit in NSCLC patients with LCM and EGFR activating mutations.

Keywords: intrathecal therapy, NSCLC, leptomeningeal carcinomatosis

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.05 NAB-PACLITAXEL MAINTENANCE IN SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): UPDATED RESULTS OF THE PHASE III ABOUND.SQM STUDY

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Background: *nab*-Paclitaxel maintenance therapy after *nab*-paclitaxel/carboplatin induction in patients with advanced squamous NSCLC was evaluated in the phase III, randomized, controlled, open-label, multicenter ABOUND.sqm trial. At the 12-month follow-up, there was no statistically significant difference in progression-free survival (PFS) between patients randomized to maintenance *nab*-paclitaxel + best supportive care (BSC) vs BSC alone. However, a trend of an overall survival (OS) advantage was observed with *nab*-paclitaxel + BSC vs BSC alone. Here we report the 18-month follow-up of OS. **Method:** Patients (aged ≥ 18 years) with histologically or cytologically confirmed stage IIIB/IV squamous NSCLC and no prior chemotherapy were eligible. Patients received four 21-day cycles of *nab*-paclitaxel 100 mg/m^2 (days 1, 8, and 15) plus carboplatin AUC 6 (day 1) as induction. Patients with radiologically assessed complete or partial response or stable disease without clinical progression after 4 cycles were randomized 2:1 to maintenance *nab*-paclitaxel 100 mg/m^2 (days 1 and 8 of each 21-day cycle) plus BSC or BSC alone until disease progression. The primary efficacy analysis was performed on the ITT population. PFS from randomization into the maintenance part of the study was the primary endpoint. Secondary endpoints included safety, OS (from randomization), and response. **Result:** 420 patients received induction therapy; 202 were randomized to maintenance *nab*-paclitaxel + BSC (n = 136) or BSC alone (n = 66). The median PFS in patients in the *nab*-paclitaxel + BSC arm vs those in the BSC-alone arm was 3.1 vs 2.6 months (HR, 0.85; *P* = 0.349), respectively; the median OS was 17.8 vs 12.2 months (HR, 0.71; *P* = 0.058), respectively. The overall response rate was 69.1% vs 57.6% (RRR, 1.20; *P* = 0.087). Following the maintenance part, 73.5% (*nab*-paclitaxel + BSC) and 68.2% (BSC alone) of patients received subsequent anti-cancer treatment. Over the entire study, the most frequent grade 3/4 TEAEs were neutropenia (53.1% vs 50.0%) and

anemia (33.1% vs 32.3%); only peripheral neuropathy occurred in ≥ 5% of patients during maintenance (13.1% in the *nab*-paclitaxel + BSC arm). **Conclusion:** Although PFS and OS differences were not statistically significant in the ITT population, the 18-month follow-up of OS demonstrated the feasibility of *nab*-paclitaxel maintenance therapy for patients with anced squamous NSCLC. ClinicalTrials.gov identifier: NCT02027428

Keywords: maintenance therapy; nab-paclitaxel; squamous non-small cell lung cancer

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.06 PH3 STUDY OF MAINTENANCE THERAPY WITH S-1 VS BSC AFTER INDUCTION THERAPY WITH CARBOPLATIN + S-1 FOR ADVANCED SQUAMOUS CELL LUNG CANCER (WJOG7512L)

K. Tanaka[1], S. Morita[2], M. Ando[3], T. Yokoyama[4], A. Nakamura[5], H. Yoshioka[6], T. Ishiguro[7], S. Miura[8], R. Toyozawa[9], T. Oguri[10], H. Daga[11], R. Ko[12], A. Bessho[13], M. Tachihara[14], Y. Iwamoto[15], K. Hirano[16], Y. Nakanishi[17], K. Nakagawa[1], N. Yamamoto[18], I. Okamoto[17]

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Background: Our previous phase 3 study established carboplatin plus the oral fluorinated pyrimidine formulation S-1 as a standard option for first-line treatment of advanced non–small cell lung cancer (NSCLC) (J Clin Oncol 2010; 28:5240). The importance of maintenance therapy for patients with advanced squamous NSCLC has been unknown, however. **Method:** WJOG7512L was designed as a randomized phase 3 study to evaluate whether maintenance therapy with S-1 improves clinical outcome after induction therapy with carboplatin plus S-1 in such patients. Before randomization, patients received carboplatin (AUC of 5 on day 1 every 3 weeks) plus S-1 (40 mg/m^2 twice per day on days 1 to 14 every 3 weeks) as induction therapy. Those who did not progress after four cycles of induction therapy were randomized to receive either S-1 plus best supportive care (BSC) or BSC alone. The primary objective was to confirm the superiority of S-1 plus BSC with regard to progression-free survival. **Result:** Of the 365 patients enrolled, 347 participated in the induction phase and 131 of these individuals were randomized to receive S-1 plus BSC (*n* = 67) or BSC alone (*n* = 64). Baseline demographics and clinical characteristics of the subjects, including the response to induction therapy, were well balanced. Patients receiving S-1 plus BSC showed a significantly reduced risk of disease progression compared with those receiving BSC alone (hazard ratio [HR], 0.548; 95% confidence interval [CI], 0.374–0.802; *P* = 0.0019). Median overall survival from randomization did not differ significantly between the two arms: 17.8 months for BSC alone and 16.7 months for S-1 plus BSC (HR, 0.890; 95% CI, 0.583–1.357). Time to deterioration in quality of life also showed no significant difference (*P* = 0.8754 for FACT-TOI, *P* = 0.9016 for FACT-LCS). The incidence of adverse events during maintenance therapy was low, with neutropenia, anemia, and thrombocytopenia of grade 3 or 4 each occurring in ~1% to 4% of patients. **Conclusion:** Maintenance with S-1 plus BSC is an effective and well-tolerated treatment option for patients with advanced squamous NSCLC.

Keywords: maintenance therapy, Squamous cell carcinoma, S-1

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.07 PHASE I/II STUDY OF CARBOPLATIN PLUS WEEKLY NAB-PACLITAXEL IN AGED ≥75 PATIENTS WITH SQUAMOUS-CELL LUNG CANCER: TORG1322

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Background: Combination chemotherapy of carboplatin (CBDCA) plus weekly nab-paclitaxel (nab-PTX) showed a favorable efficacy for elderly (70 year or older) patients with squamous non-small cell lung cancer (Sq-NSCLC) in a subgroup analysis of the CA031 study. We conducted a phase I/II study of CBDCA plus nab-PTX in chemo-naïve elderly patients with advanced Sq-NSCLC. **Method:** Patients aged ≥75 years with untreated, measurable lesion, advanced Sq-NSCLC, performance status (PS) 0-1, and adequate organ function were eligible. In a phase I study, doses of carboplatin at an area under the curve (AUC) of 5 or 6 mg/mL min on day 1 (levels 1 and 2, respectively) were administered along with weekly nab-PTX (100 mg/m^2) on days 1, 8, and 15 every 4 weeks up to 6 cycles using a modified 3 + 3 design. The primary endpoint for the phase II study was the 6-month progression-free survival (6m PFS) rate and hypothesis required 36 patients to be enrolled with expecting and threshold values for the primary endpoints of 40% and 25% (one-sided alpha = 0.05; beta = 0.2). **Result:** A total of 46 patients were enrolled in this study. The median age was 78 (range 75-85 years); male (n = 41); PS 0/1, (n = 15/31). Ten patients were enrolled in the phase I part. At dose level 1, 2/7 patients showed dose-limiting toxicities (DLTs) of grade 3 diarrhea and febrile neutropenia, and at dose level 2, 1/3 patient showed DLT of grade 3 anorexia. The recommended dose was determined to be level 2. Additional 36 patients were enrolled, and a total of 39 patients were evaluated in the phase II study. The median number of cycles was 4 (range 1-6), and the median follow-up time was 17.5 months (range 5.6-28.9). The 6m PFS rate was 59% (90% CI, 44.8-71.4), and the primary endpoint was met. The median overall survival time was 23.5 months (95% CI, 11.6-35.4), and the median PFS was 6.8 months (95% CI, 5.4-9.1). The response rate was 54% and disease control rate was 92%. Nineteen patients (49%) received post-study treatment and 14 out of 19 patients (74%) received immunotherapy. Common toxicities of grade 3 or 4 were neutropenia (61.5%), anemia (46.2%), thrombocytopenia (17.9%), and febrile neutropenia (15.4%). There was no treatment-related death. **Conclusion:** Combination chemotherapy of CBDCA plus weekly nab-PTX had a promising efficacy and acceptable toxicities in elderly (aged ≥75) patients with advanced Sq-NSCLC. Clinical trial information: UMIN000011216.

Keywords: aged ≥75 patients, squamous-cell lung cancer, carboplatin plus weekly nab-paclitaxel

MA13.09 CISPLATIN SUSTAINS LUNG CANCER METASTASIS THROUGH THE SYSTEMIC ACTIVATION OF SDF-1/CXCR4 AXIS

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Background: Standard chemotherapy regimens have limited long-term efficacy in lung cancer patients due to chemoresistance and inefficacy in controlling metastatic disease. In pre-clinical models we have shown that cisplatin treatment enriches for the chemoresistant fraction of CD133+CXCR4+ lung cancer metastasis initiating cells (MICs), increasing distant metastasis development that can be prevented by CXCR4 blockade. Therefore, we hypothesize that the SDF-1/CXCR4 axis, implied in MICs maintenance/migration and in immune and stromal cells trafficking, could play a critical role in cisplatin-induced pro-metastatic effects. **Method:** To study the effects of cisplatin in promoting a pre-metastatic niche, naïve SCID mice were treated with cisplatin plus/minus peptide R (5mg/kg), a novel inhibitor of CXCR4 and after 72h injected intravenously with metastatic H460 cell line. To assess the effect of the combination treatment in pre-clinical model, H460 subcutaneous xenografts were treated with cisplatin alone or with peptide R for three weeks. Content of MICs in xenografts, number and phenotype of lung metastasis and immune cells modulationt were evaluated by FACS and IHC **Result:** We showed that cisplatin treatment of naïf SCID mice resulted in a rapid BM expansion of the subset of CCR2+CXCR4+Ly6C^{high} inflammatory monocytes (IM), concomitantly with their recruitment to murine lungs guided by increased level of SFD-1 released by PDGFRβ+ stromal cells in response to cisplatin. Peptide R partially prevented these effects. Tail-vein injection of H460 human lung cancer cells 72h after cisplatin administration resulted in augmented number of lung metastases (p=0.003), that showed a 3.5-fold enrichment in CD133+CXCR4+ MICs (p=0.005) and increase of IM and derived macrophages. Pre-treatment with peptide R abolished these effects. We verified that the abundance of CXCR4+CCR2+IM together with increased endothelial permeability caused by cisplatin may favor tumor cells extravasations and expansion of MICs through SDF-1/CXCR4 axis activation which determined metastasis overgrowth. SDF-1 was also increased in cisplatin-treated subcutaneous H460 xenografts that expanded the subset of chemoresistant CD133+CXCR4+ MICs and recruited CXCR4+tumor associated macrophages which may allow MICs to escape primary tumor. At the metastatic site cisplatin treatment of H460 xenografts caused an increase in stromal SDF-1 and recruitment of both CXCR4+ inflammatory monocytes/macrophages (1.6-fold change p=0.01) and MICs subset (1.8-fold change p=0,04), overall resulting in a boost in micrometastases. CXCR4 inhibition prevented the co-recruitment and cross-talk of MICs and IM at distant site, counteracting the pro-metastatic effects of cisplatin. Matched case series of stage III chemo-naive NSCLC patients and cisplatin-based neo-adjuvant treated patients demonstrated a significant increased in SDF-1 after chemotherapy (p=0,0001). An high expression of tumoral SDF-1 (Score: staining intensity x % positive tumor cells >6) induced by cisplatin neo-adjuvant treatment was associated with a shorter DFS (p=0,0056) and poor OS (p=0,029). **Conclusion:** Our data reveal a paradoxical pro-metastatic effect of cisplatin that fosters MIC-IM recruitment and cross-talk via SDF-1/CXCR4 axis activation. A new combination strategy based on CXCR4 inhibition may disrupt these interactions, providing more effective and long-lasting results for lung cancer treatment

Keywords: Metastasis Initiating Cells, cisplatin, CXCR4

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.10 A PHASE II STUDY OF CARBOPLATIN AND NAB-PACLITAXEL FOR ADVANCED NON-SMALL CELL LUNG CANCER WITH INTERSTITIAL LUNG DISEASE (HOT1302)

H. Yokouchi[1], H. Asahina[2], S. Oizumi[1], K. Takamura[3], T. Harada[4], M. Harada[1], K. Kanazawa[5], Y. Fujita[6], T. Kojima[7], F. Sugaya[8], H. Tanaka[9], R. Honda[10], T. Ogi[3], E. Kikuchi[2], T. Ikari[4], H. Dosaka-Akita[11], H. Isobe[7], M. Nishimura[2]

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Background: Because of the high risk of exacerbation of pre-existing interstitial lung disease (ILD), patients with concomitant advanced non-small cell lung cancer (NSCLC) and ILD have been excluded from most clinical trials of chemotherapy, despite the high prevalence (around 10%) of all NSCLC cases. This study prospectively evaluated the efficacy and safety of albumin-bound paclitaxel (*nab*-paclitaxel) in combination with carboplatin in advanced NSCLC patients with pre-existing ILD. **Method:** Enrolled patients had treatment-naïve, advanced NSCLC with pre-existing ILD. Patients received 100 mg/m^2*nab*-paclitaxel weekly and carboplatin at area under the concentration-time curve (AUC) 6 once every 3 weeks for 4-6 cycles. The primary endpoint was overall response rate (ORR); secondary endpoints included toxicity, progression-free survival (PFS) and overall survival (OS). The interactions between histology [Squamous (Sq) vs. Non-Squamous (Non-Sq)] and treatment outcomes were also investegated. **Result:** Thirty-six patients were enrolled between April 2014 and September 2017. Sixteen patients (44.4%) had an adenocarcinoma, followed by 15 (41.7%) squamous cell carcinoma, and 5 (13.9%) non-small cell carcinoma. The median number of cycles administered were 4 (range: 1-6). The ORR, the primary endpoint, was 55.6% (95% confidence interval [CI]: 39.6-70.5%). The median PFS and OS were 5.3 months (95% CI: 3.9-8.2 months) and 15.4 months (95% CI: 9.4-18.7 months), respectively. There was no significant difference between two groups, however, numerically better treatment outcomes were observed in the Sq group: the ORR was 66.7% (95% CI: 41.7–84.8%) in the Sq group compared with 47.6 % (95% CI: 28.3–67.6%) in the Non-Sq group (P =0.254); median PFS was 8.2 months (95% CI: 4.0–10.2 months) in the Sq group vs. 4.1 months (95% CI: 3.3-5.4 months) in the Non-Sq group (HR, 0.60 [95% CI, 0.30–1.20]; p=0.15); median OS was 16.8 months (95% CI: 9.8 months–not reached) in the Sq group vs. 11.9 months (95% CI: 7.3-17.4 months) in the Non-Sq group (HR, 0.56 [95% CI, 0.24–1.28]; p=0.17). Two patients (5.6%) experienced grade ≥2 pneumonitis and one patient (2.8%) died. **Conclusion:** This is the first prospective phase 2 study of weekly nab-paclitaxel in combination with carboplatin in advanced NSCLC patients with pre-existing ILD. This treatment showed favorable efficacy and was well tolerated.

Keywords: Non-Small Cell Lung Cancer, interstitial lung disease, nab-Paclitaxel

MA13 GOING BACK TO THE ROOTS!
MONDAY, SEPTEMBER 9 14:00–15:30

MA13.11 A RANDOMIZED PHASE III STUDY OF CISPLATIN-POLYMERIC MICELLE PACLITAXEL VS CISPLATIN-SOLVENT-BASED PACLITAXEL IN 1ST LINE ADVANCED NSCLC

Y.-L. Wu[1], B. Han[2], M. Shi[3], H. Tu[1], A. Gu[2], C. Huang[4], H. Wang[5], Z. Yu[6], X. Wang[7], L. Cao[8], Y. Shu[9], H. Wang[10], R. Yang[11], X. Li[12], J. Chang[13], Y. Hu[14], P. Shen[15], Y. Hu[16], Z. Guo[17], M. Tao[18], Y. Zhang[19], X. Liu[20], Q. Sun[21], X. Zhang[22], Z. Jiang[23], J. Zhao[24], F. Chen[25], J. Sun[26], D. Li[26], J. Zhou[26]

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Background: Cisplatin-sb-Pac is the one of current standard of chemotherapy in aNSCLC, It produced 15% to 32% objective response rate (ORR) and 7.9 to 10.6 months of median overall survival (OS). Alternative nab-paclitaxel to sb-Pac only increased ORR but not improved progression-free survival (PFS) and OS. Thus the unmet medical need for new chemo regimen remains. **Method:** From May 2015 to Jan 2018 448 untreated patients (pts) with stage IIIB to IV NSCLC from 24 sites were randomly assigned 2:1 to receive 230 mg/m^2 pm-Pac and cisplatin 70 mg/m^2 on day 1 of a 3-week cycle, and then dose escalation of pm-Pac to 300 mg/m^2 from the second cycle if no prespecified toxic effects observed or 175 mg/m^2 sb-Pac plus cisplatin 70 mg/m^2 once every 3 weeks. Pts were stratified by stage and histology. The primary end point was ORR by Independent review committee (IRC) and Investigator (INV) in the intent-to-treat population. The second endpoints included PFS, OS and safety. Data cutoff was Jan 26, 2019. **Result:** 300 pts were assigned to pm-Pac and 148 to sb-Pac. Baseline characteristic were balance in both arms. Nonsquamous carcinoma (non-squ) and stage IV were 57.3% and 81.0% in pm-Pac and 58.1% and 81.8% in sb-Pac respectively. 73.2% pts in pm-Pac arm escalated their dose to 300mg/m^2, 0.7% down to 184mg/m^2. ORR and PFS in pm-Pac were significant better than that in sb-Pac (table 1). OS was immature. For histology subgroup the ORR was 58.6% v 37.1% (P=0.0054) in squamous carcinoma (Squ) and 44.2% v 18.6% (P<0.0001) in non-squ. Grade ≥3 AEs was 80.0% for pm-Pac and 79.7% for sb-Pac. No new safety issues were identified. **Conclusion:** The phase 3 trial met its primary endpoint. pm-Pac significantly improved ORR and PFS than sb-Pac, and pm-Pac regimen should be a new standard chemo for aNSCLC. (NCT 02667743).

Tab. Efficacies comparison between pm-Pac and sb-Pac

	pm-Pac	sb-Pac	P value
ORR % (95% CI)			
IRC INV	50.3 (44.5-56.1) 52.0 (46.2-57.8)	26.4 (19.5-34.2) 28.4 (21.3-36.4)	<0.0001 <0.0001
PFS (months)	6.4 (6.2-6.9)	5.3 (4.6-6.0)	HR 0.66 (0.52-0.84), P=0.0006
OS at 12 months	67.3%	61.8%	-

Keywords: advanced non-small cell lung cancer, Polymeric micelle paclitaxel (pm-Pac) /cisplatin, randomized phase III clinical trial

MA14 THE ADEQUATE MTARGET IS STILL THE ISSUE
MONDAY, SEPTEMBER 9 15:45–17:15

MA14.01 CLINICAL AND GENOMIC FEATURES OF CHINESE LUNG CANCER PATIENTS WITH GERMLINE MUTATIONS

W. Peng[1], J. Li[2], L.-P. Chang[3], J. Bai[3], Y. Zhang[3], Y. Guan[3], X. Pu[1], M. Jiang[1], J. Cao[1], B. Chen[1], X. Xia[3], X. Yi[3], J. Zhang[4], L. Wu[1]

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Background: Recent studies on next generation sequencing (NGS) data from cancer patients have demonstrated that germline mutations in genetic predisposition genes were more common than previous known in many cancer types including lung cancer. However, most previous studies have focused on western patient population and the germline mutation landscape in Asian lung cancer patients and the clinical and genomic features in these patients are largely unknown. **Method:** NGS data from a targeted panel of 1,021 known cancer genes from paired cancer and germline DNA of 1,797 Chinese lung cancer patients was analyzed to identify pathogenic or likely pathogenic (P/LP) germline variants in predisposition genes based on American College of Medical Genetics and Genomics (ACMG) 2015 guideline. **Result:** Totally, 5.95% of lung patients were found to harbor germline variants in 35 cancer predisposition genes. The prevalence of germline mutations was higher in patients under 40 compared to older counterparts (10.1% vs 5.74%, p=0.103, Chi-Square test) although it did not reach statistical significance. However, germline *BRCA1/2* mutations were associated with earlier age of onset (median 52.5 vs 60 years-old, *p*=0.0080 by Mann-Whitney test). Furthermore, patients with P/LP germline mutations had significantly more somatic mutations in *KRAS* (*p*=0.012, fisher's exact test) and *c-MET* (*p*=0.018, fisher's exact test) oncogenes, but less in tumor suppressor gene *TP53* (*p*=0.019, fisher's exact test). Compared to western lung cancer patients enrolled in TCGA, P/LP germline mutations in *BRCA2, FANCA, ATM, MUTYH, BLM, TP53, BRCA1, CHEK2, PMS2, NBN* and *FANCC* were identified in both current Chinese cohort and TCGA cohort with *BRCA2* germline mutations significantly more common in Chinese cohort than TCGA cohort (p=0.015, Fisher's exact test). In addition, *RAD51D*, *FANCD2*, *BRIP1*, *MSH6*, *PMS1*, *PALB2*, *RAD51C*, *SDHA*, *TSC2*, *BAP1*, *CDH1*, *FLCN*, *NF1* and *RUNX1*) were exclusively identified in Chinese patients, while *RET, ERCC3*, *FANCG* and *VHL* were only detected in TCGA cohort. **Conclusion:** These results implied that there might be both common and unique cancer predisposition germline mutations for lung cancer between Asian and Western patient populations.

Keywords: Germline mutation, Asian lung cancer, Somatic mutation

MA14.02 ENTRECTINIB IN PATIENTS WITH ROS1-POSITIVE NSCLC OR NTRK FUSION-POSITIVE SOLID TUMORS WITH CNS METASTASES

L. Paz-Ares[1], R. Dziadziuszko[2], A. Drilon[3], T. John[4], M. Krebs[5], G. Demetri[6], A. Shaw[7], S. Siena[8], J. Wolf[9], A. Farago[7], B. Simmons[10], C. Ye[10], X. Huang[10], R. Doebele[11]

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Background: Entrectinib potently inhibits kinases encoded by NTRK and ROS1 genes. It achieves therapeutic levels in the CNS with antitumor activity in intracranial tumor models. We report integrated analysis data (31 May 2018 data cut-off) from three Phase 1/2 entrectinib trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]) for a large cohort of adult patients with NTRK fusion-positive solid tumors (NTRK+) or ROS1 fusion-positive NSCLC (ROS1+), with baseline CNS metastases. **Method:** Patients had locally advanced/metastatic NTRK+ solid tumors or ROS1+ NSCLC by nucleic acid-based assays confirmation. Baseline CNS metastases were identified by CT/MRI. Tumor assessments were performed at baseline, week 4, and then every 8 weeks by blinded independent central review (RECIST v1.1). Primary endpoints were overall response rate (ORR), duration of response (DOR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), intracranial efficacy in patients with CNS metastases, safety. **Result:** Most patients were treated first-line or after one line of prior therapy; baseline characteristics relating to measurable CNS metastases for patients with NTRK+ solid tumors and ROS1+ NSCLC are presented (Table). Intracranial outcomes for the NTRK+ solid tumors (n=54; 18% NSCLC) and ROS1+ NSCLC (n=53) efficacy evaluable populations are reported (Table). Durability of treatment effect and potential delayed progression in the CNS was observed; time to CNS progression was 17.0 months (95% CI: 14.3–NE) for NTRK+ solid tumor patients and NE (95% CI: 15.1–NE) for ROS1+ NSCLC. In the subset of patients with NTRK+ NSCLC (n=10), 6 patients had CNS metastases at baseline (by BICR); IC-ORR was 66.7% (4/6), 2 CR; IC-DOR was NE. In both the NTRK+ and ROS1+ populations, entrectinib was tolerable with a manageable safety profile; most treatment-related AEs were grade 1–2. **Conclusion:** Entrectinib induced clinically meaningful durable responses in patients with *NTRK*+ solid tumors or *ROS1*+ NSCLC with CNS disease at baseline. Funding: This study was funded by F. Hoffmann-La Roche

	***NTRK*+ solid tumors (N=54)**		***ROS1*+ NSCLC (N=53)**	
Baseline characteristics (investigator assessed)				
Baseline CNS lesions, n (%)				
Measurable	2 (3.7)		5 (9.4)	
All	12 (22.2)		23 (43.4)	
Any prior RT of the brain, n (%)				
Yes	7 (58.3)		15 (65.2)	
Time from end of prior RT to first dose, n (%)	N=7 with prior RT		N=15 with prior RT	
<2 months	2 (28.6)		9 (60.0)	
2 to <6 months	4 (57.1)		2 (13.3)	
≥6 months	1 (14.3)		4 (26.7)	
Intracranial Efficacy (BICR assessed)				
	Measurable CNS disease (n=7)	Measurable and non-measurable CNS disease† (n=11)	Measurable CNS disease (n=12)	Measurable and non-measurable CNS disease (n=20)†
Intracranial Objective Response Rate				
Responders (CR or PR)	4	6	9	11
IC-ORR, %	57.1	54.5	75	55.0
(95% CI)	(18.4, 90.1)	(23.4, 83.3)	(42.8, 94.5)	(31.5, 76.9)
Intracranial Duration of Response (IC-DOR)				
Responders with progression, n (% of responders)	1 (25.0)	2 (33.3)	4 (44.4%)	5 (45.5)
Median, months (95% CI)*	NE (5.0, NE)	NE (5.0, NE)	12.9 (4.6, NE)	12.9 (5.6, NE)
Intracranial Progression-Free Survival (IC-PFS)				
Patients with progression, n (%)	3 (42.9)	5 (45.5)	6 (50.0)	13 (65.5)
Median, months (95% CI)*	NE (2.8, NE)	14.3 (5.1, NE)	19.3 (3.8, 19.3)	7.7 (3.8, 19.3)

Confidence Intervals (CI) calculated using the Clopper-Pearson method.
*Median and percentiles based on Kaplan-Meier estimates. †CNS metastases confirmed by blinded independent central review (BICR).
CNS, central nervous system; CR, complete response; NE, not estimable; PR, partial response; RT, radiotherapy

MA14.03 EGFR M+ SUBGROUP OF PHASE 1B STUDY OF TELISOTUZUMAB VEDOTIN (TELISO-V) PLUS ERLOTINIB IN C-MET+ NON-SMALL CELL LUNG CANCER

D.R. Camidge[1], F. Barlesi[2], J. Goldman[3], D. Morgensztern[4], R. Heist[5], E. Vokes[6], A. Spira[7], E. Angevin[8], W.-C. Su[9], D. Hong[10], J. Strickler[11], M. Motwani[12], Z. Sun[12], A. Parikh[13], P. Komarnitsky[12], J. Wu[12], K. Kelly[14]

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Background: Telisotuzumab vedotin (ABBV-399; teliso-v) is an anti-c-Met antibody conjugated with monomethyl auristatin E, a tubulin polymerization inhibitor. Preliminary activity was reported for the teliso-v + erlotinib combination in c-Met overexpressing (c-MET+) non-small cell lung cancer (NSCLC) patients, with an activating *EGFR* mutation and for whom prior EGFR TKI failed. We present mature data from the *EGFR* M+ subgroup of the teliso-v + erlotinib cohort of a phase 1b study (NCT02099058). **Method:** Teliso-v was administered at 2.4 mg/kg (dose-escalation phase) or 2.7 mg/kg intravenously once every 3 weeks, and erlotinib at 150 mg orally once a day/prior tolerated dose in adult patients with advanced NSCLC. For efficacy analysis, c-Met+ was defined as central lab IHC H-score ≥150 or local lab MET amplification (MET/CEN7 ≥2); *EGFR* M+ was defined as del19 or L858R by local lab. Pharmacokinetics were assessed. All patients who received teliso-v + erlotinib were evaluated for safety. **Result:** As of Dec 2018, 42 NSCLC patients received teliso-v + erlotinib; 37 were c-MET+ (36 evaluable: 35 H-score≥150, 1 MET amplified). Median age was 65 years, 25 patients (69%) had ECOG PS 1, 29 (81%) were *EGFR* M+ (of these: 48% had T790M, 10% had MET amplification, 3% had polysomy, 97% had prior EGFR TKI, 55% 3rd-generation TKI, 69% TKI as last prior therapy, and 62% platinum doublet). All-grade (≥20%) adverse events (AEs) were dermatitis acneiform (38%), diarrhea (36%), peripheral motor/sensory neuropathy (52%; 7% Grade 3), dyspnea, fatigue, hypoalbuminemia (31% each), decreased appetite, nausea (24% each), asthenia, vomiting (21% each). Grade ≥3 (≥10%) AE: pulmonary embolism (14%). Pharmacokinetics of teliso-v for the combination were similar to single-agent teliso-v. The table presents efficacy data.

	Patients with EGFR mutation (n=29)
Objective response rate*, % (95% CI) Complete response, n	34.5 (17.9, 54.3) 1
Median duration of response, months (95% CI)	NR (2.8, NE)
Median PFS, months (95% CI)	NR (2.8, NE)
Median follow-up, months	4
6-month PFS rate, % (95% CI)	51 (30, 69)
Median treatment duration, month (range) Teliso-v Erlotinib	3.5 (0.71–10.4) 5.3 (0.71–25.4)
Objective response rate by subgroup of interest, n (%) Received prior 3rd generation EGFR TKI C-met amplified, copy number gain, or polysomy EGFR TKI-containing regimen as last-line therapies	 6/16 (37.5) 5/7 (71.4) 8/20 (40.0)

*RECIST version 1.1. EGFR, epidermal growth factor receptor; NE, not estimable; NR, not reached; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor;

Conclusion: These data suggest acceptable safety and promising activity of teliso-v + erlotinib in patients with c-Met+ NSCLC with an activating *EGFR* mutation and for whom EGFR TKI has failed.

Keywords: teliso-v, NSCLC, Phase 1b

MA14 THE ADEQUATE MTARGET IS STILL THE ISSUE
MONDAY, SEPTEMBER 9 15:45–17:15

MA14.05 A RANDOMIZED PHASE III TRIAL OF FRUQUINTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (FALUCA)

S. Lu[1], G. Chen[2], Y. Sun[3], S. Sun[4], J. Chang[5], Y. Yao[6], Z. Chen[7], F. Ye[8], J. Lu[9], J. Shi[10], J. He[11], X. Liu[12], Y. Zhang[13], Z. Liu[14], J. Fang[15], Y. Cheng[16], C. Hu[17], W. Mao[18], Y. Hu[19], Y. Gong[20], L. Shan[21], Z. Yang[22], Y. Song[23], W. Li[24], C. Bai[25], B. Wang[26], R. Ma[27], Z. Zheng[28], M. Liu[29], Z. Jie[30], L. Cao[31], W. Liao[32], H. Pan[33], D. Huang[34], Y. Chen[35], J. Yang[36], S. Qin[37], S. Ma[38], L. Liang[39], Z. Liu[40], J. Zhou[41], M. Tao[42], Y. Huang[43], F. Qiu[44], Y. Huang[45], Y. Hua[46], Y. Chen[47], W. Su[46]

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Background: Fruquintinib, an orally active kinase inhibitor that selectively targets vascular endothelial growth factor (VEGF) receptor, demonstrated significant benefit in progression-free survival and disease control in a randomized Phase II study in patients with non-small-cell lung cancer (NSCLC) who had failed two lines of chemotherapy. This Phase III FALUCA trial is a randomized, double-blind, placebo-controlled, multicenter trial designed to confirm the efficacy in the same patient population (NCT02691299). **Method:** From December 2015 to February 2018, 45 clinical centers across China participated in the trial. A total of 730 patients aged 18-75 with advanced NSCLC who had failed two lines of chemotherapy were screened and 527 who met the eligibility criteria were enrolled into the study. Patients were stratified based on epidermal growth factor receptor mutation status and prior use of VEGF inhibitor therapy, and were randomized in a 2:1 ratio to receive fruquintinib (n=354) or placebo (n=173) once daily in a 3 weeks on/1 week off 4-week cycle. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), duration of response. The final data cutoff was on September 21, 2018. **Result:** Median OS was 8.94 months for fruquintinib and 10.38 months for placebo (hazard ratio, 1.02; 95% CI, 0.816 to 1.283; p=0.841). Median PFS was 3.68 months for fruquintinib comparing to 0.99 months for placebo, respectively (hazard ratio, 0.34; 95%CI, 0.279 to 0.425; p<0.001). The ORR and DCR were 13.8% and 66.7% for fruquintinib, compared

with 0.6% and 24.9% for placebo (both p<0.001), respectively. The most frequent treatment-emergent adverse events with fruquintinib (≥grade 3) were hypertension (20.7%), hand-foot syndrome (11.0%), and proteinuria (1.4%). A sensitivity analysis revealed that median OS was significantly prolonged with fruquintinib compared with placebo in patients who received no subsequent systemic anti-tumor therapies (7.00 months versus 5.09 months; hazard ratio, 0.65; 95%CI, 0.462 to 0.913; p=0.012). **Conclusion:** The FALUCA trial failed to meet the primary end point of OS while confirming significant benefit in secondary end points including PFS, ORR and DCR. The safety profile of fruquintinib in this patient population was acceptable and consistent with that identified in the Phase II study. A post-hoc sensitivity analysis revealed that the anti-tumor therapies that patients received post disease progression probably contributed to the failure of this study on the primary end point.

Keywords: Fruquintinib, advanced NSCLC, Vascular Endothelial Growth Factor Receptor

MA14.06 NINTEDANIB-DOCETAXEL IN 2ND LINE TREATMENT IN NO SQUAMOUS NON-SMALL CELL LUNG CANCER PATIENTS, REFRACTORY TO FIRST LINE TREATMENT (GFPC02-15)

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Background: Second line chemotherapy used in advanced Non Small Cell Lung Cancer (NSCLC) have demonstrated a slight survival benefit in patient refractory to a first line platinum based doublet chemotherapy. In exploratory analysis, Nintedanib in combination with docetaxel have shown interesting result in second line setting for refractory NSCLC patients. Objective: To assess the efficacy in terms of progression-free survival (PFS) of the nintedanib - docetaxel combination in second-line treatment in refractory no squamous NSCLC (NsqNSCL) patients **Method:** This prospective, multicentric open-label phase II trial, included patients with advanced Nsq NSCLC (EGFR, ALK wild-type), PS 0-1, progressing during the first four cycles of cisplatin-based induction chemotherapy. Patients received Nintedanib (200 mg X2 /d d2-d20)- Docetaxel (75 mg/m^2 d1-d21) combination until progressive disease or unacceptable toxicity. The primary endpoint was the PFS rate at 12 weeks. Secondary endpoints included median PFS, median overall survival (OS), overall response rate (ORR) and tolerability. Based on a A'Hern's single-stage phase II design trial (sample size determination is based on exact binomial distribution), the Nintedanib-Docetaxel strategy will be rejected if the primary endpoint was below 22/53 patients at the end of study. **Result:** The analysis included 53 evaluable patients managed in 21 centers; last patient included at the end of January 2019. Mean age 58.4 years, male 73 %, adenocarcinoma 97.5%, current/former smokers: 42/50 %, PS 0/1: 25%/75%; weight loss >5%:19%, stage IV: 100% (38% with brain metastasis, median metastasis 2). All patients received for induction chemotherapy, a platin doublet (22% with bevacizumab), number of cycle 1-2/ 3-4: 57%/ 43%. Interim analysis reviewed by the independent committee conducted as planned, after the 27 first inclusions concluded that there was no sign of unexpected toxicity (adverse events grade 3-4 :22%, grade 5 :0%) or futility (9 patients meet primary end point on 25 evaluable). The results of the final analysis on the whole population (PFS at 12 weeks (primary end point), median PFS, median OS and toxicity) will be presented at the meeting Academic grant from Boehringer Ingelheim **Conclusion:** Section not applicable

Keywords: refractory, Nintedanib, Docetaxel

MA14 THE ADEQUATE MTARGET IS STILL THE ISSUE
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MA14.07 PHASE I EXPANSION COHORT OF RAMUCIRUMAB PLUS PEMBROLIZUMAB IN ADVANCED TREATMENT-NAÏVE NON-SMALL CELL LUNG CANCER (JVDF)

R. Herbst[1], H. Arkenau[2], J. Bendell[3], E. Arrowsmith[4], M. Wermke[5], A. Soriano[6], N. Penel[7], R. Santana-Davila[8], H. Bischoff[9], I. Chau[10], B. Chao[11], D. Ferry[11], G. Mi[12], L. Paz-Ares[13]

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Background: Emerging data suggest blockade of vascular endothelial growth factor receptor 2 (VEGFR-2) with ramucirumab (R) and programmed cell death 1 protein (PD-1) with pembrolizumab (P) has anti-tumor activity. The JVDF study (NCT02443324) evaluated the safety and efficacy of R+P in locally advanced and unresectable or metastatic gastric/gastroesophageal junction adenocarcinoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, and biliary tract cancer. Data from NSCLC patients receiving R+P as first-line therapy are reported. **Method:** Eligible patients had treatment-naïve, PD-L1 positive, histopathologically confirmed nonsquamous or squamous NSCLC and received R 10 mg/kg and P 200 mg on Day 1 every 21 days for up to 35 cycles until confirmed disease progression or discontinuation for other reasons. Response and progression were assessed using RECIST 1.1 with confirmatory scans. PD-L1 was assessed using the PD-L1 IHC 22C3 pharmDx assay; PD-L1 positivity was defined as a tumor proportion score (TPS) ≥1%. **Result:** As of August 31, 2018, 26 patients were treated. Baseline characteristics were as expected for an advanced, treatment-naïve population. Median follow-up was 17.4 (13.4, 20.1) months. Adverse events were consistent with R+P, with no additive toxicities. Eleven (42.3%) patients experienced Grade ≥3 treatment-related adverse events (TRAEs), most commonly hypertension (15.4%) and myocardial infarction (7.7%). No patients discontinued because of TRAEs; the two on-study deaths were due to disease progression. Efficacy results are shown in the table.

Summary of efficacy endpoints with R+P in treatment-naïve NSCLC.

	All Patients (N=26)[a]	PD-L1 weakly positive (n=9)[b]	PD-L1 strongly positive (n=16)[c]
ORR, % (95% CI) CR, % (95% CI) PR, % (95% CI) SD, % (95% CI) PD, % (95% CI) NE, n (%)	42.3 (23.4, 63.1) 3.8 (0.1, 19.6) 38.5 (20.2, 59.4) 42.3 (23.4, 63.1) 11.5 (2.4, 30.2) 1 (3.8)	22.2 (2.8, 60.0) 0 (0, 33.6) 22.2 (2.8, 60.0) 66.7 (29.9, 92.5) 11.1 (0.3, 48.2) 0 (0)	56.3 (29.9, 80.2) 6.3 (0.2, 30.2) 50.0 (24.7, 75.3) 31.3 (11.0, 58.7) 6.3 (0.2, 30.2) 1 (6.3)
mPFS, mo (95% CI) 12-mo PFS, % (95% CI) 18-mo PFS, % (95% CI)	9.3 (4.0, NR) 45.0 (24.4, 63.6) 45.0 (24.4, 63.6)	4.2 (1.2, NR) 33.3 (7.8, 62.3) 33.3 (7.8, 62.3)	NR (4.0, NR) 56.2 (26.9, 77.6) 56.2 (26.9, 77.6)
mOS, mo (95% CI) 12-mo OS, % (95% CI) 18-mo OS, % (95% CI)	NR (13.2, NR) 72.5 (50.8, 85.9) 68.0 (45.9, 82.6)	NR (3.2, NR) 66.7 (28.2, 87.8) 59.3 (17.7, 79.8)	NR (11.3, NR) 75.0 (46.3, 89.8) 75.0 (46.3, 89.8)
DCR, % (95% CI)	84.6 (65.1, 95.6)	88.9 (51.8, 99.7)	87.5 (61.7, 98.4)

[a]One PD-L1 negative patient was inadvertently enrolled and is included in the safety population; this patient had progressive disease (PFS=1.12 months).

[b]Weakly positive PD-L1 defined as TPS 1-49%

[c]Strongly positive PD-L1 defined as TPS ≥50%

CI, confidence interval; CR, complete response; DCR, disease control rate; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; R+P, ramucirumab plus pembrolizumab; SD, stable disease; TPS, tumor proportion score.

Conclusion: In previously untreated NSCLC, R+P has a manageable safety profile and is active in patients with PD-L1 expression. Updated results will be presented at the meeting. Randomized trials in this population are warranted.

Keywords: Ramucirumab, Pembrolizumab, Lung cancer

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MA14.09 REAL-WORLD SURVIVAL OF RELAPSED COMPARED TO DE-NOVO STAGE IV DIAGNOSIS OF ADVANCED NON-SMALL CELL LUNG CANCER

K. Kerrigan[1], B. Haaland[1], B. Adamson[2], S. Patel[1], W. Akerley[1]

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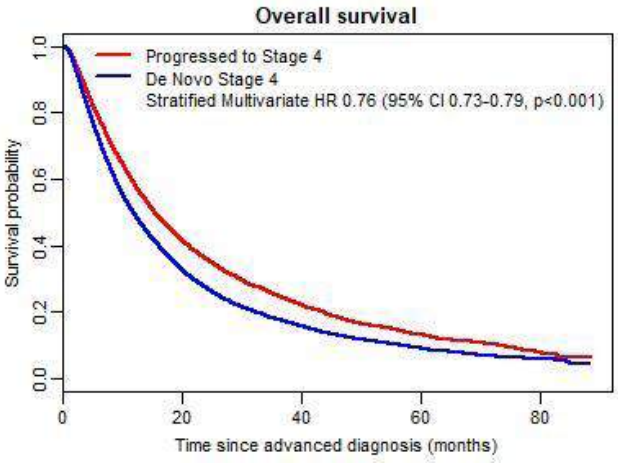
Background: Differences in tumor biology and cancer therapy in early stage lung cancer may affect overall survival (OS) of patients with relapsed stage IV disease compared to others with de-novo stage IV disease. This study aimed to compare real-world survival of these patients. **Method:** We selected patients with advanced NSCLC diagnosed between 2011 and 2017, who received at least one line of therapy, from the US Flatiron Health electronic health record-derived database. Patient data was collected through June 2018, providing at least 6 months of follow-up. OS was defined as time from advanced or metastatic diagnosis to the event of death, censored at last clinic visit or end of oral therapy. The unadjusted OS of patients was estimated using the Kaplan-Meier method. We fit multivariable Cox proportional hazards models to compare the hazard of death between groups. **Result:**



The study included 30,310 patients with median age of 68.8 years, 46.7% female, and 76.8% non-Hispanic white. We observed 22.8% had relapsed and 77.2% were de-novo stage IV. Relapsed patients had median OS of 15.5 months (95% CI: 14.9-16.2). Patients with de-novo stage IV had median overall survival of 12.0 months (95% CI: 11.7-12.2). The force of mortality among relapsed stage IV patients was 24% lower than the rate of death among de-novo stage IV patients (Hazard Ratio [HR]: 0.76; 95% CI 0.73-0.79; p <0.001), adjusting for age, gender, state, histology, smoking, race/ethnicity, and stratifying by year of diagnosis. Sensitivity analyses of an unadjusted model (HR 0.79, p <0.001) and a sub-group analysis of patients with advanced diagnoses in 2016-2017 (HR 0.74, p <0.001) suggested the results were robust. **Conclusion:** Among patients with stage IV NSCLC that received at least one treatment, those who relapsed had better OS than those who presented with de-novo stage IV disease. These findings have implications for future clinical trial design.

Keywords: realworlddata, denovovsrelapsedNSCLC

MA14 THE ADEQUATE MTARGET IS STILL THE ISSUE
MONDAY, SEPTEMBER 9 15:45–17:15

MA14.10 CLINICAL OUTCOMES IN METASTATIC SQUAMOUS LUNG CANCER WITH TARGETABLE DRIVER ALTERATIONS

W. Lewis[1], G. Simon[1], F. Mott[1], V. Papadimitrakopoulou[1], W. Rinsurongkawong[2], J. Lewis[2], J. Lee[2], J. Roth[2], S. Swisher[2], J. Heymach[1], J. Zhang[1], V. Lam[1]

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Background: Genomic profiling is not routinely performed for metastatic squamous (SCC) and adenosquamous (ASC) NSCLC. However molecular profiling may be ordered if demographic features suggest a higher likelihood of a targetable driver alteration (e.g. never or remote smoking history). Response and survival data are scant in pts with actionable alterations treated with targeted therapy. **Method:** We reviewed the clinical data and molecular profiling (FISH, PCR, tissue NGS, ctDNA) of metastatic SCC and ASC pts treated at our institution from Feb 2010-Dec 2018. Pts with typical sensitizing mutations in *EGFR* or *BRAF* V600E or fusions in *ALK* or *ROS1* treated with matched targeted therapy for ≥ 2 months were included in this analysis. Response assessment was based on RECIST v1.1. **Result:** Among 261 metastatic SCC or ASC pts with available molecular profiling, 16 total pts (6%) were found to have actionable targets, consisting of 13 SCC and 2 ASC (median age 53, 81% female, 88% never-smoker). The distribution of driver alterations in this cohort was 56% (9/16) *EGFR* ex19del/L858R/G719A, 38% (6/16) *ALK* fusion, and 6% (1/16) *BRAF*. The overall objective response rate (ORR) and median progression free survival (PFS) to targeted therapy was 69% and 5.2 months respectively. By mutational subgroup, ORR was 67% (6/9) for *EGFR*, 67% (4/6) for *ALK*, and 100% (1/1) for *BRAF*. Median PFS was only 4.5 months (95% CI 3.0 – 6.0) for *EGFR* pts and 2.8 months (95% CI 0 – 6.4) for *ALK* pts, and the lone *BRAF* pt had a PFS of 8.5 months. In *EGFR* pts with available NGS, co-mutations in *TP53* (75% [6/8]) and *PIK3CA* (38% [3/8]) were seen at rates higher than previously reported in *EGFR*+ ADC (*TP53* 55%, *PIK3CA* 12%; Blakely et al, Nat Gen 2017). In *ALK* pts with available NGS, co-mutations in *TP53* (80% [4/5]) were also higher than recently reported in *ALK*+ ADC (24%; Kron et al, Ann Oncol 2018). **Conclusion:** Despite initial responses comparable to those previously reported in ADC, matched targeted therapy in pts with SCC and ASC histology is associated with shorter PFS. A higher prevalence of adverse co-mutations such as *TP53* and *PIK3CA* may contribute to early targeted therapy resistance in these histologies. These findings may have implications for the use of targeted therapy in squamous lung cancer.

Keywords: drivermutation, metastaticsquamousnsclc, squamousdrivermutation

MA14 THE ADEQUATE MTARGET IS STILL THE ISSUE
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MA14.11 CARETRACK: AN APPLICATION-BASED METHOD OF DOCUMENTATION FOR IMPROVING PATIENT COMMUNICATION IN CANCER CARE

J. Younus, J. Raphael, P. Blanchette, F. Khan, V. Sharma, M. Black, M. Vincent, S. Kuruvilla, M. Sanatani

London Regional Cancer Program, London/Canada

Background: Patients being able to accurately understand and recall medical information correctly has been shown to improve outcomes, however, most studies suggest that patient information understanding in oncology tends to be poor with as much as 40-80% of information being relayed by healthcare professionals being forgotten (Kessels, 2003). **Method:** Our study aimed to implement the use of 'CareTrack', an easy-to-use iPad application, as a simple yet complete app-based information package that provides an appointment summary sheet with no identifying information for patients to take home. An iPad pre-loaded with the CareTrack application was provided to oncologists and they filled in the form for their patients at the end of the initial consultation for lung cancer. A hard printout copy was provided to the patient to take home and the option of an email copy was sent as well. Approximately one-week later a patient satisfaction questionnaire was administered over the phone to patients who participated in the study. **Result:** Six oncologists were recruited to the study with 35 patients consented to the study and 25 of these patients completing the follow-up surveys. Our primary objective was to assess feasibility of the CareTrack application. The average physician time to complete the CareTrack form for each patient was 1 minute and 29 seconds thus demonstrating that this is a quick and easy tool for physician use. Our secondary objective was to assess patient satisfaction with a brief survey. Ninety-six percent (24/25) of patients found the CareTrack information provided useful and 100% (25/25) of patients found the information easy to understand. Most patients did not require frequent review of the CareTrack form (28%, 7/25) nor needed the form to remember the information (56%, 14/25) or when discussing diagnosis/stage/treatment at home (44%, 11/25). Importantly, 96% (24/25) of patients were comfortable seeing their cancer information and treatment plan displayed on the CareTrack tool and 84% (21/25) of patients would like to receive additional CareTrack information in the future if their staging and/or treatment planned is changed/updated. **Conclusion:** To conclude, the CareTrack application was found to be easy to use and was able to effectively provide new lung cancer patients with a comprehensive yet easy-to-understand summary of their initial consult. In the future, we envision this project expanding province- and nation-wide as well as expanding to other disease sites (e.g. breast, colorectal etc.).

Keywords: Lung cancer, Patient education, iPad application

MA15 USAGE OF COMPUTER AND MOLECULAR ANALYSIS IN TREATMENT SELECTION AND DISEASE PROGNOSTICATION
MONDAY, SEPTEMBER 9 15:45–17:15

MA15.01 CELLULAR PRION PROTEIN TRANSCRIPTIONALLY REGULATED BY NFIL3 ENHANCES LUNG CANCER CELL LAMELLIPODIUM FORMATION AND MIGRATION

S.-C. Lin[1], C.-H. Lin[2], N.-C. Shih[3], H.-L. Liu[1], W.-C. Wang[3], K.-Y. Lin[1], Y.-C. Lin[2], Y.-C. Yeh[2], H. Minato[4], T. Fujii[5], Y.-C. Wu[2], M.-Y. Chen[1], T.-Y. Chou[2]

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Background: Tumor invasion and metastasis are the major causes of treatment failure and mortality in lung cancer patients. However, the precise molecular targets responsible for tumor invasion remain unclear. **Method:** In this study, we identified a group of genes with differential expression in in situ and invasive lung adenocarcinoma tissues by cDNA microarray analysis; among these genes we further characterized the association of the upregulation of PRNP, the gene encoding cellular Prion protein (PrPc), with lung adenocarcinoma invasiveness through immunohistochemistry and in situ hybridization analysis on clinical tissues. The roles of PrPc in lung cancer cell lines were also verified by using immunofluorescence staining, *in vitro* transwell assay and in vivo metastasis mouse model. In addition, the impact of PrPc on the activation of the JNK signaling pathway was investigated by Western blot analysis. Finally, luciferase reporter assay and chromatin immunoprecipitation assay were used to identify the transcriptional activators of PRNP. **Result:** Immunohistochemistry on clinical specimens showed association of PrPc expression with invasive but not in situ lung adenocarcinoma. Consistently, the expression of PrPc was higher in the highly invasive than in the lowly invasive lung adenocarcinoma cell lines. Knockdown of PrPc expression in cultured lung adenocarcinoma cells decreased their lamellipodium formation, *in vitro* migration and invasion, and in vivo experimental lung metastasis. Phosphorylation of JNKs was found to correlate with PrPc expression and the inhibition of JNKs suppressed the PrPc-induced up-regulation of lamellipodium formation, cell migration, and invasion. Moreover, we identified the nuclear factor, interleukin 3 regulated (NFIL3) protein as a transcriptional activator of the PRNP promoter. Accordingly, NFIL3 promoted lung cancer cell migration and invasion in a PrPc-dependent manner. High NFIL3 expression in clinical specimens of lung adenocarcinoma was also associated with tumor invasiveness and poor survival of patients. **Conclusion:** Our observations suggest that PRNP expression is associated with the invasiveness of lung adenocarcinoma, and cell line model demonstrated that PrPc serves as a critical factor for lung cancer cell lamellipodia formation, migration and invasion via JNK signaling. A novel transcription factor, NFIL3, was identified to upregulate PRNP

expression in lung cancer cells; further characterizations showed that NFIL3 promotes lung cancer cell migration through PrPc-dependent manner. Moreover, high NFIL3 expression was found to be associated with lung cancer invasiveness in clinical tissues. Overall, NFIL3/PrPc axis plays a critical role in lung cancer invasiveness and metastasis, and may be the potential therapeutic targets in the future.

Keywords: Lung cancer invasiveness, NFIL3/PrPc, Lamellipodium

MA15 USAGE OF COMPUTER AND MOLECULAR ANALYSIS IN TREATMENT SELECTION AND DISEASE PROGNOSTICATION
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MA15.02 DEEP LEARNING APPROACH FOR AUTOMATED TUMOR CELLS DETECTION AND ESTIMATION OF PD-L1 22C3 ASSAY EXPRESSION IN LUNG ADENOCARCINOMA

D. Lin[1], J. Wu[1], W. Sun[1], C. Liu[2], X. Liu[2], Y. Zhang[2], J. Zhang[2], H. Wang[1], X. Liu[1], X. Yang[1], S. Ling[2]

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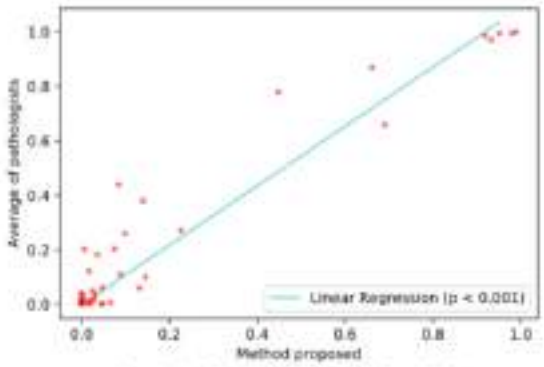
Background: It is vital and challenging to assess an accurate PD-L1 expression status on tumor cells for immunotherapy in lung cancer. The purpose of this study was to set up an automated system to detect the tumor cells and estimate the tumor proportion score (TPS) of PD-L1 immunohistochemistry (IHC) expression for lung adenocarcinoma based on deep learning, and provide a potential Artificial Intelligences (AI) assistive diagnostic tool in the quantification of PD-L1 interpretation. **Method:** Fifty PD-L1 22C3 IHC slides of lung adenocarcinoma samples on digitized whole-slide images (WSI) database was employed. We first designed a model with a fully convolutional neural network (FCNN) based on U-ResNet architecture to obtain the cancer segmentation. Representative regions were selected from each slide, and 100 regions were collected for manual annotations as a training set for cancer detection. Another 50 regions were used to validate the performance of automated cancer detection and TPS estimation as a test set. After the quality control, a whole model of automated cancer cell segmentation and membrane positive estimation was set up on standard PD-L1 22C3 IHC staining. TPS could be automatically predicted by AI tool and then compared with the interpretations of pathologists. **Result:** The results of automated lung adenocarcinoma cells segmentation on the test set of 22C3 IHC staining showed a moderate sensitivity (71.46%) with a high specificity (95.94%) which was much more crucial for TPS counting. In rest 43 out of 50 regions after a quality control, TPS estimated by the automated PD-L1 analysis based on cancer segmentation showed a significant correlation with the average scores (r=0.9609, p<0.001) and the median scores (r=0.9523, p<0.001) of pathologists' interpretations.

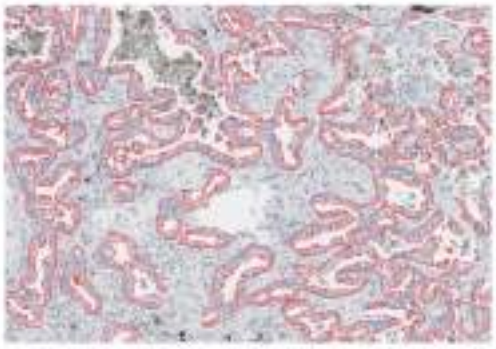
Table	Sensitivity	Specificity	Precision	Accuracy	F1-score
22c3 IHC cancer segmentation	71.46%	95.94%	92.08%	91.24%	79.68%

Performance of cancer detection model

TPS by pathologists and method proposed



Correlation between the average of pathologists and method proposed



Cancer segmentation result

Conclusion: We provide an automated tumor cells detection and TPS estimation model for lung adenocarcinoma and demonstrate the potential of using machine learning methods to access PD-L1 IHC status conveniently. A further validation of AI tool for automated scoring PD-L1 in diagnostic routine is highly recommended in the future.

Keywords: PD-L1, Tumor proportion score, Artificial Intelligence

MA15.03 EXPLORING DIGITAL PATHOLOGY-BASED MORPHOLOGICAL BIOMARKERS FOR A BETTER PATIENTS' SELECTION TO THE IMMUNE CHECKPOINT INHIBITOR OF LUNG CANCER

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Background: For eligible patients' selection for immune checkpoint inhibitor therapy (ICI), it is important to establish more accurate predicting biomarkers, in addition to PD-L1 IHC and MSI-high. We hypothesized that morphological characteristics should reflect genetic alteration, thus could predict ICI responsiveness. In this study, we examined the predictive potential of morphological characteristics using digital whole-slide images as a new biomarker for ICI-treatment on non-small cell lung cancer (NSCLC) and their relationship to PD-L1 IHC and genetic alterations. **Method:** 71 NSCLC who received ICI therapy were recruited. Digital images of H&E and PD-L1 (22C3) IHC stained slides of pre-treatment biopsied or resected materials were examined by previously reported image analysis techniques using e-Pathologist ® (NEC, Japan). Morphological characteristics of cancer cells (three and six parameters of nuclear shape and chromatin texture) were extracted as MC-scores. Of 11 cases (pilot cohort), PD-L1 IHC (22C3) and tumor mutation burden (TMB) by the NGS-based target sequence (NCC oncopanel ®) were examined. Correlation between MC-score, PD-L1 IHC, TMB status, and clinical outcome was calculated. A p-value of less than 0.05 was defined as statistically significant. Decision tree analysis for evaluating predicting ICI-responsiveness was built using statistically significant MC-scores. We also tested the predictive value of a deep learning analysis (AI model) with 5-fold cross-validation. AUC (area under the curve) of ROC analysis was calculated. **Result:** Of the responders, the MC-score of cancer cell were statistically different from those of the non-responders; nuclear texture contour complexity (11.8 vs. 8.25, median value of responder vs. non-responders; p<0.01), homogeneity (0.396 vs. 0.421; p<0.01), angular second moment (ASM) (0.0203 vs. 0.0214; p=0.049) and nuclear circularity (0.878 vs. 0.885, p=0.026). Circularity (p=0.011) and texture homogeneity (p=0.048) correlated with TMB. ASM texture correlated with PD-L1 expression (p=0.018). The decision tree model for predictive and screening purposes resulted in 0.83 and 0.62 accuracies, respectively. AUC of AI-model for ICI responsiveness resulted in fair (0.74 on average, range 0.55-0.81). **Conclusion:** Our results indicate the substantial value of the morphological feature as a biomarker for ICI therapy. Morphological characteristics are eligible from archived FFPE samples, showed good correlation to the underlying genetic alteration. Digital pathology can serve useful predictive morphological biomarkers for precision medicine of lung cancer patients, and promising the power of AI-assisted pathology.

Keywords: morphological characteristics, digital pathology, predictive biomarker for immune checkpoint inhibitor

MA15 USAGE OF COMPUTER AND MOLECULAR ANALYSIS IN TREATMENT SELECTION AND DISEASE PROGNOSTICATION
MONDAY, SEPTEMBER 9 15:45–17:15

MA15.05 COMPUTERIZED MEASUREMENTS OF CELLULAR DIVERSITY ON H&E TISSUE ARE PROGNOSTIC OF OS AND ASSOCIATED WITH MUTATIONAL STATUS IN NSCLC

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Background: Tumor heterogeneity is known to be implicated in chemotherapeutic resistance and poor prognosis for non-small cell lung cancer (NSCLC). In this study we sought to evaluate the role of computer extracted features reflecting the intrinsic cellular morphological diversity (ICMD) of tumors from digitized H&E stained images of early-stage NSCLC patients. Additionally, we sought to evaluate the association of these ICMD features in adenocarcinomas with the ALK and EGFR mutational status. **Method:** Two cohorts, D_1 and D_2, of digitized H&E stained tissue microarray images (TMA) of NSCLC, n=395 and n=91, respectively, were used for modeling the ICMD predictor. A pretrained deep learning model was used for segmentation of nuclei, and clusters of proximally located nuclei were identified. The ICMD features were then extracted as the variations in shape, size, and texture measurements of nuclei within the clusters. A Cox proportional hazard model using the ICMD features was then trained for lung adenocarcinomas (LUAD, n=270), and squamous cell carcinomas (LUSC, n=216), separately, and was validated on independent cohort from (D_3) The Cancer Genome Atlas (TCGA) (n=473) to predict Overall Survival (OS). Univariate and multivariate analyses were performed on (D_3). **Result:** In (D_3), high risk patients predicted by the ICMD features had significantly poorer survival (HR (95% CI) = 1.48 (1.06-2.06), p=0.021 for LUSC, HR (95% CI) = 1.59 (1.11-2.29), p=0.006 for LUAD) in univariate analysis. In multivariate analysis, controlling for major clinical variables, ICMD was independently associated with 5-year OS (p<0.016). (See Table 1) We also found that ICMD features were associated with driver mutations ALK (p=0.0204) and EGFR (p=0.0017) in LUAD. Table 1| Multivariate analysis for overall survival on the validation set D_3.

Multivariate Cox Proportional Hazard Model Analysis Controlling for Other Variables				
	TCGA-LUSC		**TCGA-LUAD**	
Variable	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (>65 vs <=65)	1.14(0.81-1.61)	0.451	0.89(0.63-1.28)	0.540
Smoking status	1.36(0.83-2.23)	0.221	1.14(0.64-2.01)	0.661
Overall Stage (Stage II vs I)	1.13(0.66-1.94)	0.651	1.86(1.04-3.32)	0.037
T-Stage (T2,3 vs T1)	1.26(0.85-1.87)	0.244	1.25(0.85-1.85)	0.263
N-Stage (N1 vs N0)	1.36(0.77-2.41)	0.292	3.11(1.55-6.23)	0.001
Developed Model High risk vs. Low risk 1.52(1.08-2.13)		0.016	1.55(1.09-2.22)	0.015
CI = 95% confidence interval; HR = Mantel-Haenszel Hazard ratio. Values in bold are statistically significant, p<=0.05.				

Conclusion: Computer extracted image features of cellular diversity were able to predict OS in NSCLC and were also associated with the ALK and EGFR mutational status. Future work will entail evaluating ICMD features in predicting added benefit of adjuvant therapy in early stage NSCLCs as well as correlating with gene expression data.

Keywords: Early stage non-small cell lung cancer, computational pathology, digital pathology

MA15.06 STAGE I LUNG ADENOCARCINOMA GENE EXPRESSION ASSOCIATED WITH AGGRESSIVE HISTOLOGIC FEATURES FOR GUIDING PRECISION SURGERY AND THERAPY

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Background: Stage I lung adenocarcinomas (LUADs) show heterogeneity in histologic patterns which correlate with malignant behavior. Solid, micropapillary and cribriform patterns are associated with worse survival whereas lepidic (in situ) predominance has the best prognosis. In this study, we sought to characterize histologic pattern specific gene expression in resected clinical stage I LUADs. We also aimed to train and validate a genomic biomarker predictive of histologic aggressive patterns with the ultimate goal of being able to impact surgical and therapeutic decision making for post-biopsy management. **Method:** A training cohort of 56 tumors from patients meeting NCCN high-risk screening criteria with stage I LUAD was included for pathologic annotation and whole exome RNA sequencing. Histologic pattern subtyping in 5% increments including all diagnostic slides was performed. A single representative FFPE block was chosen for RNA library-prep with Illumina TruSeq Access Kit and sequencing. Negative binomial models were used to identify gene expression differences associated with percent solid, cribriform, or micropapillary histology, and EnrichR was used for gene pathway enrichment analysis. Ss-GSEA was used to predict tumor infiltration of 20 immune cell types. A random-forest classifier for predicting aggressive histologic patterns was trained using 5-fold cross validation. A set of tumors from 16 independent patients with ≤2.0 cm clinical stage I LUAD was macro-dissected into 32 paired components (lepidic + non-lepidic regions) and subjected to RNAseq. Six tumors were defined as non-aggressive (lepidic + acinar/papillary) and ten tumors were defined as aggressive (lepidic + solid/micropapillary/cribriform). Four aggressive tumors were upstaged after surgical resection. **Result:** In the training cohort, we identified 1322 genes associated with tumor histologic composition(FDR q <0.05 and fold-change > 2). Genes whose expression differs with solid histology% are enriched for involvement in DNA replication, cell cycle regulation and inflammation (FDR q<0.001). Genes whose expression is associated with micropapillary% are enriched for involvement in tRNA-aminoacylation and decrease of T-cell activity (FDR q<0.001). The functional enrichment of genes whose expression is associated with cribiform% was less informative. LUADs with micropapillary patterns exhibited gene expression consistent with decreased antigen presentation and low T-cell infiltration, and solid patterns exhibited gene expression consistent with increased infiltration of T-regulatory and Th2 cells (FDR q<0.05). A gene expression classifier was trained to predict the presence of aggressive histologic patterns. We validated this classifier on a set of 16 tumor specimens from which we macro-dissected and analyzed tissue from the most aggressive histologic pattern (AUC = 1.00). We also found that this classifier could differentiate lepidic regions isolated from aggressive tumors from lepidic regions isolated from non-aggressive tumors (AUC = 0.74). **Conclusion:** We identified solid-, micropapillary- and cribriform-specific gene expression and associated immune response among clinical stage I LUADs, and developed a classifier predictive of aggressive histologic features using either lepidic (in situ) or non-lepidic components. As such, this biomarker has the potential to predict histologic aggressiveness even from pre-surgical tumor biopsies where all histologic patterns may not be represented. Such a biomarker may be useful in guiding clinical decision making including extent of surgical resection.

Keywords: Aggressive Histologic Features, LUAD Gene Expression, Biomarker for precision surgery and therapy

MA15 USAGE OF COMPUTER AND MOLECULAR ANALYSIS IN TREATMENT SELECTION AND DISEASE PROGNOSTICATION
MONDAY, SEPTEMBER 9 15:45–17:15

MA15.07 CIRCULATING MIRNA: A BIOMARKER FOR CLASSIFICATION OF LUNG CANCER AND BENIGN LUNG DISEASE

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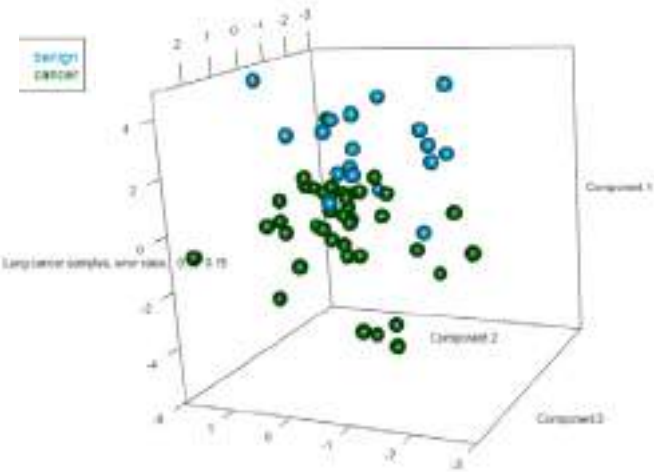
Background: Circulating biomarkers for cancer have great potential for diagnosis as well as follow up of treatment. MicroRNAs (miRNA) are involved in the expression of a majority of proteins with different cell types having different miRNA expression. The aim of this study was to create a circulating miRNA-based model to discriminate patients with lung cancer from patients with benign lung disease. **Method:** Samples were collected from patients under investigation for lung cancer at Örebro University hospital. Patients were then divided into groups based on diagnosis, which resulted in NSCLC adenocarcinoma (n=24), NSCLC squamous cell carcinoma (n=13), SCLC (n=4) and a heterogeneous group consisting of different benign lung diseases (n=19). Healthy controls were collected separately (n=17). Circulating miRNA was processed using the extraction-free library preparation miRNA Whole Transcriptome Assay with probes for 2083 human mature miRNAs and analyzed with massive parallel sequencing. Differential expression between groups was estimated using edgeR. MiRNAs that had the highest impact on patient grouping were used in a sPLS discriminant analysis. The resulting classification model was validated using the leave-one-out method. **Result:** The final model for comparison between patients with benign lung disease and patients with lung cancer contained 19 miRNAs. The model had an error rate of 15 % with errors distributed evenly between groups. A sub-analysis of patients with mutations in EGFR (n=5) and KRAS (n=6) was performed showing two distinct patterns in miRNA expression.



Conclusion: MiRNA shows promise as a circulating biomarker for lung cancer but may not be sufficient as an independent classifier. The predictive power may be improved by using several biomarkers in combination. The difference in expression between tumors with different mutations may be derived from alternate driving processes in these tumors.

Keywords: microRNA, Circulating biomarkers

MA15.09 PD-L1 STATUS IN RELATION WITH NON-SMALL CELL LUNG CANCER MAJOR SUBTYPES, DIFFERENTIATION, MOLECULAR PROFILING AND SMOKING HISTORY

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Dalhousie University/QEII HSC, Halifax/Canada

Background: Continued advances in lung cancer precision medicine have allowed targeted therapies based on an individual tumor's genetic makeup. Recent advances in immune therapy based on immune checkpoint inhibitors have provided additional promising results. Currently, the majority of lung cancer mutational data available in the literature are from advanced stage non-small cell lung cancer. Mutational data from early stage lung cancer patients is limited. There is also limited data on PD-L1 tumor status is relation to mutational status along with other pathological and clinical characteristics. In this study, we evaluated these issues in 871 cases of surgically resected lung cancer. **Method:** Multiplexed molecular profiling in 871 surgically resected lung cancer specimens was performed. A panel of genes including EGFR, KRAS, BRAF, PIK3CA, HER2 and ALK was tested. Tumor PD-L1 status was also evaluated by immunohistochemistry using pharmDx22C3. PD-L1 status was measured by tumor proportional score (TPS): <1%, 1-49% and ≥50% tumor cell positivity. Correlations between PD-L1 and gene mutation status, smoking history, histological grade, gender and age of paraffin embedded blocks were analyzed. **Result:** This cohort includes adenocarcinoma (68%), squamous cell carcinoma (SCC) (22%) and other subtypes (10%). The average age is 67. Females account for 52%. A positive smoking history was present in 93%. Well differentiated tumors (G1) account for 11%, moderately differentiated (G2) 37% and poorly and undifferentiated (G3) 52%. EGFR mutations were identified in 7.4% and KRAS mutations in 31.7%. TPS <1% accounted for 48.8%, 1-49% for 34.6% and ≥50% for 16.5%. There was no statistically significant difference in PD-L1 TPS between histological subtypes or gender. Significantly more G1 tumors had a TPS <1% (76.7%) compared to G2 (57.4%, p=0.0013) and G3 tumors (41.8%, p<0.0001). Fewer G1 tumors had a TPS 1-49% (20.9%) than G2 (34.1%, p=0.015) and G3 (35.2%, p=0.01) tumors. G3 tumors were more likely to have a TPS ≥50% (24.6%) than G1 (2.3%, p<0.0001) and G2 (7.63%, p<0.0001) tumors. Never smokers were more likely to have a TPS <1% (71.1% vs 50.6%, p=0.04) and less likely to have a TPS ≥50% (5.8% vs 16.5%, p=0.04). Tumors with EGFR mutation were more likely to have a TPS <1% than those without EGFR mutation (70.7% vs 47.3%, p=0.0003) and less likely to have a TPS 1-49% (20.0 vs 35.5%, p=0.011). Tumors with KRAS mutations were less likely to have a TPS <1% (36.6% vs 54.9%, p<0.0001) and more likely to have a TPS 1-49% (40.6% vs 31.5%, p=0.0086) and ≥50% (22.8% vs 13.6%, p=0.0007). PD-L1 IHC performed on blocks stored for 2 years or longer had a statistically significant higher rate of TPS <1% compared to blocks stored for less than 2 years. **Conclusion:** This study provides information relating to the relationship between PD-L1 levels and tumor molecular profile, histological grade and patient demographics. Additionally, we raise the possibility of false negatives on IHC performed for PD-L1 on paraffin embedded blocks stored for 2 years or more.

Keywords: PD-L1, gene mutations, Molecular profiling

MA15.10 STROMAL MARKERS OF ACTIVATED TUMOR ASSOCIATED FIBROBLASTS PREDICT POOR SURVIVAL AND ARE ASSOCIATED WITH NECROSIS IN NON-SMALL CELL LUNG CANCER

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Background: Tumor associated fibroblasts (TAFs) are essential contributors of the progression of non-small cell lung cancer (NSCLC). Most lung TAFs exhibit an activated phenotype characterized by the expression of α-SMA and fibrillar collagens. However, the prognostic value of these activation markers in NSCLC remains unclear. **Method:** We conducted a retrospective multicentric study of the prognostic value of the standard markers of activated fibroblasts. For this purpose, we conducted a quantitative image analysis of α-SMA immunostaining and picrosirius red staining of fibrillar collagens imaged by bright-field and polarized microscopy, respectively, using tissue microarrays with samples from 220 surgical patients, which elicited a percentage of positive staining area for each marker and patient. **Result:** Kaplan-Meier curves showed that all TAF activation markers were significantly associated with poor survival, and their prognostic value was independent of TNM staging as revealed by multivariate analysis, which elicited an adjusted increased risk of death after 3 years of 129% and 94% for fibrillar collagens imaged with bright-field (p = 0.004) and polarized light (p = 0.003), respectively, and of 89% for α-SMA (p = 0.009). We also found a significant association between all TAF activation markers and tumor necrosis, which is often indicative of hypoxia, supporting a pathologic link between tumor desmoplasia and necrosis/hypoxia. **Conclusion:** Our findings identify patients with large histologic coverage of fibrillar collagens and α-SMA+ TAFs to be at higher risk of recurrence and death, supporting that they could be considered for adjuvant therapy. Moreover it supports that antifibrotic drugs aiming to target tumor fibrosis may be an effective therapeutic approach to improve survival in NSCLC.

Keywords: fibrosis, staging, prognosis

MA15.11 ESTABLISHING A CELL SOCIOLOGY PLATFORM FOR THE ASSESSMENT OF TARGETABLE INTERACTIONS TO PREDICT LUNG CANCER OUTCOME

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Background: The tumor microenvironment (TME) is a complex mixture of tumor epithelium, stroma and immune cells. The immune component of the TME is highly prognostic for tumor progression and patient outcome. Immune functionality, however, is often dictated by direct cell-to-cell contacts and cannot be resolved by simple metrics of cell density (for example, number of cells per mm2 or flow cytometry). For example, direct contact between CD8+ T cells and target cells is necessary for CD8+ T cell activity, and direct contact between PD1+ and PD-L1+ cells is necessary for the efficacy of immune checkpoint inhibitors. Current immunohistochemistry (IHC) techniques identify immune cell numbers and densities, but lack assessment of spatial relationships (or "cell sociology"). Here, we develop a platform to examine these direct interactions within the TME, and assess their relationship with patient outcome in two independent non-small cell lung cancer (NSCLC) cohorts. **Method:** Tissue sections of primary tumors from lung adenocarcinoma (LUAD) patients with known clinical outcome were stained using 2 multiplex IHC panels: CD3/CD8/CD79a (Panel 1) and PD1/PDL1/CD8 (Panel 2).

Hyperspectral image analysis determined the phenotype of all cells. Using the same IHC panels, these observations were assessed in a secondary NSCLC dataset (n=674). Deconvolution of these images was used to identify cell types, and cellular 'neighborhoods' were assessed using a Voronoi approach. This cohort was also profiled by for gene expression to validate immune subset fractions. We further identified other tumor features, including the presence of tertiary lymphoid organs (TLOs; transient immune structures necessary for antibody production from B cells). **Result:** High density of intra-tumoral CD8+ T cells was associated with non-recurrence of tumors. However, we find that a non-random cell sociology pattern of CD8+ T cells directly surrounded by tumor cells was more significantly associated with non-recurrence compared to density alone. Monte Carlo re-sampling analysis determined that these cell sociology patterns were non-random. **Conclusion:** Hyperspectral cell sociology expands our understanding of the complex interplay between tumor cells and immune infiltrate. This technology improves our understanding of the tumour microenvironment and allows us to directly quantify interactions that dictate immune responses to cancers. Consequently, the implementation of this platform could improve predictions of responses to immunotherapy and lead to a deeper understanding of anti-tumor immunity.

Keywords: imaging, Immunotherapy, Histology

MA16 PRIORITIZING USE OF TECHNOLOGY TO IMPROVE SURVIVAL OF LUNG CANCER SUBGROUPS AND OUTCOMES WITH CHEMOTHERAPY AND SURGERY
MONDAY, SEPTEMBER 9 15:45–17:15

MA16.01 PROJECT PRIORITY: A PATIENT-FOUNDED AND PATIENT-DRIVEN RESEARCH PARTNERSHIP ON REAL-WORLD DATA ON EGFR-POSITIVE LUNG CANCER

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Background: Despite increases in PFS in EGFR-positive lung cancer patients due to EGFR TKIs, patients eventually develop resistance to these drugs. Project PRIORITY (**P**atient **R**eported **I**nitiative **O**n **R**esistance, **I**ncidence, **T**reatment stud**Y**) is a patient-founded and patient-driven longitudinal study aimed at understanding unmet needs of the global EGFR-positive lung cancer community. **Method:** A comprehensive 103-question, IRB-approved patient-facing survey about the diagnostic and treatment journey of patients (including risk factor exposure, treatments, symptom and side-effect management, access to biomarker testing and clinical trials) was developed with input from US FDA statisticians and expert clinicians, and then pilot-tested among English-speaking patients both locally and internationally. Differences between US and international participants were analyzed by Chi-square (for categorical variables) and ANOVA. **Result:** Of the 253 respondents, 27.7% were international participants. In line with previous studies with EGFR patients, participants reported low rates of active tobacco exposure (16.4%) and high rates of second-hand tobacco exposure (34.7%). Also, first-line use of afatinib (OR = 2.5, p <0.05) and erlotinib (OR = 3.3, p< 0.05) were associated with the development of a T790M mutation reflecting similarity in clinical characteristics. US participants were more likely to report childhood exposure to secondhand smoke, family history of cancer (other than lung cancer), use of more than one line of therapy, and combination first-line therapy (P<0.05 for all variables). International participants were more likely to report first-line treatment with 1st/2nd generation TKI, less use of tissue and plasma NGS, lower clinical trial participation, and more use of whole-brain radiation for brain metastasis (P<0.05 for all variables). **Conclusion:** This first-of-its-kind international study provides a comprehensive picture of the treatment of EGFR-positive lung cancer patients in the real-world setting and highlights the existence of diagnostic (low NGS rates) and treatment gaps (low clinical trial participation and different treatment sequencing) both within the US and internationally.

Category	Sub-category	US resident	International
	Bold values are significant	**N = 183**	**N = 70**
Year of diagnosis	Within past 5 years	83.2%	85.1%
Age in years (± S.D.)		**57.8 (11.9)**	**54 (10.5)**
NGS tissue	Once	**27.3%**	**8.2%**
	More than once	**13.4%**	**1.4%**
	Never	**32.9%**	**64.4%**
	I do not know	26.2%	26.0%
NGS liquid	Once	29.5%	26.4%
	More than once	15.5%	1.4%
	Never	**39.3%**	**59.7%**
	I do not know	15.5%	12.5%
No of lines of therapy received	One	41.5%	57.5%
	Two	28.7%	28.8%
	Three or more	29.7%	13.7%
First line of therapy	Combination of more than one treatment	**27%**	**13.8%**
	Erlotinib	**28.7%**	**36.9%**
	Afatinib	**13.3%**	**20.6%**
	Gefitinib	**0%**	**10.9%**
	Osimertinib	**34.5%**	**17.8%**
	Chemotherapy	**19.2%**	**9.6%**
	Immunotherapy	**4.8%**	**0%**
	Radiation	**19.7%**	**10.9%**
Doctor offered clinical trials	Yes	**33.7%**	**22.9%**
Ever participated in a clinical trial	Yes	**21.2%**	**12.9%**
Treatment for brain metastasis	Yes	**36.4%**	**17.1%**
Type of treatment for brain metastasis	Whole brain radiation	**14.7%**	**33.3%**
	SRS	**60.3%**	**50.0%**
	Surgery	**14.7%**	**8.3%**
	Controlled by TKI	**48.5%**	**33.3%**

Keywords: EGFR, Real-world data, targeted therapies

MA16.02 T790M ALLELIC FRACTION LEVEL DID NOT CORRELATE SURVIVAL IN T790M POSITIVE NSCLC – OBSERVATIONS FROM AN EARLY ACCESS PROGRAM

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Background: Osimertinib is an irreversible third-generation EGFR-TKI indicated for patients with metastatic EGFR T790M mutation positive NSCLC after progression of initial TKI therapy. An early access program (EAP) was started in 2015 providing ethical access of Osimertinib to patients with metastatic NSCLC running out of treatment options in Hong Kong. As some prior data suggested that T790M allele fraction (AF) correlated survival outcomes in patients receiving Osimertinib, we try to validate it with data from this EAP. Survival outcomes and safety data of Osimertinib in the real world practice under this EAP were also analysed. (NCT03219970) **Method:** This retrospective analysis included EAP patients who had advanced or metastatic NSCLC harbouring EGFR T790M mutation that progressed on prior TKI ± chemotherapy. EAP subjects received Osimertinib at 80mg daily until disease progression, intolerable toxicities or death. The T790M mutation can be assessed by any approved molecular tests in any specimen types. The AF levels in patients with T790M mutation confirmed by quantitative plasma genotyping (QPG) using ddPCR technique of the same vendor were retrieved. The primary objective was to assess the relationship of post-Osimertinib overall survival (OS) and T790M AF level. Secondary objectives included investigator-assessed response, time to discontinuation (TTD) of Osimertinib, safety (Osimertinib-related adverse events of special interest, AESIs) and OS of all EAP participants. **Result:** From Sep 2015 to Feb 2017, 156 patients enrolled in the EAP and received treatment. At time of data cut-off (11 Oct 2018), 74 (47%) were alive. Median follow-up was 23.4 (range: 1–30) months, median age 62 years, 62% female, 26% ECOG PS ≥2, 96.8% with metastatic disease. Besides T790M, 56% of patients had exon 19 deletions and 41% had exon 21 L858R mutations. Ninety-one patients had QPG using ddPCR method with AF data. OS, best response rate and TTD were not significantly related to T790M AF level as a continuous variable (p=0.20; hazard ratio 1.022, 95% CI 0.989 to 1.057), confirmed through sensitivity analysis with different AF threshold values. The investigator assessed best response rate was 41.7% (65/156) and disease control rate was 62.2% (97/156). Median TTD was 15.77 (12.43, 18.98) months. Median OS was 21.88 (95% CI 19.14–26.21) months. AESIs were reported in 7.7% of patients overall: 5.8% QTc prolongation and 1.9% pneumonitis. **Conclusion:** T790M AF level did not correlate with TTD and OS in this EAP cohort but the limitations should not be overlooked. The survival outcomes concurs other reported series.

Keywords: Osimertinib, Allelic fraction, Early access program

MA16 PRIORITIZING USE OF TECHNOLOGY TO IMPROVE SURVIVAL OF LUNG CANCER SUBGROUPS AND OUTCOMES WITH CHEMOTHERAPY AND SURGERY
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MA16.03 BIG DATA ANALYSIS FOR PERSONALIZED MEDICINE IN LUNG CANCER PATIENTS

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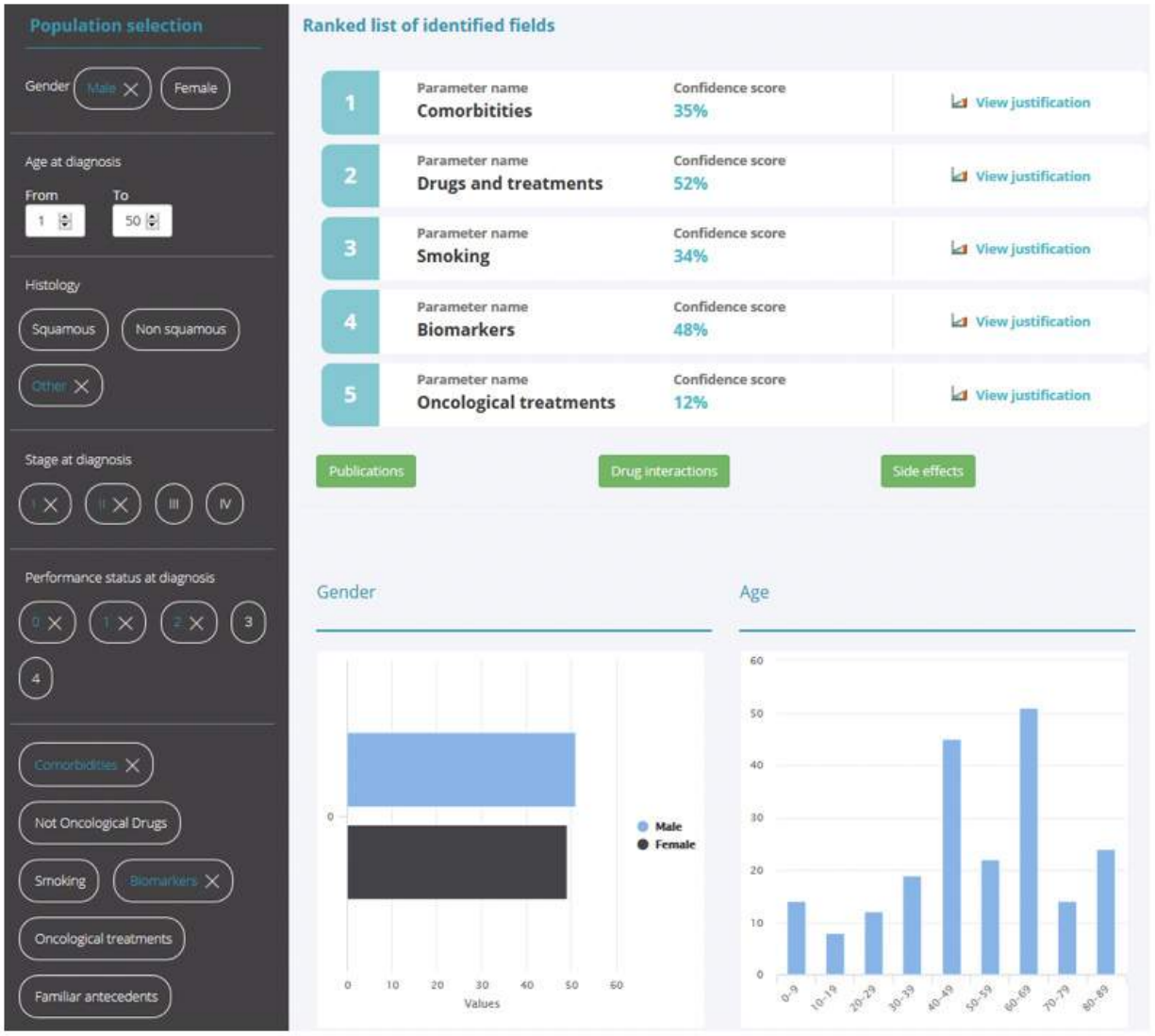
Background: The use of Big Data in healthcare is in its early days, and most of the potential for value creation remains unclaimed. Electronic Health Records (EHR) contain a large amount of information about the patient's condition, which can potentially revolutionize the clinical practice, such information is seldom considered due to the complexity of its extraction and analysis. We report on a first integration of an NLP framework for the analysis of clinical records of lung cancer in Puerta de Hierro University Hospital (HUPHM). **Method:** A cohort of 1000 patients diagnosed of non-small cell lung cancer (NSCLC) from 2009 to 2018 at HUPHM were included in this observational study. Unstructured clinical data were obtained from the EHR. The semantic indexing and the information analysis was performed by the Politecnica University of Madrid, using Big Data and machine learning techniques. Clinical notes were converted into usable data, and combined with genomic data, images and bibliography, such as PubMed or Drugbank. **Result:** A total of 251.730 documents were analyzed (240.851 notes and 10.879 reports). These heterogeneous sources of information were analyzed and integrated in an interactive user interface (Figure 1). As a result, all this large amounts of data turns into actionable and exploitable information for clinicians and authorities for planning public health policies and also create new clinical trials. The interactive platform will allow the clinician obtain immediate and personalized information of each patient and will elaborate predictive models for long survivors, identify risk patients, reduce overtreatments, etc. **Conclusion:** By using Big Data we will be able to exploit large amounts of clinical information and combine them with multiple databases developing interactive user interface, increasing lung cancer knowledge and directing medicine towards a more personalized one. This work was supported by the EU H2020 programme, under grant agreement Nº 727658 (Project iASiS).



Keywords: predictive models, Big data, interactive platform

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MA16.05 WEARABLE TECHNOLOGY FOR PRECONDITIONING BEFORE THORACIC SURGERY: A FEASIBILITY STUDY

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Background: Preconditioning before surgery can lower complication rates, but there are significant barriers to its adoption in the lung cancer population, which is characteristically older, suffers multiple comorbidities, and is averse to exercise. In an effort to overcome these barriers, we designed Move For Surgery (MFS), a home-based, preoperative preconditioning program which involves aerobic exercise using wearable technology and deep breathing exercises. We aimed to test the feasibility of MFS in preparation for a randomized controlled clinical trial. **Method:** In this prospective feasibility study, patients undergoing resection for NSCLC were preoperatively enrolled and provided with a wearable activity tracker (Fitbit) and a booklet describing various aerobic exercises, deep breathing exercises, and nutritional and smoking cessation tips. The daily step count, sleep cycle, and calories burned were synced and tracked remotely. Daily step goals were set by increasing the participants' baseline step count by 600 steps each week until the day of surgery. Participants were encouraged and motivated to reach their daily step goal by daily automatic reminders through the Fitbit. Participants completed the EQ-5D-5L health-related quality of life instrument at baseline and on the day of surgery. Data is presented as mean +/- SD and median (range). Continuous variables were compared using Student's t-test, and categorical variables were compared using Chi-square or Fischer's exact test, with a level of significance p<0.05. **Result:** Of the 40 patients screened, 62.5% (25/40) were eligible and enrolled. Of the 15 not eligible, 80% (12/15) did not have a smartphone. Participants (n=25) were enrolled from 11/2017 to 07/2018. Median age was 62 (33-82) and 72% (18/25) were women. The mean predicted FEV1 and DLCO were 88.9% +/- 23.4% and 74.9% +/- 19.8% respectively. Participants spent a median of 25 days (8-55) on trial, and wore their Fitbits 90.0% +/- 25.2% of the time. The mean baseline daily step count for this cohort was 7,586 +/- 4,082, and the participants were able to achieve the daily step goal in 40.8% +/- 30.0% of the time. Participants with higher baseline step counts (≥6,000/day) were more likely to achieve the daily step goals (52.2% vs 20.5%; p=0.0083). Significant improvement was seen in the overall health component of the EQ-5D-5L from before the intervention (76.4 +/- 15.45) to after the intervention (80.4 +/- 14.57; p=0.03). Overall, 96.0% (24/25) of the participants completed the recommended deep breathing exercises,

100% (25/25) recommended MFS for future patients, and 96.0% (24/25) stated they will buy their own Fitbits and continue this lifestyle post-surgery. **Conclusion:** A preoperative preconditioning trial with wearable technology prior to lung cancer resection is feasible based on encouraging enrollment rates, use of the device, and goal achievement, but it is only applicable to participants with smart devices. MFS motivates patients to undergo preconditioning before lung cancer resection and to continue with a healthy lifestyle after surgery. A revision of the daily step goal is required to improve compliance. A randomized trial is in progress to determine the impact of MFS on postoperative outcomes in the thoracic surgery population.

Keywords: Preconditioning, Wearable Technology, Thoracic surgery

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MA16.06 DETERIORATION IN HEALTH-RELATED QUALITY OF LIFE DIMINISHES BENEFIT OF LUNG CANCER RESECTION IN OLDER ADULTS

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Background: Outcomes of oncologic resection are related to tumor biology as well as patient-reported health factors. However, data regarding changes in functional status and health-related quality of life (HRQOL) before and after lung surgery are currently lacking. **Method:** We identified lung cancer patients from the SEER-Medicare Health Outcomes Survey (MHOS) linked database. HRQOL survey data captured physical/mental health, activities of daily living (ADLs), and medical comorbidities. Patients who underwent surgery with 1) baseline HRQOL survey prior to cancer diagnosis and 2) follow-up survey at least one year after diagnosis were selected. Patient, disease, and HRQOL measures were analyzed using Cox proportional hazards regression in regard to overall survival (OS) and disease-specific survival (DSS). **Result:** Overall, 138 patients were evaluated, of whom 67 (49%) were male. Mean age at diagnosis was 74 years. The majority of patients were Caucasian (n=112, 81%). Disease extent was localized for 75 (54%), regional for 58 (42%), and distant for 5 (4%). In general, the cohort experienced a decline in physical HRQOL, mental HRQOL, and ADLs; and an increase in the number of major comorbidities (see Table). Median OS was 74 months. Decreased OS was independently associated with male sex (HR 1.7, p=0.03), more advanced disease (regional vs. localized: HR 1.8; distant vs. localized: HR 2.1; p=0.04), and decline in ADLs (HR 1.8, p=0.02). Decreased DSS was independently associated with male sex (HR 2.2, p=0.03), more advanced disease (regional vs. localized: HR 2.9; distant vs. localized: HR 3.1; p=0.01), and decline in mental HRQOL (OR 2.1, p=0.02).

Variable		Baseline	Follow-Up
Physical HRQOL	At or above population mean (score 50+)	37 (27%)	8 (6%)
	Below population mean (score <50)	101 (73%)	130 (94%)
Mental HRQOL	At or above population mean (score 50+)	94 (69%)	83 (60%)
	Below population mean (score <50)	43 (31%)	55 (40%)
Katz ADL scores	Independence with each ADL = 1 point	5.4 (±1.1)	4.6 (±1.8)
Bathing	No difficulty	126 (91%)	102 (74%)
	Have difficulty or unable to do	10 (7%)	36 (26%)
Dressing	No difficulty	133 (96%)	110 (80%)
	Have difficulty or unable to do	5 (4%)	28 (20%)
Eating	No difficulty	135 (98%)	123 (89%)
	Have difficulty or unable to do	3 (2%)	15 (11%)
Getting in and out of chairs	No difficulty	119 (86%)	100 (72%)
	Have difficulty or unable to do	18 (13%)	38 (27%)
Walking	No difficulty	102 (74%)	77 (56%)
	Have difficulty or unable to do	36 (26%)	58 (42%)
Using the toilet	No difficulty	133 (96%)	124 (90%)
	Have difficulty or unable to do	5 (4%)	14 (10%)
Total number of self-reported comorbidities	0	72 (53%)	57 (42%)
	1	48 (35%)	56 (42%)
	≥2	17 (12%)	22 (16%)

HRQOL = health-related quality of life; ADL = activity of daily living

Conclusion: The potential survival benefit of lung resection for malignancy is diminished by declines in physical and mental health. Among older surgical patients at risk for functional and HRQOL deterioration, identification and mitigation of such deterioration may in turn optimize oncologic outcomes.

Keywords: Surgical Outcomes, patient-reported outcomes, Health-related quality of life

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MA16.07 IMPLEMENTATION OF A SMARTPHONE APP TO FACE POSTOPERATIVE PERIOD IN PATIENTS WITH NSCLC UNDERGOING LUNG RESECTION SURGERY

C. Fraile Olivero[1], L. Milla Collado[1], J. Jarabo Sarceda[2], E. Fernández Martín[2], C. Cerdan Santacruz[3], J. Gastardi[2], A. Gómez Martínez[2], P. Arribas Manzanal[4], P. Santos Capa[4], M. Martínez Tardido[4], V. Alen[2], F. Hernando-Trancho[2]

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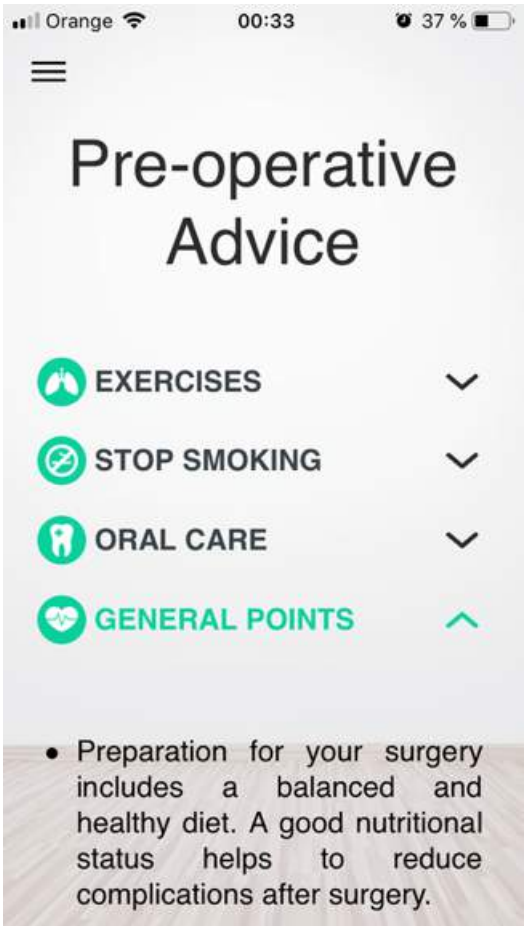
Background: Preoperative patient education and counseling helps to set expectations about surgical procedure and to prepare for it. Thoracic surgery procedures are related to postoperative complications and strategies to reduce them begin prior to surgery. Lung expansion maneuvers, the importance of early ambulation and pain control are best taught before the procedure. The aim of this prospective study was to implement the use of a smartphone application in a cohort of patients undergoing lung resection surgery and describe their feedback results. **Method:** We created a Smartphone application as a multidisciplinary tool including: peri-operative medical advice (stop smoking, mouth health, early mobilization and pain control) (Fig1), ten chest physical exercises (with animated images) and programmable Smartphone daily notifications. Complete information to download, set up and interaction with the software was given to patients. A Multiple-Choice-Question survey was applied to patients at the moment of hospital discharge in order to evaluate their experience. This prospective and observational study included clinical data and results of surveys applied.



Result: A total of 68 patients interacted with the application before surgery and answered the survey after the procedure. Median age was 66.5 years and 67.6% were males. Of them, 51 patients (75%) considered the content "very compressible". 54 patients (79.4%) considered "positive" the contribution of the application to face the postoperative period. Additionally, 31 patients (45.6%) deemed "appropriate" the quantity of time and physical effort needed to complete the interaction with the tool and reach the goals. **Conclusion:** This is the first smartphone application created by thoracic surgeons to improve patient´s education and helps them to prepare for surgery. This new technological tool was successfully implemented in our thoracic surgery department. For patients, it is easy to download, setup and contents comprehensible information that contributes to face positively the postoperative period with an adequate physical effort and quantity of time.

Keywords: Postoperative Pulmonary Complications, Chest Physical Therapy, Smartphone Application

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MA16.09 CLINICAL PRACTICE AND OUTCOMES IN PATIENTS WITH STAGE III UNRESECTABLE NON-SMALL-CELL LUNG CANCERAN ACADEMIC CENTRE, CANADA

G. Kasymjanova[1], D. Small[1], C. Pepe[1], L. Sakr[1], V. Cohen[1], M. Lecavalier[1], H. Wang[1], A. Spatz[1], M. Hurry[2], R. Walton[2], J. Agulnik[1]

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Background: The prognosis of patients with stage III unresectable non-small cell lung (NSCLC) cancer is poor: five-year OS is only 19-24% for stage IIIA and 7- 9% for stage IIIB. In light of the approval of immunotherapy maintenance treatment, after completion of CRT, we undertook a retrospective study to characterize management and report outcomes of patients with stage III, unresectable NSCLC treated with chemoradiation (CRT) at the Jewish General Hospital, Montreal. **Method:** Patients diagnosed with stage III unresectable NSCLC,and treated with combined CRT, either concurrent (cCRT) or sequential (sCRT) treatment,between January 2007 to December 2018 were included in the study. Overall survival was calculated using the Kaplan-Meier approach and calculated from the start of radiotherapy. Physician defined progression-free survival was calculated from the start of radiotherapy until documented progression based on radiologic assessment. A multivariate analysis using Cox regression was carried out to assess clinical factors impacting survival. **Result:** 134/263 patients were deemed unresectable and received combined CRT. 124/134 (92.5%) received CRT as initial treatment and 10(7.5%) received CRT after progression to stage 3 post surgery for an earlier stage NSCLC.114/134 received cCRT and 20/134 received sCRT. Patients on cCRT were significantly younger with a slight prevalence of non-squamous histology and had N1 or single station N2 disease.Median OS (mOS) was 18.7 months (95%CI, 12.4-24.8) for the overall cohort; mOS in cCRT of 23.3 months (95%CI,14.3-32.2) was significantly better compared to 11.33 months with sCRT (95% CI, 10.2-24.8 p=0.01). PFS was slightly better in patients with cCRT (7.97mo, 95%CI 1.75-11.18) compared to sCRT (5.26mo, 95% CI 4.06-6.48 p=0.08).86/134 (64%) progressed and received subsequent therapy: 49 (57%)-chemotherapy alone, 15 (17.4%)–radiation alone, 13 (15.1%)-immunotherapy and 9 (10.5%)-targeted therapy.In multivariate analysis, the tumor size (HR 1.5, 95%CI 1.08-1.97) and nodal status (HR 2.5, 95%CI 3.34-4.74) were the only prognostic factors for OS. Gender, age, ECOG, smoking status, histology, chemotherapy protocol, subsequent therapy, mutation status and cCRT were not statistically significantin multivariate analysis. cCRT was not significant, likely due to patient selection. **Conclusion:** Unresectable stage III NSCLC is a heterogenous group that is challenging to manage. Combined CRT has beenthe standard of care for this group of pts. In our patient cohort, a trend of improved survival was seen in the cCRT group. Tumor size and nodal status were prognostic factors for OS. Future studies evaluating survival with newer IO therapies is of interest.

Keywords: NSCLC, Unresectable stage III, Real world experience

MA16.10 ANTIOXIDATIVE EFFECT OF ERDOSTEINE ON PLATINUM-BASED DOUBLET CHEMOTHERAPY INDUCED NEPHROTOXICITY

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Background: Many classes of antineoplastic agents including the platinum coordination complexes are also known to generate free radicals which have a role in the side effects of chemotherapy. Despite the introduction of new treatments including target and immunotherapy, platinum-based doublet chemotherapy is one of the most widely used and most potent chemotherapy drugs to treat lung cancer patients especially with small cell lung cancer. However, side effects in normal tissues and organs, notably nephrotoxicity in the kidneys, limit the use of platinum-based doublet chemotherapy. There are several experimental evidences which support the protective effect of erdosteine in acute injury induced by a variety of pharmacological or noxious agents, mediated by products of oxidative stress. Erdosteine is a multifactorial drug currently used in lung disease. In the last decade, data from several studies to the possible antitussive and anti-inflammatory properties of erdosteine and an indirect anti-inflammatory mechanism of action related to the ROS scavenging activity was suggested. The purpose of this study is to investigate whether erdostein can reduce the renal toxicity of lung cancer with platinum-based doublet chemotherapy by antioxidant role. **Method:** This study was a prospective, randomized, double-blind clinical trial on 153 patients with lung cancer(small cell lung cancer and non-small cell lung cancer). Patients who was treated with platinum-based doublet chemotherapy were randomly assigned into 2 groups of intervention(erdostein) group and control(non-erdostein) subjects regardless of the type of lung cancer. Intervention group took erdosteine 600 mg orally twice a day. We measured CCr, serum/urine NGAL, serum/urine Cystatin C, urine KIM-1 of the lung cancer patients who underwent platinum-based doublet chemotherapy to assess renal injury. And also we measured the activity of specific antioxidant enzymes, such as catalase and superoxide dismutase to evaluate oxidative stress. Serum and urine samples were collected from the patient before and after chemotherapy. **Result:** There was no significant difference of renal status between intervention and control groups at baseline. However, Statistically there was a significant decline in CCr among control group regardless of the type of lung cancer and the resimen of chemotherapy. NGAL expression of blood and urine was decreased in intervention group (especially patient treated with cisplatin and small cell lung carcer patients) but Cystatin C levels showed no difference between two groups. The decrease in urinary KIM-1 after cisplatin-based doublet chemotherapy in intervention group were observed compared to control group. Superoxide dismutase levels of serum were approximately increased to twice the initial level to the level measured after chemotherapy in the treatment group while the level of catalase did not change significantly in both the groups. **Conclusion:** These results show that erdosteine may be a promising drug for protection against platinum-based doublet chemotherapy-induced nephrotoxicity, especially for patients with cisplatin-based doublet chemotherapy and small cell lung cancer. However, further studies with different dose of erdosteine are warranted for clarifying the issue.

Keywords: Chemotherapy, antioxidant, nephrotoxicity

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MA16.11 EARLY AND LATE SURVIVAL COMPARISON BETWEEN ONCOLOGICAL VERSUS NON-ONCOLOGICAL PATIENTS ADMITTED TO A GENERAL INTENSIVE CARE UNIT IN CHILE

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Clinica Alemana, Santiago/Chile

Background: Cancer patients are a heterogeneous population and usually admission to ICU units was discouraged due to negative outcomes. In the past years, literature supports the admission at ICU for oncological patients that need invasive mechanical ventilation (IMV) with new admission policy known as the ICU-trial, with aim to recognize a group of patients that may benefit of limited time of intensive support and treatment. The purpose of this trial is to describe the characteristics and overall survival of a prospective cohort of invasive mechanical ventilation (IMV) patients admitted to an ICU of Clinica Alemana. **Method:** This is an observational, prospective and analytical cohort study conducted in Clínica Alemana de Santiago. We included patients with cancer > 18 years old, with baseline Eastern Cooperative Oncology Group (ECOG) performance status classification from 0 to 3, who were admitted to ICU and needed IMV between October 2017 and February 2019. Demographic, physiologic, laboratory, clinical and treatment data were extracted prospectively in a database-updated daily. Survival data was obtained from national death registry database. **Result:** A total of 1,490 patients were admitted between October 2017 and February 2019. A total of 358 patients (24%) had oncological diagnosis and 100 patients were supported with IMV. According to ICU plan, 76 patients were treated as full code and 24 patients as ICU-trial. Among all IMV patients ICU mean of length of stay (LOS) was of 7 days. At the comparison between oncological vs non-oncological patients, APACHE II score and the first-day SOFA score were not statistically different between both groups. Among oncological patients, 73,3% of patients were ECOG 1 and solids tumors were more common than hematological malignancies (90% vs 10%). Lung and digestive cancer were the most frequent malignancies. Full code management was the most frequent strategy at ICU admission in comparison to ICU-trial (76% vs 24%). Survival at day 28 between oncological and non-oncological patients was 76.3% vs 79.3% respectively (p=0.588). However, survival was significantly different at day 90 (64.3% vs 78.8% respectively, p=0.015) and at end of following period (52% vs 76.2% respectively, p<0.001). Remarkably, survival adjusted by cox regression showed a significant lower survival in oncological patients with ECOG 2 and ECOG 3 while the patients with ECOG 0 and 1 had a similar survival to non-oncological patients. According to ICU plan management statistically significant difference was observed in the group of oncological patients with higher survival in full code vs ICU-trial (59.5% vs 29.2% respectively, p=0.015) with a hazard ratio 0.52 [0.28-0.94]. **Conclusion:** Our data suggest that in oncological patients the short-term survival is determined for severity of the critical illness and the late survival is lower respect to non-oncological patients if poor performance status is documented. In patients with cancer admitted under ICU-trial criteria and supported with invasive mechanical ventilation a late survival close to 30% was observed. Similar to previous studies, our study emphasizes that ICU admission should not be limited only on the basis of a patient having a neoplastic disease and different variables should be considered from patient to patient.

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MA17.01 CELL LINEAGE AND CHROMATIN LANDSCAPE OF LUNG CANCER ARE CONTROLLED BY GATA6

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Background: Thoracic malignancies are histologically and biologically heterogeneous. The underlying causes of this heterogeneity are believed to be linked to the complex cellular ontogenies of lung cancers and their relationship to pulmonary development. Lineage selective transcription factors (TFs) are critical determinants of airway cell differentiation and homeostasis, but their biological requirements are often conditional. Analogously, several developmental TFs can paradoxically enhance or inhibit lung cancer progression, depending on cellular and epigenetic contexts which remain largely undefined. In this study, we report a novel function for the endodermal and pulmonary specifying TF GATA6 in lung cancer. **Method:** To understand the role of GATA6 in lung tumorigenesis we used a genetically engineer mouse model (GEMMs) harboring Kras p53 mutations using progenitor cell specific gene targeting. We combined GEMMs biology with integrated analysis of the transcriptome and the chromatin landscape of lung cells derived from GATA6 deficient tumors. **Result:** In this study, we uncover a conditional role for the endodermal and pulmonary specifying TF GATA6 during the initiation and progression of Kras mutant lung adenocarcinoma (LUAD). Inhibition of Gata6 in genetically engineered mouse models dampens the proliferation and increases the differentiation of LUAD tumors. These effects are influenced by the epithelial cell type that is targeted for transformation, demonstrating that GATA6 expression is an important molecular determinant of the cell of origin in Kras mutant lung cancer. In LUAD cells derived from surfactant protein C expressing progenitors, we identify multiple genomic loci that are bound by GATA6. Moreover, suppression of Gata6 in these cells significantly alters chromatin accessibility, particularly at distal enhancer elements. Analogous to its paradoxical activity in the developing lungs, GATA6 expression fluctuates during different stages of LUAD progression and can epigenetically control diverse lineage programs associated with cell proliferation, alveolar specification, BMP signaling, and epithelial plasticity. In summary: 1) GATA6 expression varies during different stages of disease progression in the lung adenocarcinoma (LUAD) subtype 2) Suppression of Gata6 can diminish the proliferation and progression of LUAD in a manner that is influenced by the transforming progenitor of origin 3) GATA6 differentially modulates chromatin accessibility across the genome of LUAD cells 4) This epigenomic mechanism results in the activation of different lineage specific programs, including the BMP signaling pathway. **Conclusion:** These findings reveal how GATA6 can modulate the chromatin landscape of lung cancer cells to control their divergent lineage dependencies during tumor progression. D.X.N. has received research funding from AstraZeneca, Inc.

Keywords: Lineage Pathways, Transcription Factors, Epigenetics

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MA17.02 IDENTIFY VULNERABLE PATHWAYS AND IMPROVE TREATMENT OUTCOMES IN LKB1-DEFICIENT LUNG TUMORS

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Background: The LKB1 tumor suppressor is inactivated in about 20% of non-small cell lung cancers (NSCLC) by mutations. Cancer cells with LKB1 deficiency exert complex effects on signal transduction and transcriptional regulation, which may cause these cells more susceptible to certain therapies comparing to cells with intact LKB1 function. Phenformin, an antidiabetic medicine from the biguanides class, has shown activities against NSCLC. Phenformin as a single agent has been shown to reduce tumor burden and prolonged survival in Kras;Lkb1 compound mutant mice but not Kras;p53 mice, suggesting specific activities in tumor with LKB1 deficiency. Currently patients with unresectable locally advanced NSCLC are treated standardly with concurrent chemoradiotherapy followed by checkpoint inhibitor, durvalumab. In this project, we test treatment sensitivity to radiotherapy and/or phenformin in lung cancer cells with intact or deficient LKB1. **Method:** Human lung cancer cell lines described below were used in (1) clonogenic survival assays as well as (2) generating tumor xenograft on nude mice for tumor growth delay experiments. A549, HCC15 and Calu-1 cell lines obtained from ATCC were cultured in RPMI1640 containing 5% FBS, without antibiotics. A549 cells (LKB1 deficient, TP53 WT and KRAS mutated) or HCC15 (LKB1 deficient, TP53 mutated and KRAS WT) were transfected with empty vector or WT LKB1 or LKB1-K78I plasmids; Calu-1 (LKB1 WT, KRAS mutated and p53 deleted) transfected with empty vector or LKB1 CRIPR KO were generated as described previously. **Result:** A549 cells with transfected WT-LKB1 were significantly more resistant to ionizing radiation (IR) induced cell kill (8.7% survival at 8 Gy) comparing to cells transfected with empty vector (3.7%) or kinase-dead LKB1 genes (4.2%). Similarly, HCC15 cells with transfected WT-LKB1 are significantly more resistant to IR induced cell kill (7.5%) comparing to cells transfected with empty vector (4.1%) or kinase-dead LKB1 genes (3.4%). Calu-1 cells harbor WT LKB1, and it is significantly more resistant to IR induced cell kill (8.3%) comparing to their counterpart with LKB1 KO (Calu-1 transfected with LKB1 CRIPR KO) (4.1%). When A549 cells were pretreated with 30 μM phenformin prior to, during and after IR, there was no change in survival in cells transfected with WT LKB1; however there was significant further reduction in survival in cells transfected with empty vector (LKB1 deficient). Xenograft tumors were generated in nude mice with A549 cells with the above genetic alterations. There was significant further tumor growth delay in those with A549 with deficient LKB1 comparing to those with A549 with WT LKB1 gene add-back. This tumor growth delay was further enhanced when these mice were treated with oral phenformin prior to, during and after IR treatment, confirming the *in vitro* experimental results. **Conclusion:** Human lung cancer with deficient LKB1 are more sensitive to ionizing radiation *in vitro and in vivo*. This was regardless of the TP53 or KRAS mutation status. A549 cells with deficient LKB1 were also more sensitive to phenformin treatment. Phenformin treatment further sensitized LKB1 deficient lung cancer cells to IR. This suggested that LKB1 can serve as a predictive biomarker to triage patient treatments.

MA17 MOLECULAR MECHANISMS AND THERAPIES
MONDAY, SEPTEMBER 9 15:45–17:15

MA17.03 IMPORTANCE OF CULLIN4 UBIQUITIN LIGASE IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Loss of the tumor suppressor NF2 is frequent in malignant pleural mesothelioma (MPM). NF2 suppresses tumorigenesis in part by inhibiting Cullin4 ubiquitin ligase (CUL4) complex. Here we aimed to evaluate an importance of CUL4 in MPM. **Method:** We evaluated the expression of CUL4A and CUL4B in tissue microarrays using immunohistochemistry. We tested the efficacy of cullin inhibition by pevonedistat, a small molecule inhibiting cullin neddylation, in 13 cell lines and 3 primary cells in 2D and 3D culture. Four groups of SCID mice haboring intraperitoneal (ip.) pevonedistat sensitive (MSTO211H) or resistant (ACC-Meso1) cell lines were treated with pevonedistat (50 mg/kg; ip.) on a 5day on/5day off schedule for 3 cycles. Treatment efficacy was assessed by means of overall survival. **Result:** CUL4B expression was associated with clinical outcomes (figure 1). Five MPM cell lines (38%) were highly sensitive to pevonedistat (IC50<500 nM). This remained true in 3D spheroid culture. The treatment induced S/G2 cell cycle arrest and accumulation of cells undergoing DNA re-replication (containing >4N DNA content) known to be mediated by p21 and CDT1 accumulation. Indeed the accumulation of p21 and CDT1 was more pronounced in pevonedistat sensitive cell lines after the treatment. Two of primary cells (67%) were sensitive to pevonedistat and also showed higher CDT1 accumulation following the treatment compared to the resistant cells. *In vivo,* pevonedistat treatment significantly prolonged survival of mice bearing both sensitive and resistant MPM tumors. Pevonedistat treatment reduced growth (phosphorylated histoneH3 positive) in pevonedistat sensitive tumor but increased apoptosis (cleaved–caspase3 positive) in pevonedistat resistant tumor.

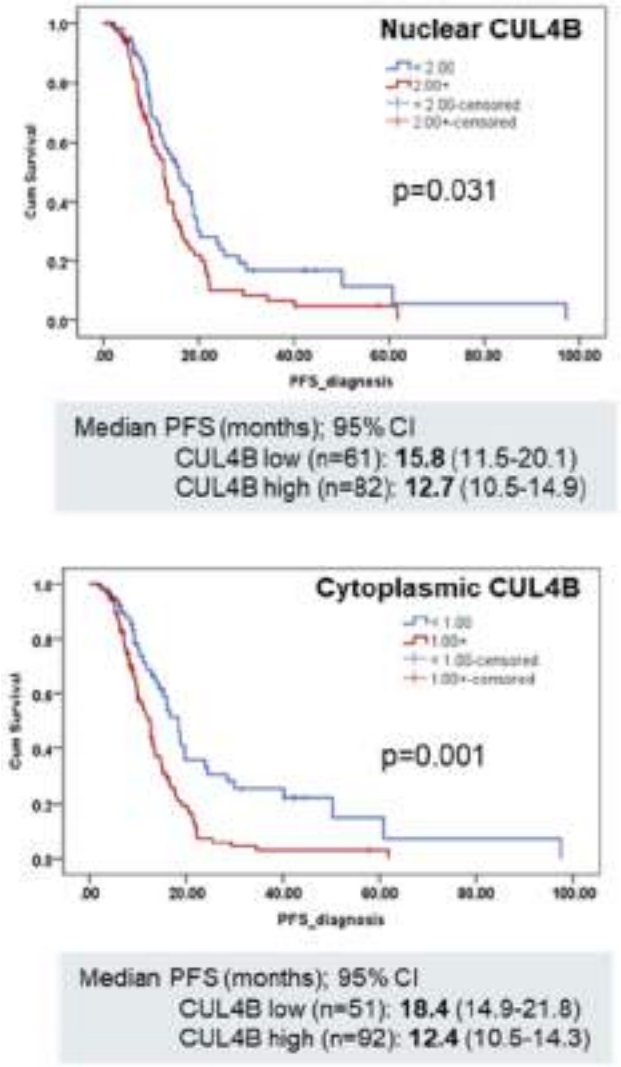

Figure 1. High expression of CUL4B was significantly associated shorter progression free survival (PFS).

Conclusion: High CUL4B expression may play a role in MPM progression. Inhibition of cullins by pevonedistat induced growth arrest and DNA re-replication strongly in a subset of MPM. The major mechanism seems to be mediated by p21 and CDT1 accumulation *in vitro*. Investigation of mechanisms *in vivo* is ongoing.

Keywords: pevonedistat, Cullins, Mesothelioma

MA17 MOLECULAR MECHANISMS AND THERAPIES
MONDAY, SEPTEMBER 9 15:45–17:15

MA17.05 DNA-BINDING AND GENE EXPRESSION PROFILES IN MAX DEFICIENT SMALL CELL LUNG CANCER

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Background: The MYC pathway is frequently altered in cancer, mostly by gene activation of the MYC-family of oncogenes (fMYC) but also by genetic inactivation of MAX, the obligate partner of MYC. While the oncogenic properties of fMYC have been extensively studied, the tumour suppressor role of MAX and the function of fMYC in MAX-mutant cells remain unclear. Further, inactivating mutations in MGA, a gene that codes for another MAX-binding partner, have been found in lung cancer. MGA is a component of the non-canonical polycomb repressive complex 1 (ncPRC1) but its precise role in lung cancer development is unknown. **Method:** RNA-sequencing, chromatin immunoprecipitation and proteomic analysis were performed to identify and compare the DNA binding and gene expression profiles of MYC, MGA and MAX in MAX-restituted human small cell lung cancer (SCLC)-derived cell lines. **Result:** SCLC is a high-grade neuroendocrine type of lung cancer with recurrent inactivating mutations in MAX. Recent findings have described two major SCLC subtypes based on the high expression of either *ASCL1* or *NEUROD1* transcription factors. According to this, *ASCL1* and *NEUROD1* control the expression of different set of genes which defines the two subgroups of SCLC. Here, we found that MAX-mutant SCLC cells belong to the *ASCL1*-transcription factor dependent group of SCLCs. In the absence of MAX, even after ectopic overexpression of MYC, there was no recruitment of MYC to the DNA. The DNA binding profile of MAX in MAX-restituted cells remained unaltered after co-overexpression of MYC, despite opposed effects in gene expression. Moreover, restitution of MAX significantly shifted the DNA occupancy of MGA, from E2F6 consensus binding sites to MYC-consensus binding sites (E-boxes). Our observations also demonstrated that ncPRC1 complex is formed regardless of the presence or absence of MAX. **Conclusion:** Our data supports that MYC lacks transactivation capabilities in the absence of MAX and that the tumour suppressor role of MAX relies on its capability to counteract the gene expression triggered by its partnering with fMYC. Further, we conclude that the tumor suppressor role of MGA may be related, in part, to the regulation of E2F6 promoters.

Keywords: SCLC, MYC, MAX

MA17 MOLECULAR MECHANISMS AND THERAPIES
MONDAY, SEPTEMBER 9 15:45–17:15

MA17.06 PLAKOPHILIN 1 ENHANCES MYC EXPRESSION, PROMOTING SQUAMOUS CELL LUNG CANCER

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Background: Plakophilin 1 (PKP1) is a member of the arm-repeat (armadillo) and plakophilin gene families, being an important component of the desmosome. Although desmosomes loss-of-function has been associated with increased cell migration and pro-oncogenic activity, we have observed consistent PKP1 overexpression in patient samples of squamous cell lung cancer (SqCLC) in comparison with lung adenocarcinoma (LUAD) and non-tumoral controls from two datasets achieved by our group, and also from three additional independent datasets. **Method:** In order to explore this paradox, we developed *in vitro* and *in vivo* PKP1 gain/loss functional models in SqCLC cell lines and also we challenged our hypothesis in some LUAD cell lines. **Result:** Greater cell dissemination but reduced cell proliferation was observed in CRISPR-Cas9 induced, PKP1-knockout clones. Furthermore, PKP1 expression promoted cell proliferation, cell survival, and *in vivo* xenograft engraftment. Interestingly, we demonstrated through several functional experiments (chromatin immunoprecipitation, RNA immunoprecipitation, direct mutagenesis combined with luciferase assays, Western blot, qPCR.. among others), and in 7 cell lines from different lung cancer subtypes (5 SqCLC and 2 LUAD cell lines), and different contexts (with and without PKP1 basal expression in order to set up gain and loss expression assays), that these pro-oncogenic activities were mediated by the functional direct relationship between PKP1 and the oncogene MYC. Specifically, PKP1 enhances MYC translation, and MYC increases PKP1 transcription, linking both proteins in a positive feedforward loop. **Conclusion:** These observations provide a new molecular mechanism of cancer development, revealing PKP1 as a novel oncogene in SqCLC, and as an effective post-transcriptional regulator of MYC, which has been described as overexpressed in around 70% of NSCLC tumors. Moreover, PKP1 unveiled as a valuable diagnostic biomarker and a potential therapeutic target for SqCLC. Importantly, PKP1 inhibition may open up the possibility of indirectly targeting MYC, not only in NSCLC (where, as mentioned before, is frequently overexpressed), but also in other tumors. This is of particular interest, because MYC is an oncogene that is dysregulated in most human cancers and is acknowledged as a "most wanted" target for cancer therapy.

Keywords: Squamous Cell Lung Cancer, PKP1, MYC

MA17.07 IDENTIFICATION OF AHR AS A NOVEL REGULATOR OF LUNG CANCER METASTASIS

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Background: Curative treatment of early stage and locally advanced non-small cell lung cancer (NSCLC) relies on surgery and radiotherapy. Adjuvant or simultaneous platin-based chemotherapy is used for risk reduction in patients with large tumors and/or lymph node metastases. Still a large fraction of curatively treated patients dies from metastatic relapse. A better mechanistic understanding of lung cancer metastasis is expected to guide the development of novel rational interventions from prevention, early detection and treatment. **Method:** Using a barcoded shRNA library we performed a functional *in vivo* screen in an orthotopic NSCLC mouse model to find target genes involved in metastatic processes. Barcoded shRNAs with significantly different representation between primary tumors and metastases were identified by next generation sequencing. Prioritized hits were functionally validated by targeted suppression in NCI-H1975 cells. Mechanistic studies were conducted in several NSCLC models *in vivo* and *in vitro*. **Result:** We identified AHR, a ligand-activated transcription factor involved in regulation of biological responses to planar aromatic hydrocarbons, as potential modulator of lung cancer metastasis. Suppression of endogenous AHR by shRNA enhanced the migratory and invasive capacity of NSCLC cells *in vitro*. Importantly, NCI-H1975 with targeted suppression of AHR showed increased metastasis formation in an orthotopic model *in vivo*. High RNA expression of AHR correlates with lower likelihood of progression and superior overall survival in patients with stage I NSCLC. Mechanistically, AHR impacts matrix remodeling genes (*MMP19*, *MMP24*) as well as asparagine synthetase (*ASNS*), all of which have been implied in metastatic progression. **Conclusion:** *AHR* is a novel metastasis-modulating factor in NSCLC. Its mechanism of action provides rational targets for diagnostic and therapeutic interventions.

Keywords: NSCLC, metastasis, AHR

MA17.09 5-AZACYTIDINE INHALED DRY POWDER FORMULATION PROFOUNDLY IMPROVES PHARMACOKINETICS AND EFFICACY FOR LUNG CANCER THERAPY

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Background: Epigenetic therapy through its ability to activate hundreds of genes silenced by promoter hypermethylation in lung cancer could produce durable and sustained tumor regression. The demethylating agent 5-azacytidine (5AZA) is unstable in aqueous solution and subject to hydrolysis and catabolism by cytidine deaminase (CDA) in liver, thereby reducing drug concentration after systemic administration prior to reaching the lung. Delivering 5AZA by inhalation could mitigate these barriers. **Method:** A stable, respirable (3.5 μM) dry powder formulation of 5AZA was generated. Pharmacokinetic (PK) studies in rats compared systemic dosing to inhaled delivery of a dry powder or aqueous formulation of 5AZA in the presence and absence of the CDA inhibitor tetrahyroduridine (THU). An orthotopic nude rat lung cancer model compared efficacy of inhaled dry powder versus aqueous 5AZA for treatment of engrafted human adenocarcinoma (Calu6, Calu3), adenocarcinoma in situ (H358), and squamous cell (RH2) tumor lines. Three weeks following engraftment (lungs contain multiple tumors), rats were treated 4 times weekly for 4 weeks, then sacrificed to assess tumor burden and genome-wide effects on the methylome in vehicle and treated tumors using the Illumina EPIC array. **Result:** Plasma PK showed a ~10-fold increase in area under the curve (AUC) and a 1.5 and 5-fold increase in maximum concentration (Cmax) comparing inhaled dry powder (0.6 mg/kg) to systemic (2 mg/kg, equivalent to the human injectable dose of 75 mg/m2) and inhaled aqueous (0.6 mg/kg) 5AZA that was augmented by THU. Inhaled dry powder and aqueous 5AZA PK in lung were similar and greatly exceeded systemic (30-fold Cmax; 47-fold AUC). PK in liver and brain were superior for dry powder with 7- and 26-fold increase in AUC and 7- and 3.3-fold increase in Cmax compared to systemic or aqueous dosing. The efficacy study comparing inhaled delivery of equivalent doses (0.6 mg/kg lung dose) showed dry powder was significantly better than aqueous with a 70–80% compared to 33–50% reduction in tumor burden for Calu6, Calu3, and RH2 and equally effective in largely curing H358 tumors. A significantly increased median number of genes (175–320 versus 25–270) exhibiting ≥30% demethylation of CpGs across their promoter region was seen for Calu6, Calu3, and H358 tumors exposed to dry powder versus aqueous 5AZA, with equivalent numbers of genes demethylated for RH2. **Conclusion:** Delivery of a dry powder formulation of 5AZA via an inhaler could be used to treat local and metastatic lung cancer (Support–CA196590).

Keywords: Inhaled delivery, 5-azacytidine, Epigenetic cytosine demethylation therapy

MA17.10 LACTATE TRANSPORTER BLOCKADE AS A STRATEGY TO OVERCOME VEGF INHIBITOR-RESISTANCE IN LKB1-DEFICIENT NSCLC

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Background: *STK11/LKB1* alterations are found in 20-30% of NSCLC and used to co-occur with *KRAS* mutations. Because LKB1 activates AMPK, many of the best known functions of LKB1 are attributed to its ability to control metabolic alterations in cells. Our laboratory have previously reported that loss of LKB1 promotes enhanced glycolysis and elevated lactate production and more recently we demonstrated that *STK11/LKB1* mutations are the strongest predictors of *de novo* resistance to immunotherapy in NSCLC. Prior studies have revealed an association between alterations in the LKB1/AMPK pathway and worse clinical outcomes in NSCLC and in patients treated with chemotherapy and bevacizumab. Given the roles of LKB1 in the regulation of cell metabolism and resistance to immunotherapy, it is feasible that LKB1 also impacts on the response to anti-angiogenic therapies. **Method:** Xenograft mouse models were established by subcutaneous injection of H460 cells (LKB1-deficient) and H460 LKB1-expressing in nude mice and LKR10 (*KRAS*^{G12D}) *LKB1* wild-type (K) or *LKB1*- knockout (KL) into 129Svmice. Mice were randomized to vehicle or B20-4.1.1 anti-VEGF antibody. Glycolytic activity of LKB1-intact and -deficient NSCLC cells was measured by Seahorse assay. We analyzed gene expression of SLC16A3 (MCT4) by qPCR and Western blot. Genetic disruption of MCT4 in the K and KL cell lines was done using CRISPR-Cas9 and mouse models were established by subcutaneous injection into mice. **Result:** Mice bearing LKB1-expressing H460 xenografts treated with anti-VEGF antibody showed a significant decrease in tumor volume ($p<0.05$) compared with their vehicle-treated counterparts. However, mice bearing LKB1-deficient H460 xenografts showed markedly reduced efficacy of anti-VEGF therapy compared with that in LKB1-expressing xenografts. Anti-VEGF therapy significantly reduced growth of LKR10 K tumors ($p<0.001$) but not in LKR10 KL tumors. Microvascular density was not increased in KL tumors following anti-VEGF treatment compared to K. Human isogenic LKB1-deficient cells showed a significantly increased rate of glycolysis and lactate secretion compared with cells expressing LKB1. Human and murine LKB1-deficient cells also had increased MCT4 expression compared

to K cells. Immunofluorescence and RPPA analysis of tumor samples from the K and KL mouse models showed that KL tumors upregulated MCT4 protein expression compared with K tumors (p<0.0001). The genetic disruption of MCT4 KL tumors significantly improved tumor volume reduction to anti-VEGF therapies *in vivo* (p<0.001). **Conclusion:** LKB1 loss is associated with increased lactate secretion and resistance to VEGF inhibition in NSCLC. The targeting of the lactate transporter MCT4 enhance the sensitivity of LKB1-deficient NSCLC to anti-VEGF therapy.

Keywords: MCT4, ANGIOGENESIS, LKB1

MA17 MOLECULAR MECHANISMS AND THERAPIES
MONDAY, SEPTEMBER 9 15:45–17:15

MA17.11 HIGH SENSITIVITY TO PD-1 BLOCKADE THERAPY AFTER LD1 DEPLETION IN KRAS-DRIVEN LUNG CANCER THROUGH CD8+/CD3+ TUMOR INFILTRATION AND PD-L1 INDUCTION

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Background: PD-1/PDL-1 inhibitors are approved for non-small cell lung cancer (NSCLC). However, many patients do not benefit and therapeutic combinations are under investigation. We have previously described Id1, involved in proliferation, angiogenesis and immunosuppression, as a prognostic factor in lung adenocarcinoma (LUAD) (Ponz-Sarvise, Clin Cancer Res 2011), Id1's role in lung cancer metastasis (Castanon, Cancer Letters 2017) and more recently shown that Id1 sustains mutant *KRAS*-driven progression and metastasis in NSCLC (Roman, Cancer Res 2019). In a previous syngeneic murine lung cancer model with depleted levels of Id1 using Id1-/- and Id1 wildtype C57BL/6 mice inoculated with Lewis Lung Carcinoma (LLC), we tested a combined therapeutic strategy targeting PD-1 and Id1, showing impaired tumor growth and increased survival (Gil-Bazo, presented at WCLC 2018). Here we study a combined strategy targeting PD-1 and Id1 in a *KRAS*-mutant murine LUAD model and the immune-related mechanisms involved. **Method:** First, a correlation between Id1 and PD-L1 mRNA expression was studied in mutant and wild-type *KRAS* LUAD cohorts from The Cancer Genome Atlas data set (TCGA). Secondly, a syngeneic tumor model using Balb/c mice through subcutaneous injection of *KRAS*-mutant LUAD (Lacun3) cells and *Id1*-silenced Lacun3 (Id1sh) cells. *In vitro,* proliferation was measured in both cell lines through MTS assays. IFNg-induced PD-L1 expression in both cell lines and flow cytometry was used to evaluate its mechanistic effects on the immune response. After tumor cells injection, mice were treated with an anti-PD-1 (RMP-1-14) monoclonal antibody or PBS, i.p. Tumor volumes according to Id1 status in tumor cells and the treatment administered were quantified. Vectra 3.0™ multispectral microscopy was used to characterize the tumor associated immune cells in paraffin-embedded tissues from our previous syngeneic murine lung cancer model using Id1-/- and Id1 wildtype C57BL/6 mice inoculated with LLC in which the combined blockade had been reported as effective. Immune marker antibodies were used to study expression of CD3, CD4 and CD8. **Result:** An inverse, moderate and statistically significant correlation between Id1 and PD-L1 expression in mutant and wild-type *KRAS* LUAD cohorts from TCGA was found in both cohorts (-0.367 and -0.351, respectively, p<0.001), indicating that Id1 depletion may lead to PD-L1 expression induction. *In vitro* assays showed that Id1 silencing reduced Lacun3 cells proliferation (p<0.001). Up-regulation of surface PD-L1 expression occurred in Id1sh cells, but not in Lacun3 cells, after receiving IFNg (p=0.0022). Mechanistically, in the syngeneic murine model, *Id1* inhibition in the injected cells, combined with anti-PD-1 treatment, significantly induced a tumor growth impairment (p<0.001). An intense CD8+ and CD3+ immune cell infiltration was observed in LLC Id1-/- C57BL/6 mice treated with anti-PD1 (p<0.05 for CD3+ TILS), compared the control groups, possibly explaining the dramatic tumor growth impairment previously shown on the treated animals. **Conclusion:** Id1 silencing may induce PD-L1 overexpression according to *in silico* and *in vitro* results. Id1 and PD-1 combined blockade in our *KRAS*-mutant syngeneic murine LUAD model significantly impaired tumor growth, compared to each strategy alone. A significantly increased CD3+ and CD8+ tumor infiltration and IFNg-induced PD-L1 tumor expression after the combined blockade may explain these findings.

Keywords: Immunotherapy, combined therapy, Id1

MA18 ADVANCES IN DIAGNOSIS OF COMMON TYPES OF NSCLC
TUESDAY, SEPTEMBER 10 11:30–13:00

MA18.01 PATIENT-DERIVED XENOGRAFTS OF LUNG SQUAMOUS CELL CARCINOMA SHOW A CHARACTERISTIC GENETIC PROFILE INDICATING A SPECIFIC BIOLOGICAL SUBTYPE

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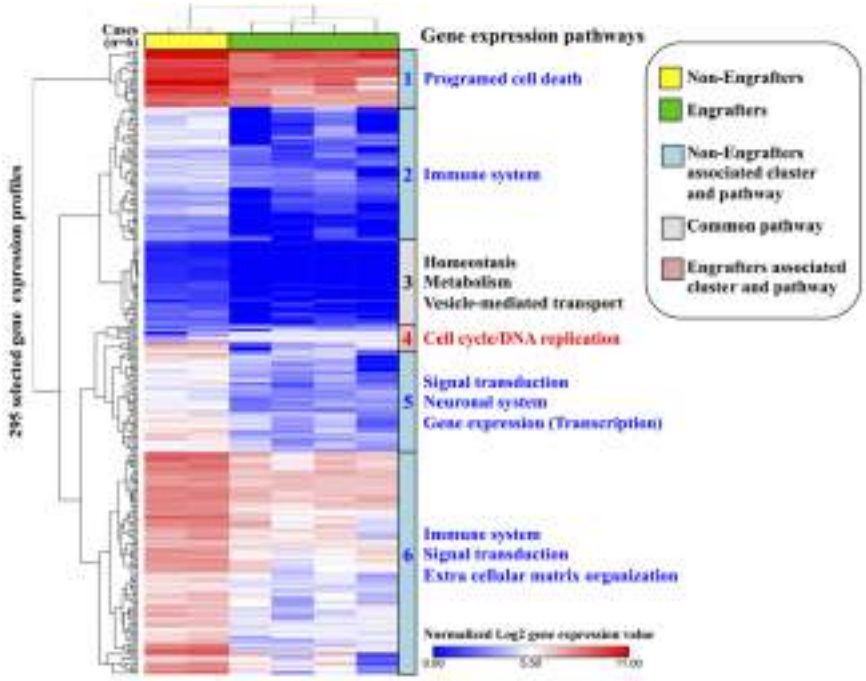
Background: Patient-derived xenograft (PDX) models are considered preferable to preclinical models for research on cancers including non-small cell lung cancers (NSCLCs). PDXs basically retain the histological features, heterogeneity, and genomic profiling of the original tumors, even after a series of passages. Among NSCLCs, a high rate of engraftment of lung squamous cell carcinoma (LUSC) into immunodeficient mice has been steadily reported. However, no previous study has examined the specific or characteristic expression profiles of LUSC, which is easy to establish in PDX. In this study, we compared the genetic profiles of resected LUSCs that had been successfully engrafted and with those that had not. **Method:** Fifty-one surgically resected NSCLCs, including 10 LUSCs, were inoculated into immunodeficient mice and xenografts were established. The resected tumors and established xenografts were examined histologically and their gene expression profiles were determined by RNA sequencing. The distinct genetic features of tumors from which PDX was successful (engrafters) and those from which PDX was unsuccessful (non-engrafters) were compared using bioinformatics methods, and their subtypes were evaluated. To validate the genetic profiling associated with engraftment and the subtype, we analyzed gene expressions, mutations, and patient outcomes obtained from The Cancer Genome Atlas (TCGA) database. **Result:** Among the 51 lung carcinomas, 38 were adenocarcinomas, 10 were LUSC, and 3 were other histological subtypes. Among the 10 LUSCs, 2 were non-engrafters and 4 were engrafters that were stably transplantable beyond passage three. RNA sequencing analysis revealed that non-engrafters had higher expression of genes related to programmed cell death, immune system, and signal transduction than engrafters, whereas engrafters showed higher expression of genes related to the cell cycle and DNA replication. Patients with non-engrafter-associated genetic profiles showed a poorer outcome than those with engrafter-associated genetic profiles. Recently, Wilkerson *et al.* classified LUSC into four subtypes – basal, classical, secretory and primitive – on the basis of biological and genetic differences. Interestingly, we found that non-engrafters had a genetic profile similar to the secretory subtype in the mid-late stage, whereas engrafters had the classical subtype of the early-mid stage of differentiation.



Conclusion: LUSC from which PDX is successful has a characteristic expression profile and shows a favorable prognosis, with a marked tendency for squamous epithelial differentiation.

Keywords: PDX, lung squamous cell carcinoma, RNA sequencing

MA18 ADVANCES IN DIAGNOSIS OF COMMON TYPES OF NSCLC
TUESDAY, SEPTEMBER 10 11:30–13:00

MA18.02 S100A10 UPREGULATION ASSOCIATES WITH POOR PROGNOSIS IN LUNG SQUAMOUS CELL CARCINOMA

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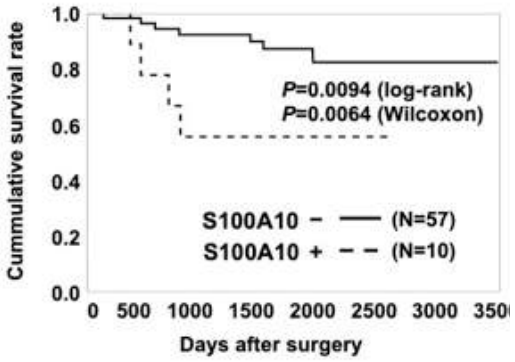
Background: S100A10 is one of the members of S100 protein family. This molecule predominantly functions in a complex with annexin A2, and stimulates plasminogen activator (tPA)-dependent plasmin formation. Plasmin cleaves and activates metalloproteases (MMPs). Several studies have established that plasmin is an important protease involved in cancer cell migration and invasion. Expression of the S100 protein family is detected in many human cancers and has been related to a poorer prognosis, but relationship between S100A10 expression and progression of human lung cancer has not been clarified. In this study, we focused on S100A10 and aimed to clarify its effect to progression in lung adenocarcinomas and lung squamous cell carcinomas (SCCs). **Method:** We investigated expressions of S100A10 and MMPs by immunohistochemistry in resected 98 primary lung adenocarcinomas and 120 primary lung SCCs, and its associations with clinicopathological parameters were evaluated. S100A10-positivity was defined when more than 10% tumor cells showed positive staining. In lung SCC cases, we particularly evaluated cancer cell surface at the invasive front. Kaplan-Meier analysis and Cox proportional hazard models were used to estimate the effect on survival. Next we observed the expression of S100A10 in 6 lung adenocarcinoma and 6 lung SCC cell lines, and performed siRNA-mediated knockdown against *S100A10* in highly-expressing cell lines. **Result:** Seventy-four (78.6%) of 98 adenocarcinomas were S100A10-positive cases, and correlations with poorer prognosis (p=0.0413), lymphatic invasion (p=0.0335), and expression of MMP2 (0.0081), were observed, although S100A10 expression was not an independent predictor of a poorer survival in the multivariable analysis (HR 1.7334, 95%CI 0.4340-11.523, p=0.4647). In the same way, 33 (27.5%) of 120 SCCs showed S100A10-positive staining and correlation with poorer prognosis (p=0.0094), p-TNM stage (p=0.0119), nodal involvement (p=0.0006), lymphatic invasion (p=0.0005), and tumor size (p=0.0003) were observed. As for lung SCCs, S100A10 expression was an independent predictor of a poorer survival in the multivariable analysis (HR 9.5916, 95%CI 1.0702-128.208, p=0.0434). Then we performed knockdown of *S100A10* in lung cancer cell lines and found that knockdown of *S100A10* suppressed cell proliferation in adenocarcinomas and SCCs, and invasion in adenocarcinomas.



	sample	5year survival rate
S100A10 −	57	87.19%
S100A10 +	10	55.56%
total	67	82.29%

Conclusion: In this study, we found that S100A10 expression associates with poorer survival in lung SCCs, but not in lung adenocarcinoma. Our present results suggest that S100A10 protein plays an important role in proliferation of lung cancer, possibly in association with invasion by MMPs. Future studies are necessary to further understanding of importance of S100A10 in progression of human lung cancer, including some differences between histological subtypes.

Keywords: lung squamous cell carcinoma, S100A10, MMP

MA18.03 DISTINCTION BETWEEN PRIMARY LUNG CANCER AND PULMONARY METASTASIS OF ESOPHAGEAL CANCER USING THE NANOSTRING NCOUNTER SYSTEM

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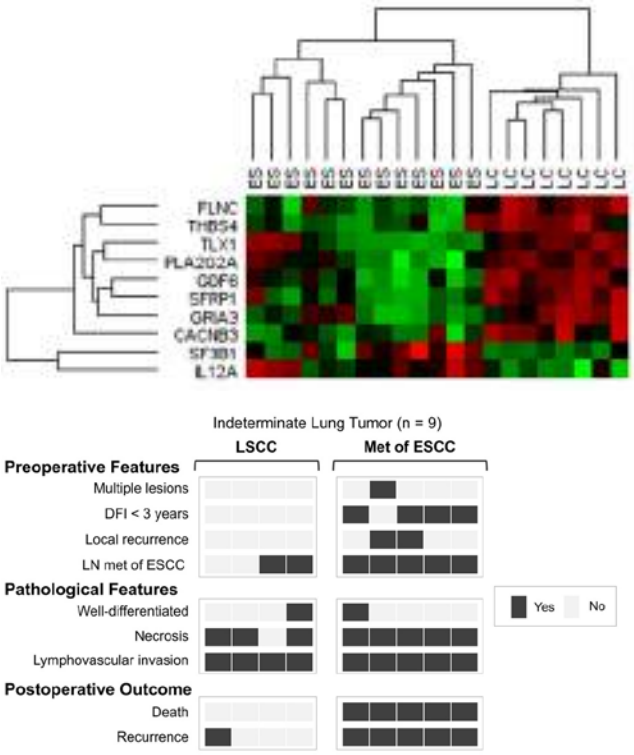
Background: It is very difficult to distinguish between primary lung squamous cell carcinoma (LSCC) and pulmonary metastasis of esophageal squamous cell carcinoma (ESCC) in patients with past history of ESCC, even by histological examination of the resected specimen. This study aimed to distinguish between LSCC and metastasis of ESCC by multiplex gene expression analysis using the Nanostring nCounter analysis system. **Method:** RNA was extracted from the FFPE samples of eight LSCCs, thirteen ESCCs, and nine indeterminate SCCs in the lung of patients with history of ESCC. We selected ten genes which were differently expressed markedly between LSCC and ESCC using the nCounter PanCancer Pathways Panel (XT-CSO-PATH1-12). We performed linear discriminant analysis between the two groups. The derived discriminant function was applied to the nine indeterminate SCCs. The nCounter diagnosis was compared to the preoperative features, pathological findings and postoperative prognosis. **Result:** Four of nine pulmonary tumors were diagnosed as LSCC and five were diagnosed as metastasis of ESCC. None of four patients with LSCC died and one developed recurrence, while all of five patients with metastasis of ESCC died and all developed recurrence. The prognosis of the latter was significantly poorer than the former (logrank test, p = 0.02). The preoperative features which indicate metastasis of ESCC (multiple lesions, short disease-free interval and presence of local recurrence) were found only in the metastasis group.



Conclusion: Multiplex gene expression analysis using the nCounter was useful for discrimination between LSCC and pulmonary metastasis of ESCC.

Keywords: Lung cancer, nCounter, esophageal cancer

MA18.05 DIAGNOSTIC DIFFERENCE BETWEEN NEUROENDOCRINE MARKERS IN PULMONARY CANCERS: A COMPREHENSIVE STUDY AND REVIEW OF THE LITERATURE

H. Brunnström[1,2], J. Staaf[2], L. Tran[1], L. Söderlund[1], B. Nodin[2], K. Jirström[1,2], H. Vidarsdottir[3], M. Planck[2,4], J. Mattsson[5], J. Botling[5], P. Micke[5]

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Background: The diagnostic distinction of pulmonary neuroendocrine (NE) tumors from non-small cell carcinomas (NSCC) is of high clinical relevance for prognosis and treatment. Diagnosis is based on morphology and immunohistochemical staining. The current WHO classification of lung tumors emphasizes synaptophysin and chromogranin A but also recommends CD56 as NE markers. The aim of the present study was to determine the diagnostic value of the insulinoma-associated protein 1 (INSM1) gene, in comparison with the established neuroendocrine markers, in pulmonary tumors. **Method:** Tissue microarrays with tumor tissue from 54 resected pulmonary NE tumors and 632 NSCC were stained for INSM1, CD56, chromogranin A and synaptophysin. In a subset, gene expression data was available for analysis. Also, 419 metastases to the lungs were stained for INSM1. A literature search identified 37 additional studies with data on NE markers in lung cancers from the last 15 years, whereof six with data on INSM1. **Result:** Depending on cut-off level (1%+ or 10%+ positive tumor cells), the sensitivity and specificity for INSM1 to separate NE tumors from NSCC were 72-91% and 98-99%, respectively. In comparison, the sensitivity and specificity for CD56 were 85-89% and 96-98%, for chromogranin A 56-67% and 98-99%, and for synaptophysin 85-93% and 86-92%, respectively. Analysis of literature data revealed that CD56 and INSM1 were the best markers for identification of high-grade NE pulmonary tumors when considering both sensitivity and specificity (see table). *INSM1* gene expression was clearly associated with NE histology.

NE marker / Type of lung cancer	CD56	Chromogranin A	INSM1	Synaptophysin
Carcinoid tumor	365/403=**91%** (83%-100%)	396/407=**97%** (93%-100%)	204/205=**99%** (98%-100%)	366/375=**98%** (94%-100%)
Large cell neuroendocrine ca.	311/362=**86%** (61%-94%)	211/363=**58%** (46%-85%)	53/70=**76%** (61%-91%)	254/363=**70%** (55%-88%)
Small cell carcinoma	511/568=**90%** (63%-100%)	243/489=**50%** (4%-83%)	295/327=**90%** (75%-100%)	375/488=**77%** (52%-100%)
NSCC (any type)	283/3664=**8%** (0%-28%)	324/4040=**8%** (0%-66%)	16/1030=**2%** (0%-4%)	497/4219=**12%** (0%-69%)
Adenocarcinoma	86/1657=**5%** (0%-22%)	41/1637=**3%** (0%-41%)	11/665=**2%** (0%-3%)	227/1698=**13%** (0%-72%)
Squamous cell carcinoma	133/1450=**9%** (0%-18%)	59/1529=**4%** (0%-26%)	5/365=**1%** (0%-4%)	86/1647=**5%** (0%-43%)

Number of evaluated and frequency of positive cases and frequency in different studies (x%-y%)

Conclusion: The solid data of our investigation and previous studies confirm the diagnostic value of INSM1 as a NE marker in pulmonary pathology. The combination of CD56 with INSM1 or synaptophysin should be the first-hand choice to confirm high-grade NE pulmonary tumors.

Keywords: Neuroendocrine markers, INSM1, Pathological diagnostics

MA18.06 GENE EXPRESSION AND CLUSTERING OF PULMONARY NEUROENDOCRINE TUMORS AT THE BORDER OF LOW/INTERMEDIATE AND HIGH GRADE MORPHOLOGY

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Background: The WHO classification of lung tumors is based on several features such as cell morphology, cell size, growth patterns, mitotic rate and presence of necrosis. Pulmonary neuroendocrine tumors are stratified into two categories, namely, low/intermediate grade (pulmonary carcinoid tumors) and high grade (pulmonary neuroendocrine carcinomas). Mitotic rate assessment on H&E stained slides play a crucial role in morphological classification of pulmonary carcinoids and high grade neuroendocrine carcinomas. Neuroendocrine tumors with 0-10 mitoses/ 2 mm^2 are classified as carcinoids and those with mitotic rate higher than 10 mitoses/ 2 mm^2 as neuroendocrine carcinomas. However, rare tumors which lie on the border of the spectrum with mitotic rates exceeding 10 mitoses/ 2 mm^2 but falling far below the average mitotic rates of high grade neuroendocrine carcinomas may actually share more molecular characteristics with carcinoids than high grade neuroendocrine carcinomas. The objective of the project was to explore gene expression of those tumors and a potential utility of molecular features in their classification. The study was based on the next generation RNA-sequencing. **Method:** Five borderline tumors that exceeded the threshold of 10 mitoses/ 2 mm^2 in 3 hot-spot areas but remained on the lowest end of the spectrum of malignity for large cell neuroendocrine carcinomas (LCNECs) were selected from institutional archives. These tumors were defined by mitotic counts of 11 to 30 mitoses/ 2 mm^2. Besides, one case with higher mitotic rate in hot-spot zone (42 mitoses/ 2 mm^2) but lower than 30 mitoses/ 2 mm^2 in the other areas was included in a group of borderline tumors. Seven pulmonary carcinoids and 6 LCNECs were selected for control groups. Ki-67 proliferation index and expression of p53 and pRB proteins were assessed by immunohistochemistry. Next generation RNA-sequencing was performed on fresh frozen tissues from all 18 samples on Illumina platform. Then, unsupervised hierarchical clustering was used to stratify the cases. **Result:** Pulmonary carcinoids and LCNECs clustered into 2 different groups with no overlap. Borderline tumors presented as a heterogenous group where 3 tumors clustered with carcinoids and the other two with LCNECs. Tumors that clustered with LCNECs expressed higher mitotic rate and presented more prominent necrosis. One of 2 cases that clustered with LCNECs had abnormal p53 expression. There were no cases with pRB loss among borderline tumors. For comparison, p53 and pRB expression was preserved in all carcinoid tumors. A subset of tumors in LCNEC group had abnormal p53 expression (strong diffuse expression or complete loss) and pRB loss. **Conclusion:** Next generation RNA-sequencing coupled with hierarchical clustering analysis allowed to demonstrate that a subset of borderline tumors classified as LCNEC by the current morphology-based WHO classification shows gene expression that is more compatible with pulmonary carcinoids. The data add to the evidence that molecular classification would prove to be a useful tool in stratification of low/intermediate and high grade pulmonary neuroendocrine tumors. However, immunohistochemistry for p53 and pRB is not sufficient for differentiation between pulmonary carcinoid and LCNEC.

Keywords: neuroendocrine tumors, pulmonary carcinoid, next generation RNA-sequencing

MA18.07 IDENTIFICATION OF NEUROENDOCRINE TRANSFORMATION IN ANAPLASTIC LYMPHOMA KINASE REARRANGED (ALK+) TUMORS AFTER TYROSINE KINASE INHIBITORS

P. Pal, A. Fares, D. Patel, E. Stewart, N. Perera-Low, A. Grindley, F. Allison, N.-A. Pham, R. Shi, N. Leighl, F. Shepherd, P. Bradbury, A. Sacher, P. Rogalla, K. Yasufuku, M. Cabanero, M. Tsao, G. Liu, S. Martins-Filho, L. Nguyen

University Health Network, Toronto/Canada

Background: Acquired resistance after ALK tyrosine kinase inhibitors treatment has multiple known mechanisms: new mutations or gene amplifications, bypass signaling and rarely neuroendocrine histological transformation. Here we describe results of a program utilizing routine biopsy post-progression in ALK+ patients for clinical and research purposes. **Method:** Since 2014, ALK+ lung cancer patients treated at the Princess Margaret Cancer Centre have undergone routine biopsies at disease progression time points upon failure of an ALK-tyrosine kinase inhibitor (TKI) for both clinical purposes and research purposes, in particular to obtain tissue for primary derived xenograft (PDX) engraftment. **Result:** All 9/9 patients consented for research sampling during clinical biopsy procedures (median 2 extra cores/passes); 2 patients were biopsied more than once; 3 PDX models from 2 patients have engrafted; 3 additional models are too early to assess engraftment. Engraftment occurred in patients with clinically aggressive tumors and poor survival outcomes. In this process, we identified 2 patients with neuroendocrine transformation post-second generation ALK TKI: (a) a 59 yo Asian female, never smoker, diagnosed six years prior with metastatic disease, heavily pretreated with crizotinib (12 months), pemetrexed (16 months), ceritinib (25 months), alectinib (6 months) and brigatinib (3 months); post-alectinib biopsy showed no transformation, while post-brigatinib liver biopsy demonstrated transformation to large cell neuroendocrine carcinoma; (b) a 75 yo Caucasian female, never smoker, diagnosed eight months prior and started on alectinib with a partial response, progressed in a single site; endobronchial biopsy demonstrated high grade neuroendocrine transformation. Both biopsies were positive for neuroendocrine markers (chromogranin and synaptophysin), TTF-1 and diffusely co-expressed ALK on immunohistochemistry. Assessment of PDX engraftment of these models is ongoing. **Conclusion:** Routine combined clinical and research biopsy of ALK+ patients at time of TKI failure helped to identify these recent cases of neuroendocrine transformation as a possible mode of resistance and provide tissue for model development. This is the first time that ALK+ transformation to large cell neuroendocrine carcinoma is reported in the literature. (PP, AFF, SNMF, LN contributed equally).

Keywords: Anaplastic lymphoma kinase, Neuroendocrine transformation

MA18.09 PROTEIN PROFILING OF SMALL LUNG ADENOCARCINOMAS: AN IN-DEPTH ANALYSIS

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Background: Among various cancers, lung cancer has one of the poorest prognoses, and adenocarcinoma is the most common histological subtype. Lung adenocarcinoma shows multistep progression from adenocarcinoma in situ (AIS) to invasive adenocarcinoma through minimally invasive adenocarcinoma (MIA). Recently, LC-MS/MS with multiple peptide labeling and a new fractionation method has made quantitative proteomic analysis feasible using small amounts of protein obtained by laser-microdissection. In this study, we performed quantitative protein profiling of AIS, MIA and early invasive lung adenocarcinoma and

selected proteins that showed statistically significant differences in expression among them. **Method:** Fresh tumor samples from five cases each of AIS, MIA and early invasive lung adenocarcinoma were collected by laser-microdissection, and proteins were extracted by the Phase Transfer Surfactant method. The samples were trypsinized, labeled with a TMT labeling kit, and fractioned with C18-SCX Stage Tip. Quantitative proteomic analysis was performed by LC-MS/MS (Q-Exactive plus) and analyzed with Proteome Discoverer software. **Result:** A total of 4278 proteins were identified. Among them, the expression of 12 proteins – EEF1A2, CRABP2, NDRG1, NOL3, SCIN, DHCR24, CEACAM5, HIBADH, AK4, PIP4K2C, ASRGL1 and IFITM3 – was two-fold or higher in invasive adenocarcinoma than in AIS, and the expression increased gradually from AIS to invasive adenocarcinoma through MIA. Among these proteins, NDRG1 and AK4 are known to be related to hypoxia, whereas NOL3 and DHCR24 reportedly have an anti-apoptosis function. **Conclusion:** Quantitative proteomic analysis of AIS, MIA and early invasive lung adenocarcinoma identified a total of 4278 proteins, 12 of which are thought to be associated with lung adenocarcinoma progression. These proteins may determine the grade of malignancy and could be potential targets for molecular therapy.

Keywords: lung adenocarcinoma, stepwise progression, proteomics

MA18.10 MULTICENTER STUDY OF INTRAOPERATIVE RAPID IHC FOR UNDIAGNOSED PULMONARY TUMOR USING NON-CONTACT ALTERNATING-CURRENT ELECTRIC-FIELD MIXING

K. Imai[1], S. Takashima[1], N. Kurihara[1], M. Atari[1], T. Matsuo[1], S. Watanabe[1], H. Iwai[1], H. Suzuki[1], Y. Minamiya[1], Y. Tanaka[2], Y. Maniwa[2]

[1]*Akita University Graduate School of Medicine, Akita/Japan,* [2]*Kobe University Graduate School of Medicine, Kobe/Japan*

Background: It is widely recognized that pathology is the most important factor for staging and selecting effective chemotherapy for patients with cancer. Immunohistochemistry (IHC) is a reliable screening method, but intra-operative diagnosis by frozen section with IHC is not possible because IHC takes approximately 6 hours. Our aim was to evaluate the clinical utility reliability and sensitivity of a novel intraoperative rapid-IHC by taking advantage of the non-contact mixing effect in microdroplets subjected to an alternating current (AC) electric field. **Method:** With the new device we have developed, we apply a high-voltage, low-frequency AC electric field to the sections. The antibody is mixed within the microdroplet as the voltage is switched on and off at specific intervals (Figure 1). The resultant coulomb force stirs the diluted solution on the sections, which increases the opportunity for contact. This rapid-IHC enables rapid detection of target cells in frozen sections and can provide a surgeon with an intraoperative diagnosis within 20 min. We will recruit total 150 patients with undiagnosed pulmonary tumor until December 2022.

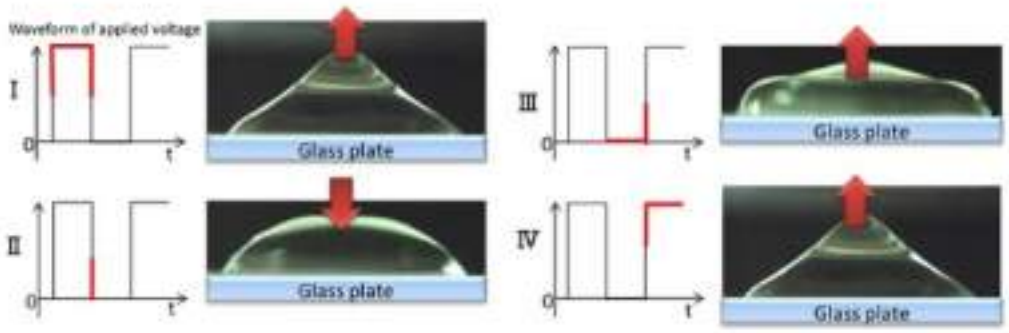


Figure 1.
Schema of the changes in the microdroplet as the voltage is switched on and off.
The antibodies are mixed within the microdroplet as the voltage is switched on and off in a time series (I→II→III→IV). The resultant coulomb force stirs the probe solution on the sections, and the opportunity for contact between the antibody and antigen is increased because as the voltage is turned on and off at regular intervals, the microdroplet's shape is transformed.

Result: We enrolled 60 patients for now (the achievement rate is 40.0%). The rate of agreement between rapid-IHC and final pathological diagnosis was 95%. In contrast, the rate of agreement between conventional H&E stain and final pathological diagnosis was 83.3%. When diagnosing pulmonary tumor intraoperatively based on rapid-IHC, we achieved a higher performance level than was achieved using H&E stain alone. **Conclusion:** We have shown that the rapid-IHC can be used as a clinical tool for prompt diagnosis in pulmonary tumor samples. Our method will help pathologists and surgeons when diagnosing intraoperatively.

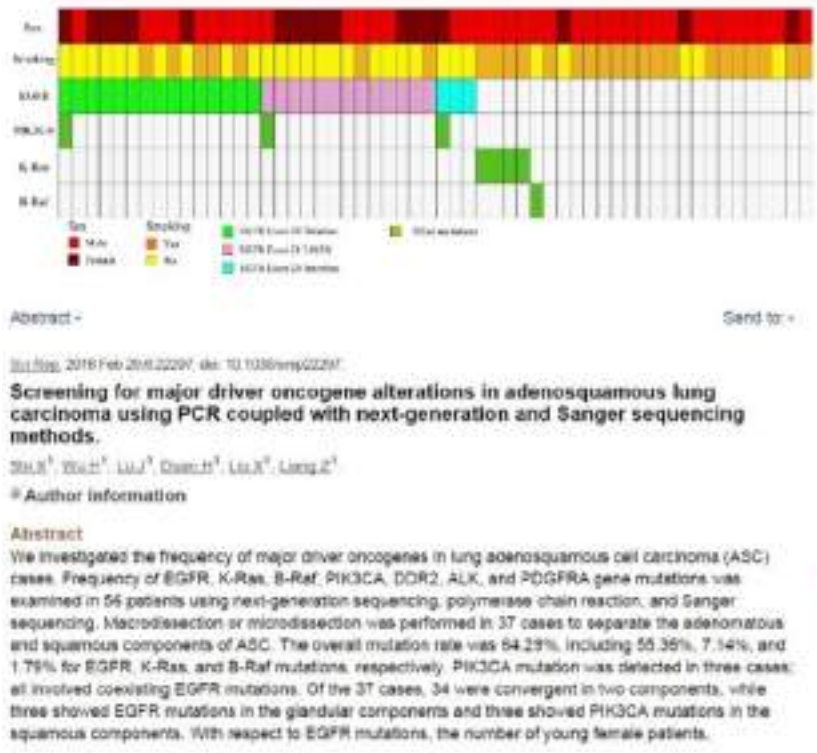
Keywords: Lung cancer, rapid immunohistochemistry, AC mixing

MA18.11 SNAI2 IS THE MOST HIGHLY DIFFERENTIAL EXPRESSED GENES BETWEEN THE ADENOMATOUS AND SQUAMOUS COMPONENTS OF LUNG ADENOSQUAMOUS CELL CARCINOMA

X. Shi, T. Feng, S. Wu, Y. Liu, X. Zeng, Z. Liang

Peking Union Medical College Hospital, Beijing/China

Background: Lung adenosquamous cell carcinoma is a hybrid tumor with adenomatous and squamous components in one tumor, it has the worst prognosis among the non small cell lung cancer. Our previous work has prooved that lung adenosquamous cell carcinoma has a similar EGFR mutation rate as lung adenocarcinoma which is 51.79% in 56 patients. Further squencing results showed that the majority of adnematous and squamous components had identical mutation type (34/37). EGFR mutated adenosquamous cell carcinoma patients are prone to be young, female and non-smokers, which are similar with the clinical charateristics of lung adenocarcinoma. Besides the corcodant mutation profile between the two different components of lung adenosquamous cell carcinoma, if there are any differentail expressed genes remained mysterious. our study will addressed this question.



Abstract ▾ Send to ▾

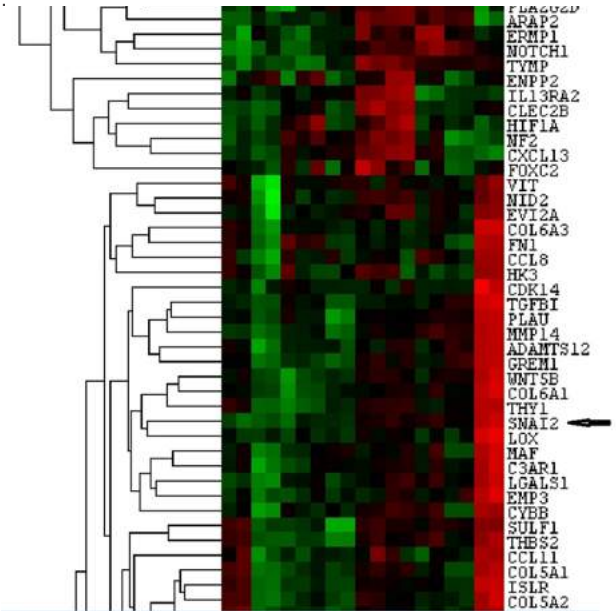
Screening for major driver oncogene alterations in adenosquamous lung carcinoma using PCR coupled with next-generation and Sanger sequencing methods.

Author information

Abstract

We investigated the frequency of major driver oncogenes in lung adenosquamous cell carcinoma (ASC) cases. Frequency of EGFR, K-Ras, B-Raf, PIK3CA, DDR2, ALK, and PDGFRA gene mutations was examined in 56 patients using next-generation sequencing, polymerase chain reaction, and Sanger sequencing. Macrodissection or microdissection was performed in 37 cases to separate the adenomatous and squamous components of ASC. The overall mutation rate was 64.29%, including 55.36%, 7.14%, and 1.79% for EGFR, K-Ras, and B-Raf mutations, respectively. PIK3CA mutation was detected in three cases; all involved coexisting EGFR mutations. Of the 37 cases, 34 were convergent in two components, while three showed EGFR mutations in the glandular components and three showed PIK3CA mutations in the squamous components. With respect to EGFR mutations, the number of young female patients.

Method: NanoString nCounter technology was employed in our study. it has been increasingly used for mRNA or miRNA differential expression studies because of its advantages of feasibility in formalin fixed paraffin embedded samples. We compared the differential expressed gene profiles between the paired matched adenomatous and squamous components in 24 adenosquamous cancer tissues. **Result:** SNAI2 is found to be the most differential expressed genes between the two components in lung adenosquamous cell carcinoma. It is higher expressed in squamous component compared with the adenomatous component. SNAI2 is a member of epithelial to mesenchymal transition signalling pathway. Other research results showed that SNAI2 played a pivotal role in controlling the epithelial and mesenchymal transdifferentiation, stem cell property of cancer cell, and the metastasis ability. **Conclusion:** Our preliminary results showed that SNAI2 which is a member of EMT signalling pathway is highly expressed in the squamous component compared with the adenomatous component of lung ASC. It may contribute to the phenotype transdifferentiated and invasion of lung ASC



Keywords: lung adenosquamous cell carcinoma, SNAI2, epithelial to mesenchymal transition

MA19 LOOKING AT PROS IN GREATER DETAIL - WHAT PATIENTS ACTUALLY WANT AND EXPECT
TUESDAY, SEPTEMBER 10 11:30–13:00

MA19.01 EMPIRICAL IDENTIFICATION OF DISTRESS CLUSTERS IN LUNG CANCER PATIENTS

T. Lillis[1], M.E. Hand[1], M. Pasquinelli[2], Z. Deliu[2], C. Weldon[3], J. Trosman[3], L. Feldman[2], M. Huber[2]

[1]*Rush University Cancer Center, Chicago/United States of America,* [2]*University of Illinois Hospital & Health Sciences System, Chicago/United States of America,* [3]*Northwestern University, Chicago/United States of America*

Background: Screening for distress from the time of diagnosis is emerging as standard cancer care. Although there is heterogeneity in patients' experience of distress, identification of subgroups of patients with unique distress profiles may inform interventions for distressed patients. Accordingly, we aimed to identify unique subgroups of patients based on their distress screening responses from a large sample of newly diagnosed lung cancer patients across two urban academic medical centers in Chicago, IL. **Method:** Lung cancer patients (N=596) were screened for distress at their diagnostic visit between (2/22/16 – 8/14/18) with the Coleman Foundation "Patient Screening Questions for Supportive Care" tool; a 34-item screener that identifies patient needs across psychological, physical, family/caregiver, and treatment and care concerns. A Two-Step cluster analysis was conducted to identify natural clusters of patients based on similar responses to distress screening items. **Result:** Cluster analysis results revealed a two-cluster outcome: "High Distress" (N=332) and "Low Distress" (N=264). The items that best distinguished High Distress patients from Low Distress patients were concerns about cancer stage/diagnosis, concerns about prognosis/long-term outcome, concerns about treatment options, and having higher average number of total concerns. Cancer stage at screening was not predictive of cluster membership. Demographic characteristics, descriptive statistics, and group difference tests for survey items by cluster and for the total sample are presented in Table 1. **Conclusion:** More than half of lung cancer patients were grouped as experiencing high distress on screening. While cancer stage was not predictive of high distress grouping, concerns about stage, treatment, and prognosis were most predictive of high distress cluster membership. An intervention to improve communication between providers and patients about these concerns may reduce distress. Table 1

	High Distress (N=332/55.7%)	Low Distress (N=264/ 44.3%)	Total Sample (N=596)	Significance Tests
Demographics				
Age	M=65.75 (SD=9.95)	M=66.25 (SD=9.71)	M=65.97 (SD=9.84)	F=.39 (p>.05)
Female	N=171 (51.5%)	N=144 (54.5%)	N=315 (52.9%)	χ^2=.55 (p>.05)
Race/Ethnicity				χ^2=30.83 (p<.01)
White	N=124 (37.3%)	N=154 (58.3%)	N=278 (46.6%)	p<.01
African American	N=161 (48.5%)	N=72 (27.3%)	N=233 (39.1%)	p<.01
Other	N=47 (14.2%)	N=38 (14.4%)	N=85 (14.3%)	p>.05
Stage IV	N=160 (48.2%)	N=118 (44.7%)	N=278 (46.6%)	χ^2=.72 (p>.05)
Physical & Psychological Health				
Psychological Distress (PhQ-4)	M=3.55 (SD=3.63)	M=1.56 (SD=2.14)	M=2.67 (SD=3.29)	F=58.86 (p<.01)
Pain	M=5.13 (SD=4.76)	M=4.76 (SD=3.45)	M=4.99 (SD=3.66)	F=1.04 (p>.05)
Fatigue	M=8.56 (SD=5.31)	M=7.63 (SD=4.74)	M=8.15 (SD=5.01)	F=4.34 (p<.05)
Physical Activity	M=12.63 (SD=7.74)	M=16.70 (SD=8.52)	M=14.42 (SD=8.33)	F=35.55 (p<.01)
Concerns				
Practical Concerns				
Childcare	N=8 (2.5%)	N=2 (.8%)	N=10 (1.7%)	χ^2=2.43 (p>.05)
Food & Housing	N=58 (17.8%)	N=13 (5.0%)	N=71 (12.2%)	χ^2=22.06 (p<.01)
Transportation	N=72 (22.0%)	N=14 (5.4%)	N=86 (14.7%)	χ^2=31.29 (p<.01)
Work/School	N=19 (5.9%)	N=8 (3.1%)	N=27 (4.7%)	χ^2=2.49 (p>.05)
Paying for Medication	N=79 (24.1%)	N=35 (13.6%)	N=114 (19.5%)	χ^2=10.19 (p<.01)
Family/Caregiver Concerns				
Children	N=46 (18.7%)	N=18 (8.0%)	N=64 (13.6%)	χ^2=11.58 (p<.01)
Partner	N=51 (20.9%)	N=24 (10.6%)	N=75 (15.9%)	χ^2=9.37 (p<.01)
Caregiver	N=23 (9.5%)	N=8 (3.5%)	N=31 (6.6%)	χ^2=6.91 (p<.01)
Ability to have children	N=8 (3.3%)	N=2 (.9%)	N=10 (2.1%)	χ^2=3.35 (p>.05)
Family	N=62 (25.6%)	N=24 (10.5%)	N=86 (N=18.3%)	χ^2=18.07 (p<.01)
Treatment & Care Concerns				
Cancer Diagnosis & Stage	N=303 (93.5%)	N=8 (3.3%)	N=311 (55.1%)	χ^2=453.34 (p<.01)
Prognosis & Long-term Outcome	N=312 (95.7%)	N=37 (15.4%)	N=349 (61.6%)	χ^2=378.04 (p<.01)
Treatment Options	N=246 (75.7%)	N=11 (4.6%)	N=257 (45.4%)	χ^2=282.43 (p<.01)
Communicating treatment wishes	N=165 (52.1%)	N=7 (2.9%)	N=172 (30.8%)	χ^2=155.09 (p<.01)
Physical Health Concerns				
Breathing	N=160 (64.3%)	N=78 (35.5%)	N=238 (50.7%)	χ^2=38.77 (p<.01)
Constipation	N=86 (43.4%)	N=41 (20.0%)	N=127 (31.5%)	χ^2=25.63 (p<.01)
Diarrhea	N=47 (27.0%)	N=17 (8.5%)	N=64 (17.1%)	χ^2=22.68 (p<.01)

	High Distress (N=332/55.7%)	Low Distress (N=264/ 44.3%)	Total Sample (N=596)	Significance Tests
Fevers	N=22 (13.3%)	N=4 (2.1%)	N=26 (7.2%)	χ^2=16.72 (p<.01)
Nausea/Vomiting	N=66 (33.7%)	N=16 (8.1%)	N=82 (20.8%)	χ^2=39.15 (p<.01)
Sleep	N=137 (59.3%)	N=58 (27.4%)	N=195 (44.0%)	χ^2=45.79 (p<.01)
Urination	N=46 (26.1%)	N=12 (6.0%)	N=58 (15.5%)	χ^2=28.79 (p<.01)
Chewing/Swallowing	N=49 (27.1%)	N=18 (9.1%)	N=67 (17.7%)	χ^2=21.01 (p<.01)
Mouth Sores	N=24 (14.5%)	N=13 (6.6%)	N=37 (10.2%)	χ^2=6.18 (p<.05)
Dry Mouth	N=116 (53.2%)	N=51 (24.5%)	N=167 (39.2%)	χ^2=36.76 (p<.01)
Swollen Arms or Legs	N=76 (39.6%)	N=21 (10.5%)	N=97 (24.7%)	χ^2=44.49 (p<.01)
Feeling full quickly or swollen abdomen	N=57 (32.0%)	N=18 (9.2%)	N=75 (20.1%)	χ^2=30.35 (p<.01)
Sexual Intimacy or Functioning	N=54 (28.3%)	N=17 (8.4%)	N=71 (18.0%)	χ^2=23.37 (p<.01)
Dry/Itchy or Blistered Skin	N=94 (46.3%)	N=43 (20.7%)	N=137 (33.3%)	χ^2=30.37 (p<.01)
Tingling in hands/feet	N=84 (43.5%)	N=33 (16.8%)	N=117 (30.1%)	χ^2=32.93 (p<.01)
Appearance	N=31 (19.35)	N=14 (7.2%)	N=45 (12.7%)	χ^2=11.52 (p<.01)
Use of Alcohol or Drugs	N=3 (2.0%)	N=1 (.5%)	N=4 (1.2%)	χ^2=1.59 (p>.05)
Total # of Concerns	M=7.84 (SD=3.71)	M=2.53 (SD=2.47)	M=5.49(SD=4.16)	F=400.82 (p<.01)

Keywords: Distress Screening, prognosis, Patient Reported Outcomes

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MA19.02 PSYCHOLOGICAL DISTRESS IN NEVER, EX, CURRENT, AND PASSIVE SMOKERS DIAGNOSED WITH LUNG CANCER - ANALYSES FROM THE ENRICH PROGRAM

B. Brown[1], J. Simes[1], M. Boyer[2], P. Hogg[1], A. Joshua[3], J. Young[1], C. Brown[1]

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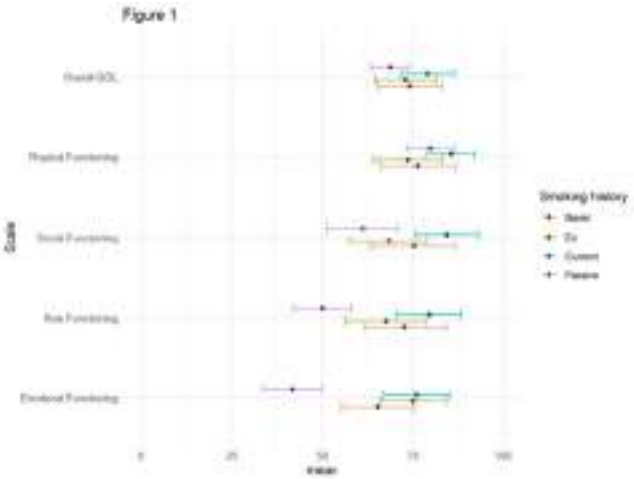
Background: Lung cancer is associated with greater psychological distress than any other cancer. In Australia, the prevalence of anxiety and depression in those with lung cancer is nearly 30% higher than the average of other major cancers. More than 50% of patients experience distress, anxiety and/or depression, resulting in diminished quality of life (QoL), and a fourfold increase in likelihood of suicide than the general population. Lung cancer stigma, arising from presumption about tobacco exposure and associated smoking stigma, contributes to high levels of distress. A national survey found that more than a third (35%) of Australians believe those living with lung cancer "have only themselves to blame" and almost 40% indicated, before expressing concern, the first question they would ask someone diagnosed with lung cancer is whether they smoked. This stigma makes lung cancer patients reluctant to seek psychosocial support and reduces their sense of entitlement to care and empathy. However, approximately one fifth (21%) are life-long never-smokers. This study aimed to describe differences in levels of psychological distress in never-and ever-smokers enrolled in the Sydney Catalyst EnRICH Program, a prospective clinical cohort of patients with lung cancer in New South Wales, Australia. **Method:** Measures: EnRICH incorporates patient-reported outcome measures (PROMs) that assess dimensions of anxiety, depression, emotional function, and psychological distress, namely, the: (i) EORTC QLQ-C30; and (ii) NCCN Distress Thermometer. Sample: All patients with newly diagnosed lung cancer presenting to study hospitals are eligible for the EnRICH cohort. Consenting patients who completed PROMs comprise the sample for the current analyses. Statistical Methods: Subscales of the QLQ-C30 reflecting overall QoL and emotional function, and scores on the NCCN Distress Thermometer, were compared between patient groups by smoking status. Groups were combined into never-smokers (never, passive) and ever-smokers (ex, current) for analyses. Mean differences and 95% confidence intervals were computed. **Result:** Among 205 patients who completed PROMs (69% of consenting patients), there were 52 never-smokers, 5 passive-smokers, 161 ex-smokers and 52 current-smokers at the time of diagnosis. Emotional function was worse in never-smokers (ever=75.3, never=63.2, difference=12.1 points 95%CI 2.4-21.7). There were no differences in other subscales. Although numbers are small, passive-smokers had the lowest mean scores for emotional-, role-, and social-functioning (Figure 1). Distress thermometer scores were 1.2 points worse in never-smokers [95%CI (0.56-1.8)].



Conclusion: Never-smokers had worse emotional function and higher distress than other lung cancer patients. If confirmed in larger studies, additional supportive care services may improve outcomes for these patients.

Keywords: Smoking status, Psychological distress

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MA19.03 DIFFERENCES IN SYMPTOM BURDEN BETWEEN RESPONSIVE AND PROGRESSIVE DISEASE IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC)

L. Williams[1], Q. Shi[1], B. El Ferjani[1], M. Hirschmann[1], D. Ponce[1], S. Dibaj[1], S. Chandwani[2], E. Roarty[1], W. Rinsurongkawong[1], J. Lewis[1], T. Burke[2], C. Cleeland[1], J. Lee[1], J. Roth[1], S. Swisher[1], J. Heymach[1], J. Zhang[1], G. Simon[1]

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Background: We have established a real-world Advanced Non-Small Cell Lung Holistic Registry (ANCHoR) to assess how immunotherapy impacts treatment choice, clinical outcomes, and patient-reported outcomes (PROs) of aNSCLC. Our aim in this analysis was to assess the ability of the MDASI-LC to differentiate between patients who are responding or who are progressing during treatment. **Method:** Between May 2017 and December 2018, patients with aNSCLC at a single institution were enrolled in ANCHoR and completed the MDASI-LC prior to therapy (PTT) and at routine clinic visits. The MDASI-LC consists of 16 symptom severity and 6 interference items rated on 0-10 scales (0 = no symptom or interference, 10 = worst imaginable symptom or complete interference). MDASI-LC scores from PTT to first recorded response determination (FRD) were compared by response group using linear mixed modeling (LMM). **Result:** One hundred one patients completed the MDASI-LC PTT and at FRD. Mean patient age was 63.8 years (standard deviation = 10.29) and 55% were males. Fifty percent of patients received chemotherapy (CTX), 22% immunotherapy (IM), 19% CTX+IM or angiogenesis inhibitor, and 9% targeted therapy. Median time from PTT to FRD was 105 days (lower quartile = 63, upper quartile = 224). Forty-six percent of patients had a complete or partial response (RECIST criteria CR, PR), 14% had stable disease (RECIST SD), and 41% progressed (RECIST PD). LMM showed progressing patients had significantly more fatigue (estimated effect [est] =1.39; p = 0.031), sleep disturbance (est=1.37; p = 0.046), and drowsiness (est=1.33; p = 0.037) and reported significantly more interference with work (est=1.67; p = 0.016) over time than responding patients. **Conclusion:** The MDASI-LC differentiated the symptom burden of patients with responding disease from that of patients with progressive disease. Patients with progressive disease had more fatigue, disturbed sleep, drowsiness, and greater interference with work than those with responsive disease. Further research is needed to determine if the MDASI-LC can predict response to therapy in patients and may be useful in delineating treatment benefit.

Keywords: advanced non-small cell lung cancer, symptom burden, patient-reported outcome

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MA19.05 IMPROVING LUNG CANCER OUTCOMES AND QUALITY IN THE US COMMUNITY SETTING WITH THE CREATION OF LUNG CANCER CENTERS OF EXCELLENCE PROGRAM

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Background: The Addario Lung Cancer Foundation community hospital Centers of Excellence (COE) Program encourages community cancer centers in the US to implement 'best practices' across the lung cancer care continuum, including provision of coordinated, multidisciplinary care. By comparing performance metrics within and outside the network of COEs, the program seeks to ensure that lung cancer patients (pts) receive the highest quality of care in their local area whilst also enabling COE hospitals to gain insights that facilitate the rapid implementation of quality improvement cycles. **Method:** The Impact Study was launched to conduct a comprehensive comparative analysis of COE member and non-member institutions across numerous quantitative and qualitative metrics from within the lung cancer care continuum. The 2018 analysis included 17 COE sites and 19 non-COE community hospitals representing approximately 5,000 pts in each cohort. The COE Impact study captured pts' demographic and clinical information as well as performance metrics from early stage screening through late stage diagnosis and all aspects of pts' care. Result:

Variable	COE	Non-COE	P value
# Cancer centers/hospitals	17	19	
Answers collected by nurse navigator	41%	100%	<0.001
Average # of hospital beds	565	342	0.104
Average # of lung cancer pts/institution	497	470	0.968
Lung cancer screening program	94%	42%	0.001
Endoscopic Bronchoscopy Ultrasound (EBUS)	23%	16%	0.323
Screening of pts for clinical trials	81%	35%	<0.001
Race: Caucasians	81%	37%	<0.001
Pathologist in tumor boards	100%	67%	0.012
ER visits the first 4 months of therapy	14%	32%	0.022
Molecular testing of pts with metastatic disease	81%	48%	0.001
Next generation sequencing	58%	22%	0.009

Conclusion: Improved structure and processes of care delivery at COE hospitals may translate into improved quality of care, outcomes, and patient experiences. The Lung Cancer COE program, now including 38 community cancer centers encompassing 12,000 lung cancer patients, plans to conduct this study annually with prospective, longitudinal data collection for future trend analyses as a means of facilitating continuous quality improvement in community-level lung cancer care.

Keywords: Quality, centers of excellence, Lung cancer

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MA19.06 SUCCESSFUL DEVELOPMENT OF REALTIME AUTOMATICALLY UPDATED DATA WAREHOUSE IN HEALTH CARE (ROOT-S)

H.A. Jung, S. Hong, J. Park, M.R. Park, J.-M. Sun, S.-H. Lee, J.S. Ahn, M.-J. Ahn, K. Park

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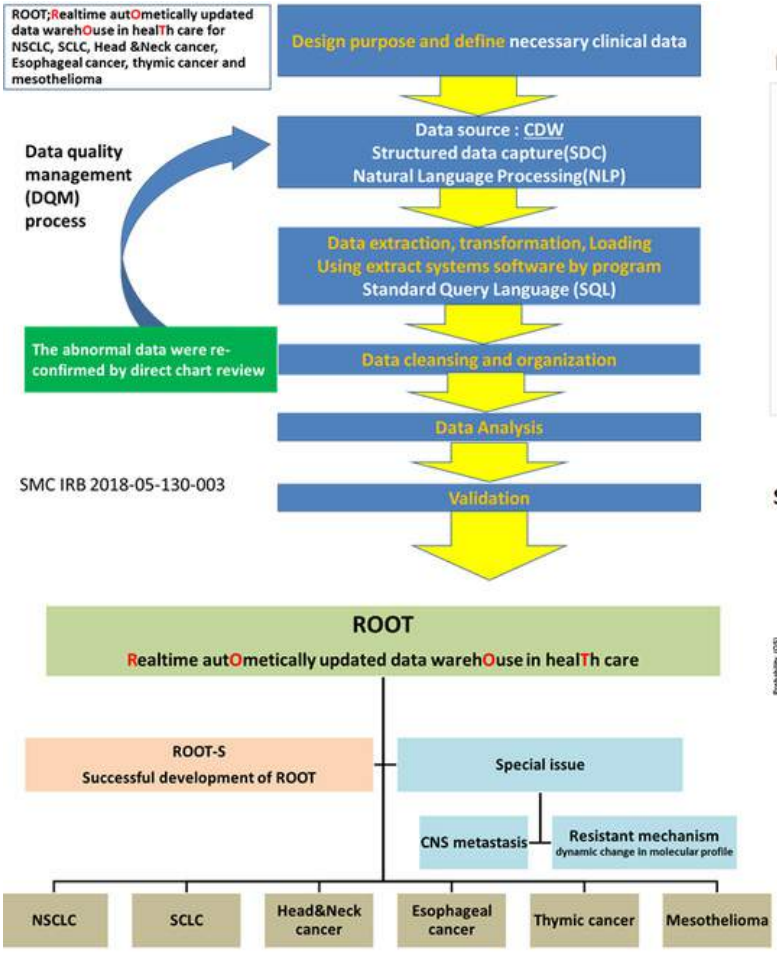
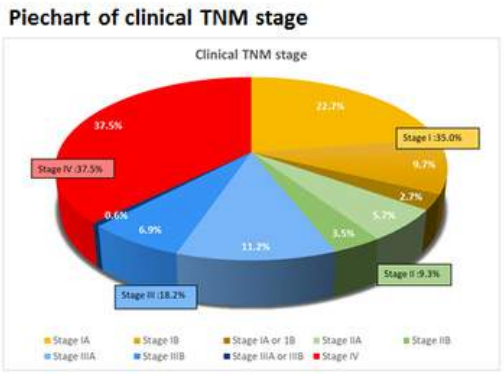
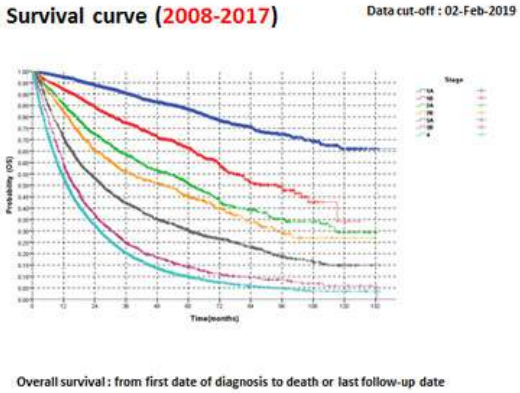
Background: Clinical information is often not recorded in an organized way, and converting it to a structured format can be a time-consuming task that may not successfully capture all facets of the information. Clinical Data Warehouse is a real time database that consolidates data from a variety of clinical sources to present a unified view. However, the clinical data extracted from the CDW have not only structured data (SD) but also natural language (NP) generated during clinical practice, and there is a limitation that it is difficult to apply to clinical trials because it is not structured and formatted to find key-point contents. This study aims at developing a systematic and comprehensive cohort through an automatic real-time update system called CDW. **Method:** The aim of this study was to evaluate clinical data of non-small cell lung cancer, small cell lung cancer, head and neck cancer, thymic cancer, and mesothelioma. In this study, we developed a unique algorithm that is optimized for each disease category using comprehensive natural language processing (NLP) systems and structured information from unstructured free text and structured data capture (SDC). We developed an algorithm using clinical information of patients diagnosed and treated during the past 10 years and designated validation sets of patients diagnosed and treated in 2018 for validation that these algorithms work automatically. **Result:** We collected clinical data of 23,735 NSCLC patients, 2,077 SCLC patients, 5,032 head and neck cancer patients, 3,948 esophageal cancer patients, 747 thymic cancer patients and 138 mesothelioma patients diagnosed at Samsung Medical Center. We could demonstrate using the validation set that the program accurately extracts the data needed for the cohort of each cancer.

The program is updated automatically every 24 hours, the source of each data is indicated separately, and the data that need to be integrated is transformed and systematically organized. The biggest advantage is that the scattered information is systematically integrated and automatically buildup to match the patient's cohort, so you can capture most updated survival or test results or treatment outcomes almost in real time. Data on the development of this program will be presented. **Conclusion:** This study is the first study that successfully developed and validated real-time updated cohort using CDW. This study suggests a blueprint for constructing a big data -based cohort for clinical research and is expected to be a landmark trial. The detailed analysis of each cancer through the development of the program will be presented.







Keywords: Cohort, Automatically updated, Structured query language

MINI ORAL SESSIONS

MA19 LOOKING AT PROS IN GREATER DETAIL - WHAT PATIENTS ACTUALLY WANT AND EXPECT
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MA19.07 TESTING AN OPTIMAL CARE COORDINATION MODEL (OCCM) FOR LUNG CANCER IN A MULTI-SITE STUDY

M. Smeltzer[1], T. Asfeldt[2], N. Faris[3], A. Kramar[4], C. Amorosi[5], V. Nolan[1], M. Ray[1], M. Dawkins[4], M.C. Nalan[1], W. Stevens[3], L. Lucas[4], R. Oyer[6], C. Lathan[7], R. Osarogiagbon[3]

[1]*University of Memphis, Memphis/United States of America,* [2]*Sanford USD Medical Center, Sioux Falls/United States of America,* [3]*Baptist Cancer Center, Memphis/United States of America,* [4]*Association of Community Cancer Centers, Rockville/United States of America,* [5]*Health Quality Solutions, Washington/United States of America,* [6]*Lancaster General Hospital, Lancaster/United States of America,* [7]*Harvard Medical School, Boston/United States of America*

Background: Medicaid-insured lung cancer patients have worse outcomes than others. To address barriers to optimal care in the US Medicaid population, the Association of Community Cancer Centers (ACCC) created and tested the OCCM. **Method:** The OCCM included 13 assessment areas: Patient Access to Care, Prospective Multidisciplinary Case Planning, Financial/Transportation/Housing, Care Coordination, Electronic Health Records, Survivorship Care, Supportive Care, Tobacco Cessation, and Clinical Trials. Each area had 5 defined levels of quality care delivery. With support from the Bristol-Myers Squibb Foundation, we pilot tested the model in 7 US cancer centers. Sites selected 1-2 assessment areas to evaluate using OCCM, developing relevant data benchmarks. Sites enrolled patients on Medicaid and Non-Medicaid controls. The ACCC team worked with each site to develop quality improvement projects with bi-weekly conference calls and 2 on-site visits. Data were collected and analyzed at a centralized data coordinating center. Statistical analyses were performed with Kruskal Wallis and chi-squared tests. **Result:** Seven sites spanning 3,081 miles evaluated 10 of the 13 OCCM areas. Total enrollment was 927 patients (257 Medicaid/ 670 Non-Medicaid). The Medicaid population had an average age of 62 years, ranging from 58-68 across sites. The clinical stage distribution was 40% stage I/II and 60% stage III/IV. Medicaid patients were 47% adenocarcinoma histology, 29% squamous cell, 14% small cell, and 10% other. Sites differed by patient age (p=0.0041), race (p<0.0001), and smoking status (p=0.028). Three sites evaluated models for prospective multidisciplinary case planning for Medicaid patients including: bi-weekly tumor board (BTB), virtual tumor board (VTB), and multidisciplinary team huddle (MTH). VTB and MTH allowed for presentation of higher percentages of eligible patients (BTB: 23%, VTB: 100%, MTH: 100%, p<0.0001). BTB and MTH discussed all cases prospectively, while VTB achieved 80%. Median days from diagnosis to presentation were 18 (BTB), 14 (VTB), and 9 (MTH,

p=0.14). Two sites evaluated smoking cessation programs. One, using trained cessation counselors, had 62% (18/29) active smokers, of whom 56% (10/18) expressed readiness to quit. Another site, using the freedom from smoking initiative, had 50% (11/22) active smokers and 55% (6/11) readiness to quit. 83% of those who started the cessation program quit smoking. Patient access to care was evaluated with timeliness of care metrics at two sites: one found 13 days (median) from lesion discovery to diagnosis and 21 days from diagnosis to treatment in Medicaid patients, which did not differ from Non-Medicaid controls (p=0.96 and 0.38). 94% met the site goal of treatment initiation within 45 days. Another site found 16 days (median) from discovery to diagnosis and 27 days from diagnosis to treatment (did not differ from Non-Medicaid controls, p=0.68 and 0.83). **Conclusion:** Sites successfully used the OCCM to identify areas to improve and developed meaningful data benchmarks. The OCCM is a valuable tool for cancer centers to identify specific areas to target to improve lung cancer care delivery.

Keywords: access to care, Quality of care, care coordination

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MA19.09 ASSESSING CLINICAL FRAILTY IN ADVANCED LUNG CANCER PATIENTS - AN OPPORTUNITY TO IMPROVE PATIENT OUTCOMES?

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The Christie NHS FT, Manchester/United Kingdom

Background: The median age of non-small cell lung cancer (NSCLC) diagnosis in England is 73 years. At that age, 40% of the general population has some degree of clinical frailty which may impact survival, quality of life, anti-cancer treatment tolerability and access to clinical trials. However, clinical frailty is often not addressed or managed at the time of anti-cancer treatments. This project was designed to integrate frailty assessments and build frailty pathways within an advanced cancer care setting in order to better support patients and improve outcomes. **Method:** This quality improvement project that used Plan-Do-Study-Act (PDSA) methodology. Phase one of the project focused on establishing a multidisciplinary team to integrate a frailty screening tool, the Rockwood Clinical Frailty Scale (CFS), into standard clinical practice. The primary aim was to implement and screen ≥80% of all new lung cancer patients at a high-volume tertiary cancer centre. The secondary aim was to explore the correlation of CFS with age, performance status (PS), treatment selection and systemic anti-cancer treatment (SACT) tolerability. Specialised training was provided to the clinical team and the CFS was integrated from 26/11/2018 on an electronic form routinely completed by clinicians. A digital dashboard was set-up to monitor real-time data and the frail group was defined as CFS score >3. Data cut-off for this analysis was 29-03-2019. **Result:** 335 lung cancer patients were screened using CSF by a team of 20 clinicians with a compliance rate of 89%. There was a strong correlation between PS and CFS (r= 0.77, p<0.01). The distribution of both CFS and PS correlated with ageing (r= 0.2 and r= 0.17, respectively; p<0.01). Patients ≥70 years were more likely to be frail (56% vs 40%; OR 1.4, 95%CI 1.2-1.7; p<0.01). Frailty reduced the likelihood of receiving any anti-cancer treatment by 20%. Amongst those who started SACT, patients classed as frail were less likely to go beyond the first cycle of treatment (64% vs 91%; OR 0.7, 95%CI 0.5-0.9; p<0.01). **Conclusion:** CFS screening is feasible within a busy clinical practice when incorporated as a digital tool. CFS helps to identify patients who may potentially benefit from specialised frailty assessment and management. This could ultimately be used to better inform on treatment selection, and support requirements during treatment, to improve outcomes for patients in the future.

Keywords: frailty, elderly, Lung cancer

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MA19.10 ESTIMATION OF QUALITY-ADJUSTED LIFE EXPECTANCY FOR STAGE AND SYSTEMIC TREATMENT IN NON-SMALL CELL LUNG CANCER IN RAJAVITHI HOSPITAL, THAILAND

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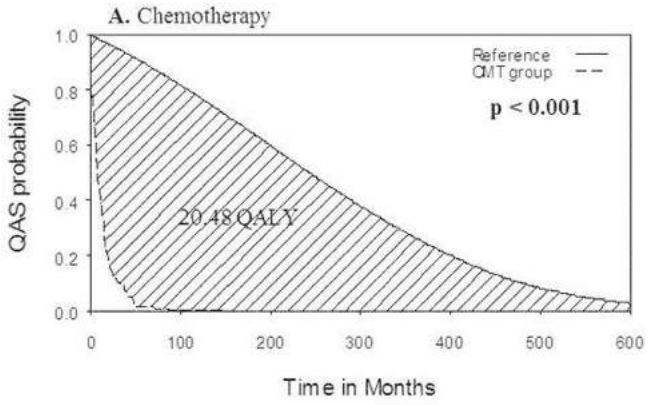
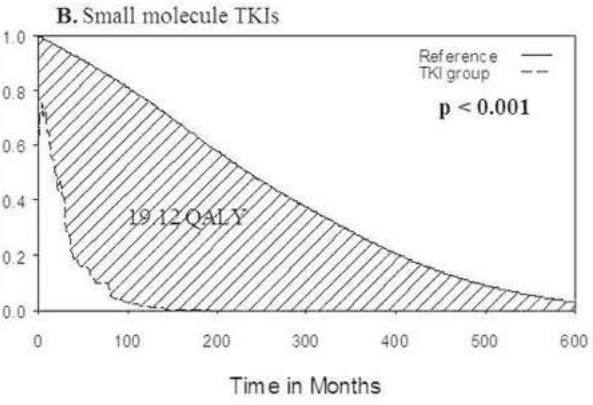
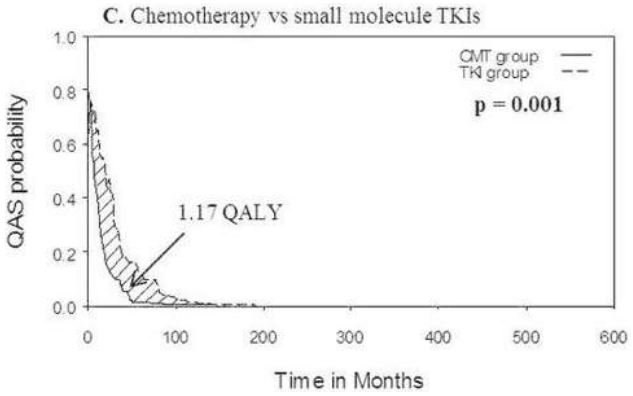
Background: Owing to the high mortality and rapidly growing costs related to lung cancer, it is worth examining the health benefits of treatment in this cancer. This study attempts to quantify the real-life practice quality-adjusted life expectancy (QALE) of non-small cell lung cancer (NSCLC) patients with different stages and systemic treatments. **Method:** This cross-sectional study was conducted by reviewing and collected quality of life (QoL) data from 256 eligible all stages NSCLC patients treated at Rajavithi hospital from May 1st to October 31st, 2018. The iSQoL statistical package was used to evaluate QALE compared with the reference Thai population in different stage of disease. For advanced stage, QALE was compared among treatment groups (chemotherapy and Epidermal growth factor receptor tyrosine kinase inhibitors; EGFR TKIs) **Result:** The QALE for patients with early and advanced stage NSCLC were 4.49 ± 0.43 and 1.03 ± 0.08 QALY, with the corresponding loss-of-QALE were 14.02 ± 0.44 and 20.13 ± 0.09 QALY, respectively. The difference of QALE between early and advanced stage was 3.46 QALY (p<0.001). Based on systemic treatment in advanced stage, The QALE for patients who received chemotherapy and TKIs were 1.05 ± 0.08 and 2.19 ±0.28 QALY, with the corresponding loss-of-QALE were 20.48 ± 0.09 and 19.12 ± 0.29 QALY, respectively. The difference of QALE between treatment with chemotherapy and TKIs was 1.17 QALY (Figure, p=0.001).







Conclusion: The utility gained from treatment with TKIs in advanced NSCLC is substantial. Early stage had better QALE than advanced stage NSCLC patients.Future study will assess the cost-effectiveness of targeted therapy in Thailand.

Keywords: Non small cell lung cancer, EGFR TKIs, quality-adjusted life expectancy

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MA19.11 POPULATION BASED ANALYSIS OF END OF LIFE TREATMENT PATTERNS IN THORACIC MALIGNANCIES

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Background: Active cancer treatment within the last month of life is unlikely to meaningfully benefit patients and ASCO guidelines recommend chemotherapy treatment rates be kept as low as possible. Patients with thoracic malignancies often have rapidly progressive disease and significant symptom burden and there is little population based data on patterns of care near end of life. **Method:** The Evaluation of Cancer Outcomes Registry records clinical information on all newly diagnosed cancer patients within a region of Victoria, Australia. Core diagnostic, demographic, treatment and outcome details were extracted for all patients diagnosed from 2009-2015 with death data through to end of 2016. Patients with thoracic malignancies were further analysed for treatment patterns at end of life. Details of palliative radiotherapy (pRT) and active systemic treatment (AST – intravenous chemotherapy, targeted therapy and/or immunotherapy) were recorded for all patients. Details on oral chemotherapy and stereotactic radiotherapy were not recorded. **Result:** The total cohort during the study period comprised 12760 patients. Of these, 1328 patients were recorded with a thoracic malignancy (TM) (non small cell lung cancer 82%, small cell lung cancer 10%, mesothelioma 7%) and 1118 of these died. At total of 39% (518) and 41% (538) of the 1328 TM patients received AST and pRT respectively at some point. Of these patients 15% (77/518) received AST and 23% (121/538) pRT within 30 days of death, compared with 7.0% (242/3436) (p<0.01) and 19% (178/965) (p=0.06) respectively for the total cohort excluding TM patients. Patients receiving AST within 30 days of death had a similar median age (66.7 vs. 67.8 years, p=NS) but shorter median survival from diagnosis (146 v. 281 days, p<0.01) than patients receiving final AST within 1-6 months. The frequency of some change in AST agents within the prior month was highest in the last month of life. The most common AST agents used in the final month of life were pemetrexed, etoposide and gemcitabine and most patients were treated with single agents. More pRT treatments were started in the last 30 days of life than in any other month near end of life. Patients receiving pRT in the last month of life also had a shorter median survival from diagnosis (113 v. 215 days, p<0.01) and the sites most commonly treated with pRT in the last month of life were chest/lung, spine and whole brain. **Conclusion:** Patients with thoracic malignancies have higher rates of AST treatment within the last 30 days of life than other patients with cancer in the same geographic region. Those treated within 30 days of death also have shorter median overall survival and higher frequencies of changing AST agents or starting pRT, possibly suggesting aggressive, symptomatic and poorly responding disease.

Keywords: Chemotherapy, radiotherapy, end of life

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.01 GLOBAL QUANTITATIVE MASS SPECTROMETRY REVEALS POTENTIAL NOVEL ACTIONABLE TARGETS IN THYMIC EPITHELIAL TUMORS (TET)

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This abstract is under embargo until September 10 10:45 CET

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.02 GAD1 EXPRESSION AND ITS METHYLATION BECOME INDICATORS OF MALIGNANT BEHAVIOR IN THYMIC EPITHELIAL TUMOR

S. Soejima, K. Kondo, M. Tsuboi, R. Kishibuchi, K. Muguruma, B. Tegshee, K. Kajiura, Y. Kawakami, N. Kawakita, M. Yoshida, H. Takizawa, A. Tangoku, N. Wusiman

Graduate School of Biomedical Sciences, Tokushima University, Tokushima/Japan

Background: Genome-wide screening for aberrantly methylated CpG islands was performed in 7 thymic carcinoma (TC) samples and 8 type-B3 thymoma samples using HumanMethylation450 K BeadChip (Illumina, Santa Clara, CA, USA) analysis. We identified 93 genes as commonly hypermethylated in TC comparing to type-B3 thymoma. *GAD1* (glutamic acid decarboxylase 1) was one of the most significant hypermethylated genes in TC. GAD1 catalyzes the production ofγ-aminobutyric acid (GABA). Some recent reports showed that GAD1 expression is significantly increased in neoplastic tissues. However, the underlying mechanism of elevated GAD1 remains elusive. In this study, we examine mRNA and protein expressions and DNA methylation of *GAD1* in thymic epithelial tumors (TETs). **Method:** In total, 95 thymic tumor samples (A; 9, AB; 11, B1; 19, B2; 21, B3; 14, carcinoma; 21) and 22 paired normal tissues were obtained from patients with histologically proven TET, who underwent surgery at the Tokushima University Hospital (Tokushima, Japan) between 1990 and 2016. The methylation status of thymic epithelial tumor samples was validated by pyrosequencing. The expression status was analyzed by quantitative polymerase chain reaction (qPCR) and immunohistochemistry (IHC). **Result:** The previous study (Oncogene 2015, 1–14) showed that the key locus responsible for GAD1 reactivation was mapped to DNA methylation-sensitive CTCF-binding site (CTCF-BS3) within the third intron of *GAD1*. We targeted this region for pyrosequencing, which confirmed that DNA methylation of *GAD1* in TC was significantly higher than in thymoma (32.8% versus 4.0%, P<0.001). It revealed a high degree of both sensitivity and specificity for discriminating TCs and thymomas (AUC=0.936). There was no significant difference in the methylation rate between thymoma and normal thymus (P = 0.917); however, the DNA methylation rate in TC was higher than in normal thymus (P=0.015). qPCR revealed that GAD1 mRNA expression levels in TC were higher than in thymoma (qPCR; 2.03 vs 0.38, P < 0.001). IHC showed statically different GAD1 expression between TC and thymoma (93.75% vs 28.98%, P < 0.001). There was a slight positive correlation between the mRNA expression levels and methylation levels (Spearman's rank correlation coefficient, ρ = 0.427); however, no differences of DNA methylation and expression of GAD1 was observed among subtype of thymoma according to WHO histologic classification. **Conclusion:** TC had frequent DNA methylation of CTCF-binding site 3 in *GAD1*, and high levels of mRNA and protein of GAD1. *GAD1* may resent an epigenetic therapeutic target in TC.

Keywords: Thymic carcinoma, GAD1, DNA methylation

MA20.03 DNA METHYLATION OF MT1A AND NPTX2 GENES PREDICT MALIGNANT BEHAVIOR OF THYMIC EPITHELIAL TUMORS

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[1]*Graduate School of Biomedical Sciences, Tokushima University, Tokushima/Japan,* [2]*Department of Thoracic, Endocrine Surgery and Oncology, Tokushima/Japan*

Background: Our previous studies showed that DNA methylation of cancer-related genes, such as *DAP-K*, *p-16*, *MGMT*, *HPP1* was higher in thymic carcinoma (TC) than in thymoma (Lung Cancer 64:155-, 2009, 83:279-,2013). Genome-wide screening for aberrantly methylated CpG islands was performed in 7 TC samples and 8 type-B3 thymoma samples using HumanMethylation 450 K BeadChip (Illumina, Santa Clara, CA, USA) analysis. We identified 93 genes as commonly hypermethylated in TC comparing to B3 thymoma.We chose 2 candidate cancer-related genes; *MT1A* and *NPTX2*. *MT1A* which is an isozyme of metallothioneins is related to metabolism of trace elements, such as zinc, copper. DNA methylation of *MT1A* was higher in malignant melanoma than in normal melanocytes. *NPTX2* has studied as synapse-related proteins. DNA methylation of *NPTX2* was higher in some cancers than in normal tissues. **Method:** In total, 48 thymic tumor samples (thymoma;31, carcinoma; 17) and 22 paired normal tissues were obtained from patients with histologically proven thymic epithelial tumor (TET), who underwent surgery at Tokushima University Hospital (Tokushima, Japan) between 1990 and 2016. The methylation status of TET samples was validated by pyrosequencing. The expression of mRNA in *MT1A* and *NPTX2* genes was validated by RT-PCR (SYBR® Green method). **Result:** DNA methylation of *MT1A* gene was significantly higher in TC compared to thymoma (26.4% versus 9.5%, *P*<0.01). It revealed high degrees of sensitivity and specificity for discriminating TCs and thymomas (AUC=0.903). Although DNA methylation was significantly higher in TC than in normal thymus, there was no significant difference between DNA methylation of thymoma and normal thymus. No differences of *MT1A* DNA methylation was observed among subtype of thymoma according to WHO histologic classification. In *MT1A* gene, there was no correlation has observed between DNA methylation and mRNA expression. On the other hand, *NPTX2* gene was also significantly higher in TC compared to thymoma (38.0% vs 17.5%, *P*<0.01). It revealed high degrees of sensitivity and specificity for discriminating TCs and thymomas (AUC=0.765). Although DNA methylation was significantly higher in TC than in normal thymus, there was no significant difference between DNA methylation of thymoma and normal thymus. No differences of *NPTX2* DNA methylation was observed among subtype of thymoma according to WHO histologic classification. There was no correlation has observed between DNA methylation and mRNA expression in all TETs, there was a reverse correlation in thymic carcinomas. The mean value of the frequency of the DNA methylation of was *MT1A* and *NPTX2* divided into higher and lower level groups. A significant difference was observed in the relapse-free survival between the higher and lower level groups (p=0.015, p=0.042). **Conclusion:** DNA methylation of *MT1A* and *NPTX2* was significantly higher in TC compared to thymoma and normal thymus. Epigenetic alteration may be related to progression and malignancy in TET. In *NPTX2* gene, there was a reverse correlation between DNA methylation and mRNA expression in thymic carcinomas. It may act as tumor suppressor gene.

Keywords: MT1A, NPTX2, Thymic carcinoma

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.05 FOLLOW-UP UPDATE OF 2 PHASE II STUDIES OF PEMBROLIZUMAB IN THYMIC CARCINOMA

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Background: Two phase II studies of pembrolizumab 200 mg every 3 weeks in advanced thymic carcinoma have recently been published (Giaccone et al. Lancet Oncol. 2018, study #1; Cho et al. JCO 2018, study #2). Both studies reported a response rate in about 20% of patients and a rate of autoimmune disorders that is higher than in other tumor types. **Method:** This report provides a follow-up update of these 2 studies, with particular emphasis on duration of response, and occurrence of autoimmune disorders. Both studies included patients with thymic carcinoma who had progressed after at least one line of chemotherapy. **Result:** In study #1 a total of 40 patients with advanced thymic carcinoma were treated, with a median follow up of 40.6 months. The response rate did not change (22.5%) compared to the original publication, however one patient who had developed myositis, myocarditis and myasthenia gravis (MG), continues to be in nearly complete response after only two cycles of pembrolizumab, 36 months from initiation of treatment. One patient who had developed myositis and hepatitis with unclear signs of MG developed overt MG symptoms several months after the interruption of therapy. No other new autoimmune disorders were observed (6/40 = 15%). Five patients completed 2 years of treatment according to protocol and 4 of them elected to continue treatment. Three patients who had been off therapy were rechallenged with pembrolizumab upon progression (one responded). Median duration of response was 38 months (from 22.4 in initial report), median PFS was 4.2 months (identical) and median survival was 25.8 months (24.9 in the initial report). At completion of this study, an amendment was introduced to add epacadostat 10 mg BID to pembrolizumab in the same patient population. Four patients were treated before the study was closed after the results of a randomized trial of the combination in melanoma failed to meet its primary endpoint. No patient responded (2 stable and 2 progressions). One patient developed grade 2 myocarditis. In study #2 a total of 26 patients with advanced thymic carcinoma were included, with a median follow up of 33.4 months. The response rate (19.2%) did not change, and no other autoimmune disorder appeared since the initial publication (5/26 = 19%). Median duration of response (9.7 months), median PFS (6.1 months) and median survival (14.5 months) did not change compared to the initial publication. No additional autoimmune disorders were documented compared to the original publication. A total of 5 patients received 2 years of pembrolizumab according to protocol; no patient continued beyond 2 years or was retreated upon progression with pembrolizumab. **Conclusion:** These two studies confirm definite activity of pembrolizumab in advanced thymic carcinoma. Recently pembrolizumab was included in the NCCN guidelines for thymic carcinoma. No additional autoimmune disorders were noted after discontinuation of pembrolizumab. There are significant differences in duration of response and overall survival in the 2 studies and potential factors are being investigated. In study #1 pembrolizumab was continued beyond 2 years in several patients and rechallenge was an available option.

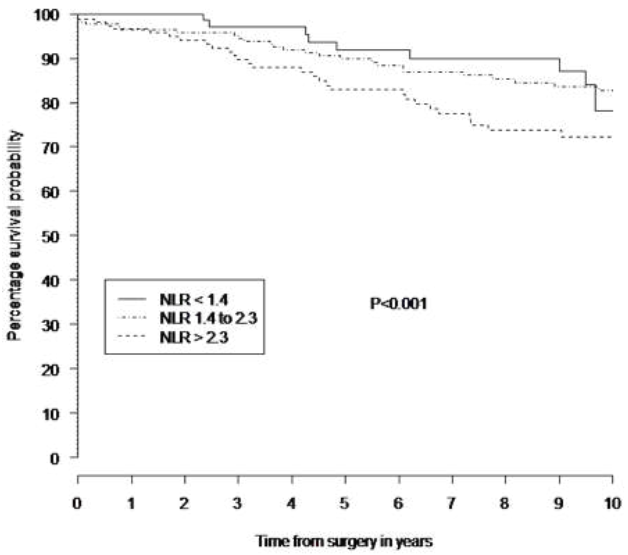
Keywords: Thymic carcinoma, Pembrolizumab, autoimmune disorders

MA20.06 NEUTROPHIL TO LYMPHOCYTE RATIO IS AN INDEPENDENT PROGNOSTIC PREDICTOR IN THYMOMA

P. De Sousa[1], F. Gallina[2], A. Tamburrini[3], M. Nizami[1], C. Igwe[1], K. Amer[3], E. Lim[1], V. Ambrogi[2]

[1]*Royal Brompton & Harefield NHS Foundation Trust, London/United Kingdom,* [2]*Tor Vergata University Policlinic, Rome/Italy,* [3]*University Hospital Southampton NHS Foundation Trust, Southampton/United Kingdom*

Background: Thymoma is the most common primary neoplasm of the anterior mediastinum in adults and conventional prognostic factors include Masaoka Stage, WHO histology and completeness of resection. Little is known of preoperative peripheral neutrophil-to-lymphocyte ratio (NLR) as an independent additional discriminator of prognosis. **Method:** We performed an international multicentre retrospective cohort study (UK Health Research Reference 19/HRA/0440 and EU internal approval reference xxxxxx). We included patients who underwent complete resection for thymoma and data was acquired through patient medical records with follow up data obtained through national database and hospital records. NLR calculated on pre-operation bloods results. **Result:** From July 1987 to December 2017, 433 patients underwent surgery for thymoma. The majority were male 228(53%) with a mean age (SD) of 55(15) years. The surgical approach was sternotomy in 335 patients (77%), thoracotomy in 23(5%) and VATS in 75(17%). The WHO classification was type A 63(15%), AB 126(29%), B1 98(23%), B2 55(13%) and B3 86(20%) patients. The Masaoka-Koga stage was I in 135(33%) II in 194(47%), III in 54 (13%) and IV in 31(7%) patients. Median (IQR) follow-up time was 86 (30 to 152) months with a 5 and 10-year survival of 88% and 79% respectively. The median NLR was 2.1 (1.5 to 3.1), when split into three groups (NLR < 1.4, NLR between 1.4 and 2.3 and NLR > 2.3), higher NLR was associated with poorer survival (log rank P<0.001) that persisted on Cox regression after adjustment for WHO grade and Masaoka stage with a HR of 1.69 (95% CI 1.20 to 2.39; P=0.002).



Conclusion: Pre-operative NLR is a simple, low cost biomarker that can stratify risk of death independent to WHO grade and Masaoka stage in patients undergoing surgery for thymoma.

Keywords: THYMOMA, surgery, neutrophil to lymphocyte ratio

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.07 THYMOMECTOMY AND TOTAL THYMECTOMY OR SIMPLE THYMOMECTOMY FOR EARLY STAGE THYMOMA WITHOUT MYASTHENIA GRAVIS: AN ESTS THYMIC WORKING GROUP STUDY

F. Guerrera[1], C. Filippini[1], L. Voltolini[2], F. Londero[3], P.-E. Falcoz[4], G. Lo Iacono[5], C. Zisis[6], P. Mendogni[7], L. Molins[8], N. Martucci[9], G. Rocco[9], A. Toker[10], M. Esch[11], C. Aigner[12], I. Bravio[13], S. Mantovani[14], B. Moser[15], N. Novoa[16], B. Verdonck[17], B. Du Pont[18], M. Congregado[19], L. Ampollini[20], P.A. Thomas[21], E. Ruffini[1]

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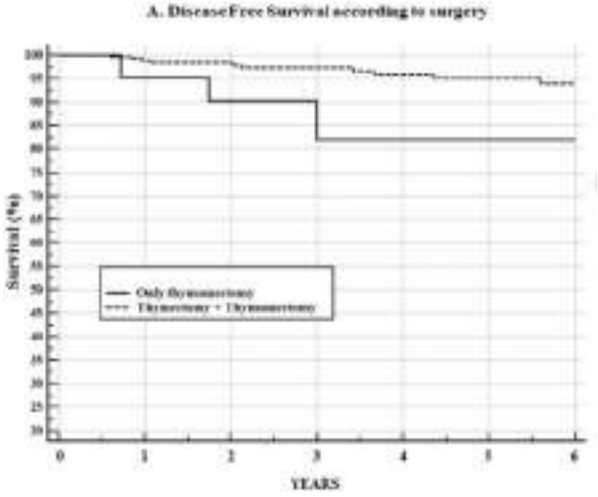
Background: Resection of thymic tumors has traditionally included removal of the tumor and the thymus gland (thymothymomectomy). Nevertheless, in recent years, some authors questioned the need to remove the thymus gland in non-MG thymomas, suggesting that resection of the tumor (simple-thymomectomy) is enough from an oncological point of view in Stage I (TNM stage classification) thymoma patients. The aim of our study was to compare short- and long-term outcome of thymothymomectomy vs. simple-thymomectomy using European Society of Thoracic Surgeons (ESTS) Thymic Database. **Method:** We investigated 1131 patients with thymic epithelial tumors included in the ESTS-Thymic Database. Three-hundred twenty-four clinical stage I (cT1N0M0, according to the 8th edition of the UICC/AJCC TNM stage classification) without Myasthenia Gravis (non-MG) thymoma cases were evaluated from 23 contributing centers (2000-2017), of which 300 (93%) thymothymomectomy and 24 (7%) simple-thymomectomy. Surgical upstaging was evaluated. In pathological stage I, we compared the completeness of resection, the rate of complications, the 30-day mortality, the overall survival and the disease-free survival (DFS).



Result: Overall, we observed an upstaging to stage III in 10 (3%) patients. We did not observe any significant difference between the two techniques in terms of the completeness of resection, the rate of complications and the 30-day mortality. The 5-year overall survival rate was 94% in the thymothymomectomy group and 56% in the simple-thymomectomy group (Figure 1 - P= 0.0004). The 5-year DFS was 95% in the thymothymomectomy group and 82% in the simple-thymomectomy group (Figure 1 -P= 0.013). **Conclusion:** Patients affected by stage I TNM non-MG thymoma submitted to thymothymomectomy presented a significantly better DFS and overall survival than those submitted to simple-thymomectomy. Thymothymomectomy should be considered the procedure of choice in Stage I TNM non-MG thymomas, also considering the not negligible rate of pathological upstaging.

Keywords: THYMOMA, Thymomectomy, Recurrence

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.09 BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA: OUTCOMES OF A NEWLY-RECOGNIZED MALIGNANCY OF THE THORACIC WALL

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Background: In 2016, the World Health Organization provisionally classified breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as a novel lymphoma and the National Comprehensive Cancer Network (NCCN) established evidence-based consensus guidelines for the diagnosis and surgical management of the disease. BIA-ALCL progresses locally as a solid tumor, invading the chest wall and mediastinum and leading to respiratory compromise in advanced cases. Local disease is treated surgically while aggressive disease involving regional lymph nodes and metastasis are currently managed with systemic chemotherapy, most commonly CHOP regimens (cyclophosphamide, vincristine, doxorubicin and prednisone). The goal of this study is to evaluate the efficacy of different therapies in the treatment of BIA-ALCL with chest wall invasion. **Method:** A prospective study of all institutional cases from 2013 to 2018 was performed for patients with advanced disease (Stage IIA-III) locally invasive into the chest wall. Pathologic findings, treatments, and outcomes were reviewed. **Result:** Eighteen consecutive patients were identified with BIA-ALCL Stage IIA-III. The median and mean follow-up times were 42 and 27 months, respectively (range, 6 to 226 months). Patients who underwent a complete en bloc resection had better OS (P = .022) and EFS (P = .014) than did patients who received partial resection, systemic chemotherapy, or radiation therapy. Perioperative complications included one pneumothorax. Two disease recurrences (7.8%) were noted at an average of 5 months from surgery. All patients eventually achieved complete remission (100%). The median overall survival (OS) time after diagnosis was 13 years, and the OS rate was 94% and 90% at 3 and 5 years, respectively. Patients presenting with chest wall invasion demonstrated significantly longer time from diagnosis to definitive surgery (21 versus 8 months, P = 0.039). Partial tumor resection resulted in disease hyperprogression in two cases. **Conclusion:** BIA-ALCL with chest wall invasion may be a consequence of a delay in diagnosis or treatment. Complete en bloc surgical excision is essential for curative treatment of BIA-ALCL. Patients who receive textured surface breast implants need to be advised of the risk of developing BIA-ALCL, as well as the common presenting symptoms, such as a mass or delayed onset (>1 year) of effusion. When treated appropriately and in a timely fashion, BIA-ALCL has an excellent prognosis. Future research is warranted to determine modifiable risk factors and stratification of at-risk populations.

Keywords: anaplastic large cell lymphoma, breast implant, rare chest wall tumor

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.10 LONG-TERM PROGNOSTIC FACTORS AFTER MINIMALLY INVASIVE ESOPHAGECTOMY (MIE) FOR ESOPHAGEAL CANCER

Y.-H. Huang, P.-W. Yang, K.-C. Chen, P.-M. Huang, J.-M. Lee

National Taiwan University Hospital, Taipei City/Taiwan

Background: MIE has been demonstrated to associate a better peri-operative outcome to treat esophageal cancer as compared to that done by open surgery. However, the long-term clinical impact of MIE and its prognostic factors still requires further clarification. **Method:** In current study, we evaluated the survival results and the factors influencing the prognosis of patients with esophageal cancer who received total minimally invasive esophagectomy using thoracoscopic and laparoscopic esophagectomy and esophageal reconstruction. **Result:** A total of 483 patients were included in the study with 179 and 304 receiving Ivor Lewis and McKeown MIE respectively. Neoadjuvant chemoradiation was administered to 379 (78 %) of the patients. The overall and disease progression-free survival curves of all the patients were constructed with five-year survival rates of 48.3% and 40.3% respectively. Multivariate analysis revealed that pathological tumor stage was a significant factor for prognosis after surgery both in the patients treated with and without neoadjuvant CCRT (P< 0.05). Of the patients with patholoigical stage I or ypStage I esopahgeal cancer after CCRT, overall survival was significantly improved with the increased number of dissected lymph nodes (P=0.022). **Conclusion:** The survival of patients with esophageal cancer undergoing MIE was influenced by their tumor staging, irrespective the use of neoadjuvant CCRT. Of these patients with stage I and ypStage I disease, improved survival can be facilitated with increased number of dissected lymph nodes during MIE.

Keywords: minimally invasive esophagectomy (MIE), esophageal cancer

MA20 THYMIC TUMORS: FROM MOLECULAR TO CLINICAL RESULTS AND NEW CHALLENGES IN OTHER RARE THORACIC TUMORS
TUESDAY, SEPTEMBER 10 11:30–13:00

MA20.11 SURGICAL TREATMENT FOR METASTATIC LUNG TUMORS FROM SARCOMAS OF SOFT TISSUE AND BONE

H. Yamamoto[1], K. Namba[1], H. Yamamoto[1], T. Toji[1], J. Soh[1], K. Shien[1], K. Suzawa[1], T. Kurosaki[1], S. Ohtani[1], M. Okazaki[1], S. Sugimoto[1], M. Yamane[1], K. Takahashi[2], T. Kunisada[1], T. Oto[1], S. Toyooka[1]

[1]*Okayama University Hospital, Okayama/Japan,* [2]*Center for Sarcoma, International University of Health and Welfare, Mita Hospital, Tokyo/Japan*

Background: Sarcoma is one of the refractory malignant tumors and often develops pulmonary metastasis. The purpose of this study was to evaluate the impact of surgical resection for metastatic lung tumors from sarcomas of soft tissue and bone retrospectively. **Method:** Between 2006 and 2015, we had a total of 158 patients with metastatic lung tumors from soft-tissue and bone sarcomas who underwent pulmonary metastasectomy for the first time. In total, 265 surgical procedures were performed in Okayama University Hospital in this period. We analyzed the age, sex, site of primary lesion, histology, extent of primary tumors at the initial diagnosis, extent of pulmonary metastases at the first pulmonary metastasectomy, presence or absence of local recurrence and/or extrapulmonary metastases with or before pulmonary metastases, operative procedures, size of the largest lesions resected, maximum number of the resected tumors, postoperative complications, and the prognosis at the end of 2018. **Result:** Average number of resected tumors per intervention was 4.0 (range 1-19). These sarcoma patients consisted of 36 males and 122 females, and their average age was 53.7 years (range 14-88 years). Leiomyosarcoma was the most common histological subtype (n = 92, 58.2%) and uterus was the most common location of the primary disease (n = 71, 44.9%). Operative procedures were composed of 202 partial resections, 35 segmentectomies with or without partial resections, 26 lobectomies with or without partial resections, 1 pneumonectomy, and 1 basal segmental auto-transplantation after pneumonectomy. The postoperative complications were limited, showing that pulmonary metastasectomies for sarcomas are acceptable. Overall 3-year survival after the first pulmonary metastasectomy was 50.6%. In univariate analysis, the survival was significantly better for the group with disease-free interval of more than 2 years from the date of the initial treatment for primary disease until the date of diagnosis for the first pulmonary metastasis, the one who underwent pulmonary resections three times or more, and the one in which size of the largest resected lesion was 20 mm or less. Those factors significant in univariate analysis were all significant in multivariate analysis. **Conclusion:** Surgical resections for metastatic lung tumors from sarcomas of soft tissue and bone were performed without major complications, indicating the acceptable feasibility. If disease-free interval is more than 2 years and the size of the largest resected lesion is less than 20 mm, patients may maximally benefit from pulmonary resection. In order to increase the opportunities of pulmonary resections, we should preserve the lung parenchyma as much as possible when performing pulmonary metatstasectomy, resulting in the better survival.

Keywords: metastatic lung tumor, sarcoma, metastasectomy

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.01 GENERATION AND CHARACTERIZATION OF NOVEL PRECLINICAL DISEASE MODELS OF NSCLC WITH NRG1 REARRANGEMENTS TO IMPROVE THERAPY

E. Gladstone, M. Vojnic, M. Offin, L. Delasos, A. Lui, E. Siau, H. Sato, R. Benayed, R. Kurth, M. Mattar, I. Khodos, E. De Stanchina, R. Daly, A. Schram, A. Drilon, M. Ladanyi, R. Somwar

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Background: Chimeric proteins encoded by NRG1 rearrangements retain the EGF-like domain of NRG1, a HER3 ligand that triggers HER3-HER2 heterodimerization and drives tumor growth. Activating NRG1 fusions have been identified in a variety of cancers including lung, pancreatic, breast, head and neck, etc, and previous work by our group has shown that anti-HER3 antibody (GSK2849330) therapy was effective at inducing a durable response in a NSCLC patient with a CD74/NRG1-fusion. It is possible that targeting both HER2 and HER3 would be more effective than targeting HER3 alone given that HER3-HER2 dimerization is necessary for tumorigenesis induced by NRG1 rearrangements. However, this has not been explored extensively due to a paucity of well-characterized preclinical models of NRG1-driven NSCLC. We aimed to establish patient-derived xenograft (PDX) and cell line models with NRG1-rearrangements to evaluate signaling networks and the role of novel therapies for this recently identified oncogene. **Method:** Approximately 30,000 tumor samples were evaluated for the presence of NRG1-fusions by targeted DNA and RNA sequencing (using the MSK-IMPACT and MSK-Fusion panels, respectively). Fresh tumor samples were collected and implanted into immune-compromised mice to generate PDX models and/or used to generate cell lines. Separately, NRG1-fusions were genomically engineered using CRISPR-Cas9 systems or by lentiviral transduction of cDNAs into immortalized human bronchiolar epithelial (HBEC) cells. RT-PCR and Sanger sequencing were used to verify NRG1-fusion mRNA expression, whereas western blot analysis examined fusion protein expression and phosphorylation. Subsequently, cell viability following inhibition of HER2, HER3 and downstream signaling pathways was assessed. **Result:** NRG1 fusions were identified in 24 patients (9 NSCLC); and we successfully generated two PDX models with corresponding cell lines from two NSCLC surgical specimens (2/2). One model harbors a CD74/NRG1 fusion whereas the second harbors a SLC3A2/NRG1-fusion. Using CRISPR-Cas9 mediated gene editing, we are introducing NRG1 fusions that were identified in NCSLC (CD74/NRG1, SLC3A2/NRG1, VAMP2/NRG1) into HBEC cells, and have generated a stable cell line with VAMP2/NRG1 fusion to date. In addition, we established a CD74/NRG1-positive model in HBEC cells using lentiviral transduction. Treatment of NRG1-fusion positive cells with small molecule inhibitors of HER2 (afatinib, neratinib, sapitinib) or trastuzumab inhibited growth, induced caspase 3/7 activity and blocked activation of PI3K and ERK signaling. Neratinib was more potent than other small anti-HER2 molecules. The PI3K inhibitor pictilisib inhibited growth of NRG1 fusion-positive cells as a single agent with little effect on non-tumor control cells. **Conclusion:** We generated novel NSCLC PDX and cell line models with verified NRG1 chromosomal rearrangements. *In vitro* studies show that targeting HER2 and PI3K effectively inhibits growth and induces apoptosis. Studies exploring the efficacy of additional agents targeting HER2, HER3 and PI3K alone or in combination using in vivo models are ongoing and results will be presented.

Keywords: NRG1, NSCLC

MA21.02 GENOMIC ORIGIN AND EGFR-TKI EFFICACY OF PULMONARY ADENOSQUAMOUS CARCINOMA

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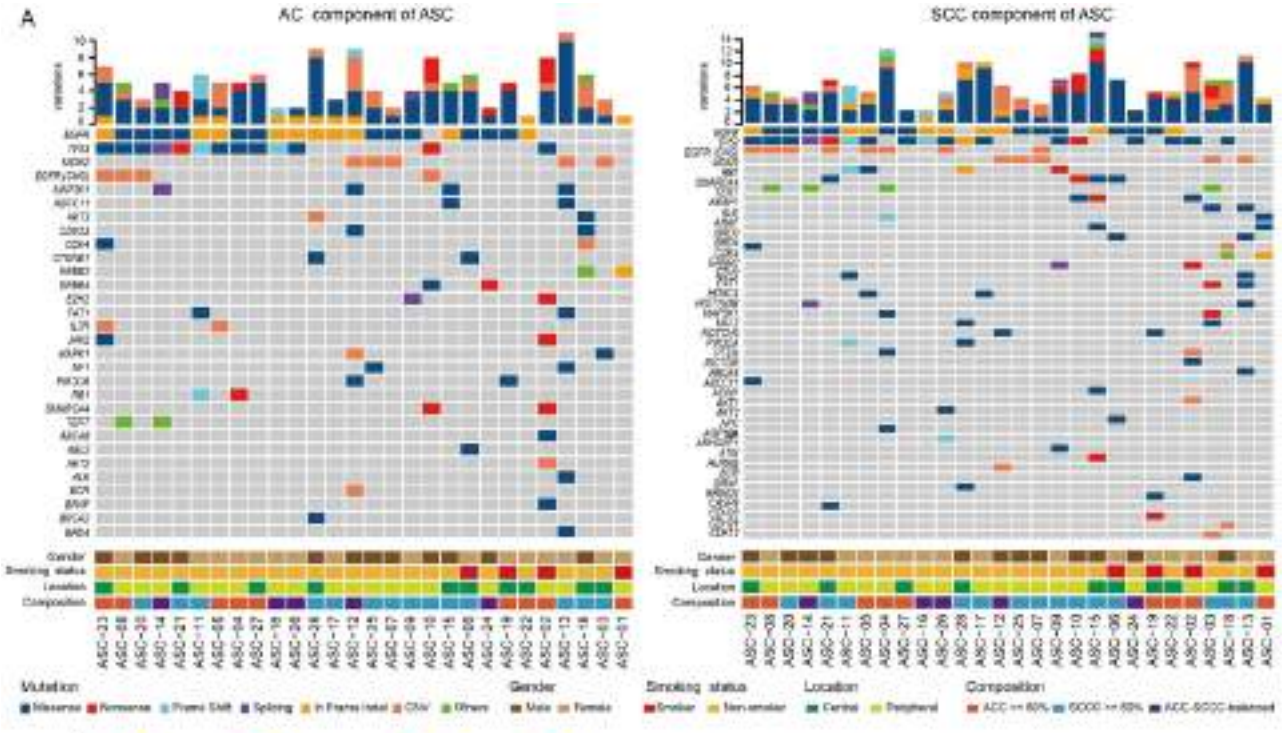
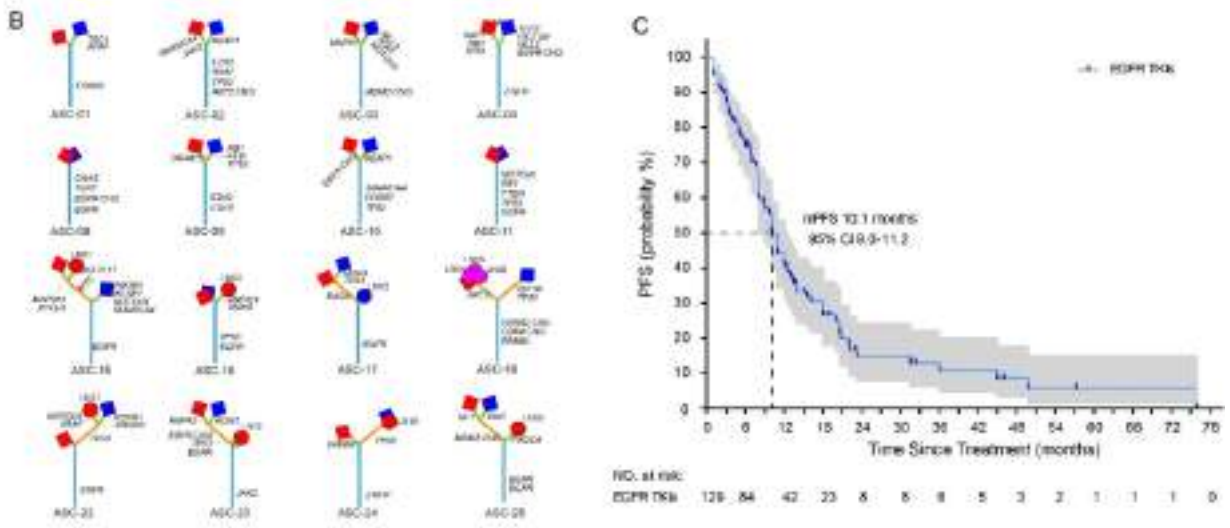
Background: Lung adenosquamous carcinoma (ASC) is a heterogeneous disease that comprises of both adenocarcinoma (AC) and squamous cell carcinoma (SCC) components. Their genomic profile, evolutionary origin, and clinical management remain controversial. Objective of this study is to define the genomic origin of this heterogeneous tumor by independent genomic analyses of the AC and SCC components. **Method:** Surgical ASCs were collected. AC component and SCC component were obtained separately by microdissection, and Lymph node (LN) metastases were gathered. Targeted sequence was performed for the two components using a 1021-gene panel, independently. Evolutionary relationship of the two components was analyzed. The independent cohorts of adenocarcinoma (n=170) and squamous cell carcinomas (n=62) were used for comparison. *EGFR* and concomitant mutations with response to EGFR-TKI were analyzed. Retrospective 517 ASCs underwent *EGFR* detections were collected from 11 centers. Objective response rate (ORR), disease control rate (DCR) and progression free survival (PFS) were analyzed in *EGFR*-positive patients received EGFR-TKIs. **Result:** 28 ASCs were collected. NGS was performed on AC component and SCC component samples, respectively. The most frequent alterations in 28 ASCs were *EGFR* mutation (79%), *TP53* mutation (68%), *MAP3K1* mutation (14%), *EGFR* amplification (32%), and *MDM2* amplification (18%). 27 patients had trunk variations in the both components suggesting the monoclonal origin of ASCs. The prevalence of trunk mutations was correlated to those of AC, indicating that ASC might originate from AC. Only one patient did not carry any trunk variations between AC and SCC components, which were clearly and geographically distinguishable under the microscope. 22 had AC component or/and SCC component specific variations suggesting the common event of branch evolution. The 23 LNs of 13 patients mainly contained AC and ASC components (AC, SCC, and ASC: 11, 1, and 11, respectively), and each of the LNs carried the trunk mutations of the primary ASC. Like pure AC, the alterations of L858R and Exon 19 Dels of *EGFR* were common in the 28 ASCs. Unfortunately, these patients have not been treated with TKIs. Further, of 517 retrospective ASCs from 11 centers, 51.8% were *EGFR*-positive. For the 129 *EGFR*-positive ASCs who had received TKIs, the ORR and DCR were 56.6% and 89.1%, respectively. The median PFS was 10.1 months (95% CI: 9.0-11.2).





Conclusion: The AC and SCC components share a monoclonal origin, and a majority have branching evolution. ASC may represent a subtype of adenocarcinoma with *EGFR* mutation being the most common genomic anomaly and sharing similar efficacy to EGFR-TKIs.

Keywords: Monoclonal origin, EGFR-TKI efficacy, Adenosquamous carcinomas

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.03 THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER (IASLC) GLOBAL SURVEY ON MOLECULAR TESTING IN LUNG CANCER

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Background: Evidence-based standards for molecular testing of lung cancer have been established, but the global frequency and practice of testing are not well understood. The IASLC conducted an international survey to evaluate current practice and barriers to molecular testing. **Method:** Distributed to IASLC members and other healthcare professionals, content included: 7-question introduction, 32 questions for those requesting tests/treating patients, 45 questions on performing/interpreting assays, and 24 questions on tissue acquisition. All respondents were asked to provide 3-5 barriers to implementing/offering molecular testing. Respondents' countries were grouped by geography or developing/developed using IASLC and World Bank criteria. Surveys were available in 7 languages. Regional comparisons used the Chi-squared test or ANOVA; free-text was analyzed with Nvivo. **Result:** We obtained 2,537 responses from 102 countries. Respondents were 45% Medical Oncologists, 12% Pulmonologists, 12% Thoracic Surgeons, 9% Pathologists, and 22% scientists or other. 56% of responses were from developing countries, 44% developed. Regions included: 52% Asia, 19% Europe, 11% Latin America, 11% US/Canada, 7% Other. 1683 (66%) chose the requesting/treating track (50% government, 42% academic, 8% other). 61% reported most patients in their country do not receive molecular testing, with the lowest rates in Latin America/Other (p<0.0001). 39% were not satisfied with the conditions of molecular testing in their country. Indications for requesting testing included: adenocarcinoma (89%), never-smoker (61%), female (57%), and young (54%) (variable by region, p<0.0001). 99% ordered EGFR, 95% ALK, 84% PDL1, 79% ROS1, all other tests <50%. 56% typically received results within 10 days. Only 67% were aware of CAP/IASLC/ AMP guidelines, least frequently in Asia/Other (p=0.041). 37% have trouble understanding molecular testing result reports, most of whom cited a need for more technical and scientific knowledge. 75% had multidisciplinary tumor boards, but 23% met <1/month. The 316 (12%) testing track respondents were from laboratories that were 49% academic, 35% government, and 16% private/other. 94% of laboratories offered EGFR, 83% ALK, 69% KRAS, 68% BRAF, 64% ROS1, 56% HER2, and others <50%; 68% tested for PDL1. 57% offered Multiplex assays, less frequently in Latin America/Asia (p=0.0294). 69% tested blood-derived DNA, less frequently in US/Canada/ Other (0.0013). 23% of respondents reported >10% of cases are rejected due to inadequate samples; however, 47% stated there is no policy or strategy to improve the quality of the tissue samples in their country. 52% reported patients/physicians are not satisfied with the state of molecular testing in their country. Respondents performing/interpreting assays (334, 14%) were typically informed of biopsy results (91%), and notified when the sample was inadequate (84%). The most frequent barrier to molecular testing in every region was cost, followed by quality/standards, turnaround-time, access, and awareness. After cost, time was the most common barrier in developed countries, while it was quality in developing countries. The second largest barrier was quality in Asia, access in Europe/Latin America/Other, and turn-around time in US/Canada. **Conclusion:** These preliminary analyses show molecular testing usage varies across the globe. Barriers vary by region, and one-third of respondents were unaware of evidence-based guidelines. Global and regional strategies should be developed to address barriers.

Keywords: Molecular Testing

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.05 PHASE II TRIAL OF THE COMBINATION OF ALECTINIB WITH BEVACIZUMAB IN ALK-POSITIVE NONSQUAMOUS NON-SMALL CELL LUNG CANCER

S. Watanabe[1], N. Matsumoto[2], J. Koshio[3], A. Ishida[3], T. Tanaka[4], T. Abe[5], D. Ishikawa[6], S. Shoji[1], K. Nozaki[1], K. Ichikawa[1], R. Kondo[1], A. Otsubo[1], A. Aoki[7], T. Kajiwara[8], K. Koyama[8], S. Miura[8], H. Yoshizawa[9], T. Kikuchi[1]

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Background: Alectinib is a 2nd generation highly selective anaplastic lymphoma kinase (ALK) inhibitor. Although alectinib has improved progression-free survival (PFS) in patients with *ALK*-positive Non-Small Cell Lung Cancer (NSCLC), there are limited treatment options after progression of alectinib. Recent evidences have described promising results of the combination of bevacizumab with EGFR-TKIs, cytotoxic chemotherapies and immune-checkpoint inhibitors. We report the results from a phase II study of the combination of alectinib with bevacizumab in *ALK*-positive Nonsquamous NSCLC patients who were treated with alectinib and showed disease progression (UMIN 000017828). **Method:** Patients with *ALK*+ Nonsquamous NSCLC who had progressed after alectinib treatment were enrolled. Primary objective of this study was PFS and safety. Secondary endpoints included overall survival, objective response rate and disease control rate. **Result:** Twelve patients received alectinib (600 mg/day) with bevacizumab (15 mg/kg, Q3W). Nine patients were treated with crizotinib and alectinib, and 2 patients were treated with crizotinib, alectinib and ceritinib before enrollment to this study. The median PFS was 3.1 months (95% CI 1.2-16.1) and the median survival time was 32 months (95% CI 8.3-NE). The median treatment cycle was 5 (range, 1-37) and 3 patients received alectinib with bevacizumab more than 20 cycles. The objective response rate and disease control rate were 8% and 67%, respectively. The most common treatment related adverse events were decreased appetite (42%), proteinuria (42%), hypertension (33%), anemia (33%) and fatigue (33%). Treatment related adverse events of grade ≥ 3 were anemia (8%), proteinuria (8%), diarrhea (8%) and hypokalemia (8%). No severe adverse events were observed. **Conclusion:** This is the first study to investigate the combination of alectinib and bevacizumab. This combination had clinical efficacy and was well tolerated.

Keywords: alectinib, ALK, Bevacizumab

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.06 PRELIMINARY PHASE 1 RESULTS OF U3-1402 — A NOVEL HER3-TARGETED ANTIBODY–DRUG CONJUGATE—IN EGFR TKI-RESISTANT, EGFR-MUTANT NSCLC

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Background: Treatment options are limited for epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) resistant to EGFR tyrosine kinase inhibitors (TKIs), in particular osimertinib. Overall, 57%–83% of NSCLC tumors express human epidermal growth factor receptor 3 (HER3). Because signaling through HER3 is not an established mechanism of resistance to EGFR TKIs, treatment with an anti-HER3 antibody–drug conjugate (ADC) presents an approach to targeting diverse resistance mechanisms in EGFR-mutant NSCLC. U3-1402 is a HER3-targeted ADC with a fully humanized antibody, novel cleavable peptide-based linker, and topoisomerase I inhibitor payload. Here, we present the safety/tolerability and antitumor activity data from the dose-escalation phase of an ongoing, multicenter, phase 1 study (NCT03260491). **Method:** Patients had locally advanced or metastatic EGFR TKI-resistant, EGFR-mutant NSCLC. Patients with stable brain metastases were eligible. Dose escalation was based on dose-limiting toxicities (DLTs) guided by a Bayesian logistic regression model. U3-1402 was administered every 3 weeks via intravenous infusion. Pretreatment tumor tissue was required for retrospective HER3 immunohistochemistry analysis. Next-generation sequencing analysis was performed on available tumor tissue. Primary objectives included safety, tolerability, and identification of the recommended dose for expansion (RDE). **Result:** As of May 2019, 30 patients were enrolled across 4 doses (3.2 [n=4], 4.8 [n=9], 5.6 [n=12], and 6.4 [n=5] mg/kg). Thirteen patients (43%) have discontinued (progressive disease [n=9], clinical progression [n=1], consent withdrawal [n=2], adverse event [AE; n=1]). All 30 patients received prior *EGFR* TKIs, of which 28 (93%) received prior osimertinib, and 15 (50%) prior chemotherapy. Activating EGFR mutations were reported in all patients (Ex19del: 57%; L858R: 40%; L861Q: 3%). All 25 evaluable tumors demonstrated HER3 expression (median HER3 membrane H-score, 183 [range, 56–290]). History of central nervous system (CNS) metastases was reported in 15 patients (50%). Treatment-emergent AEs were reported in 29 patients (97%; 13 patients [43%] reported grade 3/4). Two DLTs (grade 3 febrile neutropenia and grade 4 platelet count decrease) were reported in 1 patient (5.6 mg/kg) and 3 DLTs (all grade 4 platelet count decrease) in 3 patients (6.4 mg/kg). Of patients with a history of CNS metastases, 9 have progressed (2 with CNS progression; 3 with both CNS and non-CNS progression). One patient without a history of CNS metastasis progressed with new CNS disease. Of 26 efficacy-evaluable patients, 6 had confirmed partial responses (2 each at 4.8, 5.6, and 6.4 mg/kg), including 2 patients with an EGFR C797S mutation. Median best percentage change in sum of diameters (SoD) was −25.7% (range, −82.6% to 13.3%), including decreases in SoD in patients with *CDK4* amplification (–25.7% and –17.8%), *HER2* amplification (–28.6%), and both *CCNE1* amplification and *PIK3CA* mutation (–28.8%). **Conclusion:** U3-1402 demonstrated tolerable safety and antitumor activity in this ongoing study. Antitumor activity of U3-1402 was seen in cancers with EGFR-mediated and other resistance mechanisms. These findings support the hypothesis that targeting HER3 with U3-1402 may provide clinical benefit to patients with *EGFR*-mutant NSCLC with diverse mechanisms of resistance. RDE evaluation is ongoing.

Keywords: antibody drug conjugate, U3-1402, EGFR TKI-resistant NSCLC

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.07 CIRCULATING TUMOR DNA ANALYSIS DEPICTS POTENTIAL MECHANISMS OF RESISTANCE TO BRAF-TARGETED THERAPIES IN BRAF+ NON-SMALL CELL LUNG CANCER

S. Ortiz-Cuaran[1], L. Mezquita[2], A. Swalduz[3], M. Aldea[2], J. Mazieres[4], C. Jovelet[5], W.R. Chumbi Flores[6], L. Lacroix[5], Y. Loriot[2], L. Friboulet[2], V. Westeel[7], M. Ngocamus[5], A. Pradines[8], C. Tissot[9], C. Clement Duchene[10], C. Raynaud[11], X. Quantin[12], R. Gervais[13], E. Brain[14], I. Monnet[15], E. Giroux Leprieur[16], V. Avrillon[17], C. Mahier-Aït Oukhatar[18], N. Hoog-Labouret[19], F. De Kievit[20], K. Howarth[20], J.-F. Guichou[21], C. Morris[20], E. Green[20], M. Perol[22], B. Besse[23], J.-Y. Blay[3], P. Saintigny[1], D. Planchard[5]

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Background: Oncogenic BRAF-V600 mutations are observed in 1-2% of non-small cell lung cancer (NSCLC). Targeted therapies including vemurafenib (V), dabrafenib (D) or combination of

dabrafenib plus trametinib (D+T) are associated with favorable outcomes in these patients (pts). The mechanisms of resistance to BRAF-targeted therapies (BRAF-TT) in NSCLC are largely unknown. **Method:** We performed genomic profiling of serial circulating-tumor DNA (ctDNA) in a cohort of 79 metastatic BRAF-mutant NSCLC pts (96% V600E, 4% non-V600). BRAFmutational status was ascertained based on local testing. Plasma samples were collected, from 2014-2018 in 27 Hospitals, from pts treated with V (n=34), D (n=2) or D+T (n=23). We collected 41 plasma samples at baseline to BRAF-TT, 40 at progressive disease (PD) and ~200 samples during treatment follow-up, concomitant to routine radiological evaluation. Inivata InVisionSeq™ assay was used to detect the presence of SNVs, indels and CNAs in 36-cancer related genes. **Result:** At baseline, 72,5% of BRAF mutations (V600E and non-V600E) were detected in plasma. BRAF-V600E detection in plasma was associated with the presence of liver metastasis, versus BRAF-V600E-negative cases (22% vs. 7%, respectively). Co-occurring molecular alterations at baseline, besides BRAF-V600E, were observed in 18/26 (70%) cases: FGFR2 (1pt), PIK3CA (2pts), ERBB2 (1pt), CTNNB1 (2pts) and IDH1 (2pts). FGFR2, PIK3CA or CTNNB1 alterations were associated with PD as the best response to the subsequent BRAF-TT. TP53 and STK11 mutations were observed in 54% (14/26) and 8% (2/26) of pts, respectively. Complete clearance of BRAF-V600E in plasma at baseline was observed at the first CT-scan evaluation in 42% (3/7) and 82% (9/11) pts treated with V or D+T, respectively. These pts were in complete or partial response, suggesting that monitoring BRAF-V600E levels in plasma on treatment may be a clinically useful marker of tumor response. At PD, a consistent rebound in BRAF-V600E plasma levels was observed in 60% (24/40) pts. Resistance to V was associated with alterations in the MAPK pathway: 1pt (KRAS), 1pt (GNA11), 1pt (NRAS and GNAS) and 1pt (MAP2K1 and NFE2L2). Activating PI3KCA mutations were observed in 4 pts who progressed in <6 months on V treatment. ctDNA analyses at PD under D+T revealed that, similar to what we observed in patients who progressed on V, alterations in KRAS, NRAS, PIK3CA and CTNNB1 are associated with D+T resistance. Prediction of the impact of these alterations, at the protein level, was assessed using in silico structure modeling and will be presented. **Conclusion:** ctDNA monitoring might be an informative tool for assessing disease response and resistance in NSCLC pts treated with BRAF-TT. MAPK reactivation remains an important resistance mechanism to BRAFi-monotherapy or to BRAFi and MEKi combination therapy.

Keywords: braf, resistance, circulating-tumor DNA

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.09 TYROSINE KINASE INHIBITORS' PLASMA CONCENTRATION AND ONCOGENE-ADDICTED ADVANCED NON-SMALL LUNG CANCER (ANSCLC) RESISTANCE

A. Geraud, L. Mezquita, E. Auclin, D. Combarel, J. Delahousse, C. Naltet, C. Jovelet, P. Lavaud, A. Gazzah, L. Lacroix, J. Remon, C. Caramella, D. Planchard, O. Mir, A. Paci, B. Besse

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Background: The development of TKIs against driver molecular alteration has changed treatment paradigm in aNSCLC patients (pts). All tumors eventually progress and a resistance mechanism is identified in only a fraction of pts. Plasma concentration of TKI can decrease after chronic exposition but limited data are available. Our hypothesis is that an insufficient plasma exposure could contribute to tumor progression (PD). **Method:** We assessed the plasma concentration of TKI in pts with aNSCLC harboring *ALK* rearrangement, *EGFR* or *BRAF V600E* mutation. We defined chronic exposure as a treatment administered > 3 months. Patients' characteristics and co-medications were collected. Residual plasma concentrations were measured using Ultra Performance Liquid Chromatography coupled with tandem mass spectrometry validated methods. We compared results to currently recommended therapeutic targets and correlated exposure levels to treatment benefit. **Result:** Between Apr. 2014 and Feb. 2019, 51 samples were prospectively collected (gefitinib n=11, osimertinib n=10, erlotinib n=13, crizotinib n=7, dabrafenib + trametinib n=5) in 41 pts. Median time of exposure was 20.3 months (range 2.18 - 67.813). Low plasma concentration was observed in 31 (61%) samples. Out of 14 samples collected in pts with ongoing benefit, 10 (71%) had low plasma exposure. Smoking status was associated with low plasma TKI concentration (P=0.01) whatever the TKI used. A total of 37 samples were collected at PD, 21 (57%) had low plasma exposure. The median time to treatment failure (TTF) in the 'low exposure group' (n=31) was 14.9 months (95% CI 12.48 – 33.2) vs. 24.6 months (95% CI 8.65 -not reached (NR) in the 'normal exposure group' (P=0.55). No significant impact of protons pump inhibitors on TTF was found (p=0.12), including with gefitinib and erlotinib (p=0.76; n=24). In case of isolated brain PD (n=4), 3 pts (75%) had low plasma exposure. TKI dose was reduced in 14 pts because of toxicity, median TTF was 17.0 months (95% CI 10.4-NR) vs. 20.1 months (95% CI 10.4-59.8, P=0.45 in pts treated with standard dose. In the *EGFR* mutated aNSCLC population at PD (n=19), T790M resistance mutation was more frequent in the 'normal exposure group' (37.5%, n= 3/8,) than in the 'low exposure group' (9.1%, n=1/11), OR=0.13 95%CI (0.01-1.29), p=0.08. **Conclusion:** TKI is underdose in the majority of aNSCLC patients at PD. Low TKI concentration were more frequent in pts without tumor resitance mechanism. Altogether, it suggests that low TKI exposure might contribute to PD.

Keywords: resistance mutations, pharmacokinetics, Tyrosine Kinase inhibitors

MA21 NON EGFR/MET TARGETED THERAPIES
TUESDAY, SEPTEMBER 10 14:30–16:00

MA21.10 PHASE II STUDY OF 160MG OF OSIMERTINIB IN EGFR T790M POSITIVE NSCLC WITH BRAIN OR LEPTOMENINGEAL METASTASES WHO PROGRESSED ON PRIOR EGFR TKI

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Background: EGFR tyrosine kinase inhibitor (TKI) has successfully improved clinical outcome in non-small cell lung cancer (NSCLC) with activating EGFR mutation. However, up to 40% of TKI treated patients present with disease progression in the central nerve system (CNS) either as brain metastases (BM) or leptomeningeal metastases (LM). Osimertinib is a 3rd generation EGFR TKI effective in T790M mutant NSCLC and characterized by high blood-brain barrier penetration. In this phase II, multicenter prospective single-arm two cohort study, the clinical efficacy of 160mg of osimertinib in T790M mutant BM or LM patients progressed on prior EGFR TKI was evaluated. (NCT0325712) **Method:** BM only patients were included in the BM cohort (n=40). Patients with cerebrospinal cytology confirmed LM with or without BM were included in the LM cohort (n=40). 3rd generation TKI, including 80mg of osimertinib, was exposed to 18 patients in BM and 16 patients in LM cohort. T790M need to be identified from either tissue, plasma or cerebrospinal fluid. The primary endpoint was overall response rate (ORR) (H_1=30%) for BM cohort and overall survival (OS) (H_1=5months) for LM cohort, respectively. **Result:** Median follow-up duration was 7.9 months for BM and 8.3 months for LM cohort. In BM cohort, median progression-free survival (PFS) was 7.3 months (95% confidential interval [CI] 3.6-13.7), and median OS was not reached (NR). Intracranial ORR and disease control rate (DCR) was 40.0% and 77.5%. Extracranial ORR and DCR was 30.0% and 67.5%. In LM cohort, median PFS was 8.9 months (95%CI 5.6-NR) and median OS was 13.2 months (95%CI 8.0-NR). When response of leptomeningeal lesion is separately evaluated, CR rate was 25.0% (n=10) and non-CR/non-PR rate was 65.0% (n=26). Extracranial ORR and DCR was 22.5% and 85.0%. Intracranial median PFS was not reached in both BM and LM cohort. Grade 3 adverse event (AE) was observed in 7 BM and 11 LM patients. Four patients required dose reduction due to AE. Among the patients who previously received 3rd generation TKI, 33.3% (6 out of 18) in BM cohort and 81.2% (13 out of 16) in LM cohort showed an intracranial DCR to 160mg of osimertinib. Extended survival analyses and exploratory outcomes will be presented at the conference. **Conclusion:** In this study, 160mg of osimertinib demonstrated promising ORR and survival benefit with tolerable safety profile in EGFR T790M positive NSCLC patients with CNS metastasis who progressed on prior EGFR TKI.

Keywords: Osimertinib, Brain metastases, leptomeningeal metastases

MA21 NON EGFR/MET TARGETED THERAPIES
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MA21.11 A MULTICENTER PHASE II STUDY OF LOW-DOSE ERLOTINIB IN FRAIL PATIENTS WITH EGFR MUTATION-POSITIVE, NON-SMALL CELL LUNG CANCER: TORG1425

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Background: We conducted a multicenter phase II trial evaluating the efficacy of low-dose erlotinib (ERL) in frail patients with EGFR-mt non-small cell lung cancer (NSCLC). The primary endpoint was met, with the objective response rate (ORR) of 60%. Here we present the final overall survival (OS) results. Furthermore, we investigated the effect of ABCB1 genetic polymorphisms on the ERL plasma concentration pharmacokinetics (PK) and pharmacodynamics (PD). **Method:** Chemotherapy-naïve NSCLC patients with *EGFR* mt who had frailty were enrolled and received ERL 50 mg/d. Patient's frailty was defined as follows: (Group 1) 20 to 74 years of age with Eastern Cooperative Oncology Group performance status (PS) ≥2 or Charlson Comorbidity Index (CCI) ≥6 points; (Group 2) 75 to 80 years of age with PS ≥1 or CCI ≥6 points; (Group 3) ≥81 years of age with any PS and CCI. ABCB1 gene polymorphism analysis were using the i-densy™ genetic testing platform, and blood samples for the ABCB1 genetic testing were collected prior to treatment. Steady-state trough plasma ERL concentration was measured with a high-performance liquid chromatograph-tandem mass spectrometry at 15 days (±7 days) after initiating ERL administration. **Result:** From December 2014 and April 2017, 80 patients were enrolled: males/females 26/54; median age 80 (range 49-90); Group 1/2/3 15/28/37; Ad/Sq/Others 76/1/3. *EGFR* mt types were: exon 19/21 42/38. All 80 patients were included in efficacy and safety analysis. Median progression-free survival and OS were 9.3 (95%CI: 7.2-11.4), 26.1 (95%CI: 21.9-30.4) months respectively. The trough of ERL could be measured in 48 patients, and 45 of these patients were analyzed for ABCB1 genetic polymorphism. The ORR for the 48 patients was 62.5%, and their median trough of ERL was 685ng/ml (range 153-1950), which surpassed the reported "effective" level (500ng/ml). Nine (60%) of 15 the patients who failed to achieve the level responded. Genetic polymorphisms were not correlated with ERL PK, nor were they associated with efficacy and adverse events. **Conclusion:** This is the first prospective study evaluating low-dose ERL for frail patients with *EGFR* mt NSCLC. This treatment was safe and effective, and the ABCB1 genetic polymorphisms did not affect ERL PK/PD. Clinical trial information: UMIN 000015949.

Keywords: erlotinib, frail, NSCLC

MA22 PARTNERING WITH PATIENTS TO UNDERSTAND STIGMA, DISPARITIES AND VALUES LEADING TO IMPROVED LUNG CANCER CARE
TUESDAY, SEPTEMBER 10 14:30–16:00

MA22.01 LUNG CANCER PATIENTS' UNIQUE VALUES AND PREFERENCES LEAD TO CLINICAL TRIAL PREFERENCES

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Background: Only about 5% of cancer patients participate in clinical trials. We previously conducted a survey of U.S. lung cancer patients and found that only 22% reported discussing clinical trials with their oncologist at the time of making treatment decisions. We hypothesize these low rates of trial discussion and participation may be due in part to current clinical trial designs not reflecting unique values and preferences of lung cancer patients that differ from other non-cancer conditions. **Method:** Utilizing an online survey inquiring about clinical trial attitudes of patients with several different clinical diagnoses in the United States, we chose to compare a group of lung cancer patients (LC group) to patients diagnosed with a non-cancerous condition (chronic allergies or asthma) (AA group). 229 participants in the LC group and 367 in the AA group were asked to indicate the personal impact of several information sources for finding out about clinical trials and several potential motivators for clinical trial participation. **Result:** The LC group reported the doctor's office as their main information source for clinical trials, while the AA group indicated advertisements as their primary source for finding out about trials. In terms of motivation to join trials, 60% of the LC group said having their doctor's support for joining a given trial was very important to them (only 33% of the AA group said so). Being paid for participation was reported as being motivating by 69% of the AA group versus only 23% of the LC group. When asked about what they valued when looking for a clinical trial, the LC group said extending quality and length of life and receiving access to otherwise unavailable therapy options were very important. The AA group placed much less importance on these same values. **Conclusion:** We should consider the unique ways lung cancer patients seek information and what they value when designing a strategy to recruit to or educate about a clinical trial. Effective, tailored strategies may include increasing the use of providers as primary trial educators and focusing outreach surrounding trials on lung cancer patient motivators that differ from those with other diagnoses.

Keywords: clinical trials, Lung cancer

MA22 PARTNERING WITH PATIENTS TO UNDERSTAND STIGMA, DISPARITIES AND VALUES LEADING TO IMPROVED LUNG CANCER CARE
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MA22.02 THE IMPACT OF PATIENT ENGAGEMENT ON STUDY DESIGN AND PATIENT RECRUITMENT IN A PRAGMATIC TRIAL TO IMPROVE CANCER CARE DELIVERY

A. Bell-Brown[1], S. Sullivan[2], G. Lyman[1], D. Hershman[3], K. Watabayashi[1], K. Kreizenbeck[1], S. Shirley[1], A. Ciccarella[4], G. Walia[5], J. Johnson[4], C. Seigel[4], G. Mason[6], F. Kurttila[4], B. Segarra-Vazquez[7], S. Ramsey[1], B. Haddock Lobo Goulart[1]

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Background: SWOG trial S1415CD is a pragmatic study comparing outcomes of Colony Stimulating Factor (CSF) use in usual care with care that uses guideline-informed standing CSF orders. A 21-person External Stakeholder Advisory Group (ESAG), including 10 patient partners, has informed the design, implementation, recruitment and dissemination planning for the study. Recruitment has been a challenge for study sites, specifically around approaching and consenting patients in the window between diagnosis and first cycle of chemotherapy. This abstract explores the impact of the ESAG patient partners on the patient recruitment process for S1415CD. **Method:** Patient partners are convened each year over monthly teleconferences, one in-person meeting and targeted email communication. Patient partner input from 2014-present has been tracked and reviewed for impact on the patient recruitment process. After the start of accrual in October 2016, a teleconference was held in spring 2017 focused on barriers to patient accrual, specifically patient approach. Study sites submit monthly screening logs detailing reasons for patient ineligibility. **Result:** Prior to the start of accrual, patient partners collaborated with the research team to create 2 resources to assist clinic staff with presenting the trial in lay terms: a patient brochure and a summary handout for clinical research associates (CRAs). CRAs reported high use of the brochure as a valuable, simple tool for explaining the trial to eligible patients. Patient partners were also engaged in developing consent forms for trial participants. In addition, patient partners developed strategies for approaching patients in the timeframe between diagnosis and first cycle of chemotherapy which were compiled into a document for study sites and incorporated into the trial's frequently asked questions. Between October 2016-June 2017, the approach and consent process (i.e. the inability to consent patients in the narrow timeframe) accounted for 22% of all reported ineligible patients, however after the implementation of patient-formulated strategies, during June 2017-December 2018, the approach and consent process has accounted for only 10% of all reported ineligible patients. **Conclusion:** Sustained engagement and active participation of patient partners throughout S1415CD has provided unique experiential knowledge and feedback to improve the patient approach and consent process across study sites, leading

to increased opportunities for patient recruitment. Engaging patient partners early and throughout the study design and conduct phases of the research has been successful in providing patient-centered solutions to recruitment and implementation challenges, including the challenge of timing, to ensure success in reaching the study accrual goals.

Keywords: HICOR, Advocacy, patient engagement

MA22 PARTNERING WITH PATIENTS TO UNDERSTAND STIGMA, DISPARITIES AND VALUES LEADING TO IMPROVED LUNG CANCER CARE
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MA22.03 THE ROS1DERS: PARTNERING TO DRIVE RESEARCH AND IMPROVE OUTCOMES IN ROS1+ CANCERS

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The ROS1ders, Mountain View/United States of America

Background: ROS1 fusions are found in a dozen types of cancer. However, these fusions are rare, occurring in a small fraction of patients (e.g.,1%-2% of non-small cell lung cancer). The small population hampers gathering sizeable patient cohorts and investment in medical research. The ROS1ders are a group of patients and caregivers dealing with ROS1-positive (ROS1+) cancer who strive to better outcomes for all ROS1+ cancers by supporting patients and caregivers, increasing awareness and education, accelerating research, and improving access to effective diagnosis and treatment. **Method:** We created a private ROS1+ Facebook group for sharing personal information and support among patients and caregivers. We created a public Facebook group for outreach. We launched a website at ROS1cancer.com to share sourced information about ROS1 drugs, clinical trials, expert clinicians, and research developments as well as patient blogs and tips for living with our disease. We attended medical conferences and met with cancer advocacy organizations, clinicians, researchers, and industry; we collectively began working on projects to accelerate research into our disease through the Global ROS1 Initiative. We are active in developing and implementing our projects as well as serving as fundraisers and the ROS1+ public face. **Result:** The ROS1ders is the largest cohort of ROS1+ patients and caregivers ever collected. We add new members weekly, and have grown to include 400+ members from 28 countries. We network with ROS1+ communities who communicate in languages other than English in Europe, China and Japan. Expert ROS1 clinicians collaborate with us to ensure we provide accurate information about our disease in our Facebook groups and our website. ROS1+ patients have donated fresh tissue and pleural fluid specimens to the ROS1 Cancer Model Project to create cell lines and patient-derived xenograft (PDX) mice; the resulting cell lines have been shared with several institutions in academia and industry. We have contributed data to an epidemiological study. We are collaborating to develop a registry-based study of blood clots in ROS1+ and other lung cancer patients. Some ROS1ders are developing new projects in their home countries. **Conclusion:** The ROS1ders are breaking new ground, sharing current information, collecting data and biospecimens from ROS1+ patients, and enabling research and development of treatments for our cancer in ways that were not possible before. The Global ROS1 Initiative is truly a partnership between patients, caregivers, advocacy organizations, clinicians, researchers, and industry.

Keywords: oncogene-focused patient group, ROS1, patient-partnered research

MA22 PARTNERING WITH PATIENTS TO UNDERSTAND STIGMA, DISPARITIES AND VALUES LEADING TO IMPROVED LUNG CANCER CARE
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MA22.05 ASSESSMENT OF GENDER DIFFERENCES IN THE PSYCHOSOCIAL AND ECONOMIC IMPACT ON PATIENTS WITH STAGE IV NON-SMALL CELL LUNG CANCER

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Background: Incidence of lung cancer in women is rising overtime reporting evident gender-based differences in epidemiology, biology, and treatment outcome. However, little is known about gender-differences regarding psychological, economic and social aspects. The objectives of this prospective study are to evaluate the psychosocial and economic impact of metastatic non-small cell lung cancer (NSCLC), according to gender. Additionally, to assess the emotional burden and the economic impact of the disease on the primary caregiver from a gender perspective **Method:** Multicenter, prospective, observational, study of two cohorts of patients with metastatic NSCLC (male and female) in Oncology departments of 20 Spanish hospitals. The following measurement tools were used: the APGAR questionnaire (family functionality: adaptability, partnership, growth, affection, and resolve), the Relationship impact scale, the DUKE-UNC scale (perceived socio-affective support), the patient and the caregiver economic impact scale and the Zarit scale (caregiver burden). All questionnaires were performed at the first visit, repeated 4 months later and following the first and second disease progression. **Result:** Of the 333 pts included, 104 were females and 229 male, of whom 63% and 97%, respectively, were smokers/ex-smokers (p=0.0001). More women than men (85% vs 70%) had adenocarcinomas. The median overall survival was longer in women but did not reach statistical significance [17.1 vs 11.0 months, HR 0.732 (95% CI 0.534 to 1.005), p=0.0524]. Most families considered themselves functional (high score in APGAR questionnaire) with no changes in their partner relationship and social support was evaluated as optimal for majority of patients. Around a quarter of interviewed patients said their economic situation was a little worse after the lung cancer diagnosis, without remarkable differences by gender. Statistically significant differences were found between both groups regarding the caregiver´s relationship to the patient (more parents were the caregiver in females than in males) (p <0.0001) and the caregiver's employment situation (more employed caregivers in females) (p<0.0001). Most caregivers of both sexes considered that taking care of their relative did not pose a significant burden. No remarkable differences by gender were found between the different variables across the study. **Conclusion:** This study provides a preliminary insight into gender-related characteristics in the management of advanced NSCLC and its impact on the emotional, social and economic burden of patients and their caregivers, and recall the high priority of researching in cancer from a gender perspective

Keywords: non-small-cell lung cancer, gender characteristics, caregivers

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MA22.06 LONGER LUNG CANCER TIME INTERVALS AMONGST CULTURALLY AND LINGUISTICALLY DIVERSE PATIENT THAN ANGLO-AUSTRALIAN PATIENTS

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Background: Lung cancer is the leading cause of cancer mortality worldwide. Culturally and Linguistically Diverse (CALD) patients are especially vulnerable, with poorer outcomes than non-immigrant patients. The LEAD (Lung cancer diagnostic and treatment pathways: A comparison between CALD and Anglo-Australian patients) study aimed to measure and compare the lung cancer diagnostic and treatment pathways between CALD and Anglo-Australian patients. **Method:** LEAD is a mixed-method, observational cohort study. The presentation reports findings from the quantitative arm comprising a patient questionnaire and reviews of patients' hospital and general practice records. A total of 577 (407 Anglo-Australian and 170 CALD) patients were recruited from Melbourne, Sydney and Brisbane, and their hospital records were reviewed. The questionnaire was returned by 189 patients (135 Anglo-Australian and 54 CALD) and a record review was completed by the General Practitioners (GPs) of 99 patients (76 Anglo-Australian and 23 CALD). Survival and Cox regression analyses were conducted to examine differences in time intervals between the two groups. LEAD is funded by Cancer Council Australia with the assistance of Cancer Australia. **Result:** CALD patients reported longer time intervals from referral to diagnosis (Median = 30 days, 95% CI = 26 - 34) than Anglo-Australian patients (Median = 17, 95% CI = 14 - 20), p =. 003, Exp (B) = 1.32. This difference persisted after the impact of relevant factors, such as age and stage of lung cancer, was taken into consideration. CALD patients also reported longer time in five other intervals, including from 1) symptom notification to GP presentation, 2) GP presentation to referral, 3) referral to treatment, 4) symptom notification to treatment, and 5) symptom notification to diagnosis. However, the differences in these five intervals failed to reach significance. **Conclusion:** LEAD is the first Australian study to comprehensively measure and compare the time intervals along the lung cancer pathways amongst CALD and Anglo-Australian patients. It found that CALD patients have longer time intervals from referral to diagnosis than Anglo-Australian patients.

Keywords: ethnicity, culture, diagnostic pathway

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MA22.07 A CULTURALLY SAFE ADVOCACY MODEL OF CARE FOR INUIT CANCER PATIENTS AND THEIR FAMILIES

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Background: The Ottawa Hospital is the tertiary care center for Inuit living in the Baffin Island region of Nunavut, in Canada's far North. Inuit – once relatively cancer free – now have among the highest lung cancer rates in the world (Young et al., 2016). Approximately 30% of Inuit diagnosed with cancer between 2000 and 2010 did not access any cancer services (Asmis, 2016), for which they must travel thousands of kilometers where they are displaced from family, community and culture. Colonization has had a detrimental impact on the social determinants of health for Inuit in Nunavut and has created a lack of trust in government institutions. This context creates an advocacy need at the individual and systems level to address access and equity issues, with the goal of advancing positive health outcomes. **Method:** The Champlain Indigenous Cancer Program (CICP) team has developed a patient-centered, culturally appropriate, land-based approach to support Inuit patients using the principles of the "Supportive Care Framework" (Fitch, 1994) as a guiding ideology. Recognizing the social and economic inequities (Inuit Tapiriit Kanatami, 2019), the Nurse Navigator developed an unconventional approach to connect with Inuit patients. She prioritizes developing therapeutic, trusting relationships with patients and families based on the observation that Inuit patients often feel most comfortable outside the confines of a hospital office. Developing these relationships on the land has become a cornerstone of her work. **Result:** The approach that the CICP has implemented has achieved far-reaching success. Between the first six months and latest six months of tracking (through 2017-2018) there has been a 400%+ increase in patient encounters with the Nurse Navigator role. Clinicians report an increased awareness and understanding of the unique context of Inuit patients and families, resulting in increased numbers of referrals to CICP. Within the Inuit community, there is a recognition and appreciation of the Inuit-specific approach, leading to an increase in self-referrals. **Conclusion:** The CICP is continuing to actively pursue tracking and reporting initiatives to demonstrate a shift in access to cancer care and the long-term outcomes for Inuit patients and families. The program is also continuing to increase access to cultural awareness education for staff to combat misunderstandings about Inuit. By sharing experiences and stories garnered through this work, the Nurse Navigator will help attendees to question and redefine the perception of the traditional role of a cancer nurse.

Keywords: Unconventional, Redefining, Inuit

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MA22.09 CHALLENGING NEGATIVE STEREOTYPES AROUND LUNG CANCER IN IRELAND

A.-M. Baird[1], J. Cimerman[2], H. Forristal[2], L. Yeates[2]

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This abstract is under embargo until September 10 10:45 CET

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TUESDAY, SEPTEMBER 10 14:30–16:00

MA22.10 THE ROLE OF STIGMA IN DIFFERENTIAL CARE FOR LUNG CANCER PATIENTS: A DECADE OF PATIENT AND ONCOLOGIST ATTITUDES

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Background: The presence of lung cancer stigma is well documented (Chapple et al, 2004; Chambers et al, 2012; Marlow et al, 2015) and has been shown to impact the care and treatment of lung cancer survivors (Tod et al. 2008; Carter-Harris et al 2014). In 2008, a large survey of over 200 patients, 200 oncologists, and 1000 members of the general population revealed that most participants felt that lung cancer was principally caused by external factors, that it was preventable, and that lung cancer patients were at least partly to blame for their illness (Weiss et al. 2014; Weiss et al. 2017). The last decade has brought significant changes in the treatment paradigm for lung cancer but it was unknown if the perceptions that affect the care of lung cancer patients have changed. **Method:** 1001 members of the general public, 208 patients with lung cancer, and 205 oncologists who treat lung cancer were surveyed with the identical survey instrument from 2008 survey along with 5-15 additional questions at the end. The survey was carried out by phone and online between June 6 and July 26, 2018. Statistical analysis was performed comparing 2008 and 2018 datasets using paired t-tests if normally distributed or Mann-Whitney U tests for continuous data and Chi-squared or Fisher's exact test for categorical data. **Result:** In 2018, significantly more oncologists feel they have adequate treatment options for metastatic lung cancer

(67% vs 36%, p<.001) and the majority of patients report being satisfied with their medical care (87%) and treatment options (71%). Nevertheless, significantly more patients felt that there was a stigma associated with having lung cancer (70% vs. 54%, p<.0001) and that society treats them differently (63% vs 45%, p<.0001). There was a non-significant increase in oncologists indicating that there is a stigma associated with lung cancer (68% in 2018 vs 60% in 2008) and that patients blame themselves (67% vs 57%). Despite the improvements in lung cancer treatment over the past decade, stigma is still evident in care for those with lung cancer. Similar to 2008, 57% of oncologists indicated that patients with different types of cancer were thought about, approached, or handled differently and lung cancer patients were most frequently cited. In 2018, more patients reported that patients with lung cancer are treated differently by doctors and nurses (40% vs. 26%, p=.01). For both groups, the most common differential treatment referenced was "received less sympathy from medical staff." **Conclusion:** After a decade of research progress in lung cancer, stigma surrounding the disease remains a critical problem even in a healthcare setting. Patients are perceiving stigma at higher levels and oncologists are not reporting any improvement. This work underscores the need to address stigma with proactive multilevel approaches including the need for medical providers to practice empathic communication.

Keywords: stigma, survivorship, treatment

MA22 PARTNERING WITH PATIENTS TO UNDERSTAND STIGMA, DISPARITIES AND VALUES LEADING TO IMPROVED LUNG CANCER CARE
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MA22.11 AN EMPATHIC COMMUNICATION SKILLS TRAINING MODULE TO REDUCE LUNG CANCER STIGMA IN PATIENTS WITH LUNG CANCER: PILOT RESULTS

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Background: Most patients diagnosed with lung cancer report experiencing stigma, with 48% reporting stigma attributable to interactions with health care clinicians. Lung cancer stigma may result in multiple negative psychological outcomes such as misreporting and underreporting of symptoms and smoking behaviors and avoidance of help-seeking. One promising intervention strategy for reducing patients' experiences of lung cancer stigma is improving empathic communication in lung cancer patient-clinician interactions. This abstract describes the conceptual model, development, and preliminary evaluation of a clinician-targeted empathic communication skills training to reduce lung patient's experience of stigma. **Method:** The goal of this new training module was to enhance responsiveness to lung cancer patients' expression of stigma and psychological distress focusing on greater use of seven communication strategies: agenda setting, history taking, recognizing or eliciting a patient's empathic opportunity, shared understanding of the patient's emotion/experience, empathic responding, coping and connection to social support, and closing the conversation. Participating cancer care clinicians learned specific communication skills such as providing a rationale for tobacco use discussion, normalizing, acknowledging, preparing patients for recurring smoking questions, and encouraging expression of feelings. The 2-hour training module was delivered to thoracic oncology clinicians (physicians, advanced practice clinicians) (n=28) using a brief didactic presentation (30 min) with exemplary video demonstrations, followed by experiential role play exercises (90 min) with standardized patients. **Result:** We examined preliminary efficacy of the empathic communication module by assessing participant evaluation of the training and their perceived self-efficacy before and after the training. Overall, participating clinicians reported favorable evaluations of the training, with 93% participants agreeing or strongly agreeing to all 12 training module evaluation items. Of note, perceived self-efficacy to communicate empathically with lung cancer patients increased significantly, t(27)=-4.42, p<.001 from pre- (M=3.64,SD=.68) to post-training (M=4.36,SD=.49). **Conclusion:** Overall, results indicate that the new empathic communication skills training module was well received by thoracic oncology care clinicians and demonstrated significant improvements in self-efficacy from pre- to post-training. Examination of patient outcomes is needed.

Keywords: Lung cancer stigma, Psychosocial Support, Empathic Communications Skills

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
TUESDAY, SEPTEMBER 10 14:30–16:00

MA23.01 PHASE II TRIAL OF AN ORAL FGFR INHIBITOR AZD4547 AS SECOND OR THIRD LINE THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA: FINAL RESULTS OF FRAME STUDY

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Background: Treatment options are limited after first line platinum-based therapy for malignant pleural mesothelioma (MPM). FGFR-9 is a mitogenic ligand that activates the FGF-receptor (FGFR) family and is overexpressed in pleural fluid and tumour samples from mesothelioma patients. In mesothelioma mouse models, FGF-receptor inhibitors reduce tumour burden. Hence, we examined the efficacy of the FGFR tyrosine kinase inhibitor, AZD4547 as second/third line therapy in MPM. **Method:** From April 2016 to January 2019, we conducted a single-site, single arm, open-label study of AZD4547 in patients with MPM. Eligible patients had histologically or cytologically confirmed mesothelioma, measurable disease and had progressed after first or second line therapy. Patients received oral 80mg twice-daily AZD4547 with protocol dose reductions as required. The primary end point was 6-month progression free survival (PFS6); key secondary endpoints included PFS, response rate, overall survival, and safety and tolerability. Using a Simons' two-stage design, 26 patients would be recruited to the first stage and the study would be declared negative if fewer than 7 (27%) of 26 patients achieved PFS6. **Result:** 24 patients (21 (87%) male), median age 69.5 (range 53-84) were recruited. Histological subtype was epithelioid (83.3%), biphasic (8.3%), sarcomatoid (8.3%). Most patients had one prior regimen (14; 58%). Common toxicities included grade 1 and 2 hyperphosphataemia, nail changes, stomatitis, and ophthalmological changes, consistent with reported toxicities of this drug class. No adverse events required hospitalisation. There were two partial responses (8%); 17 patients (70%) had stable disease (SD) for at least 6 weeks, and 5 patients (21%) had progressive disease as their best response. Three of 24 patients (12%) were progression free at 6 months. Hence, the study fulfilled stopping criteria regardless of further recruitment and was discontinued once the criteria for progressing to stage 2 could not be met. Progression free survival was 3.9 months and overall survival was 9.3 months. One patient remained on study with SD for 16 months, experiencing ongoing grade 2 hyperphosphatemia, alopecia of body and facial hair and grade 2 onycholysis. **Conclusion:** The FGFR inhibitor AZD4547 was ineffective for patients with MPM who had progressed on first or second line therapy. Continuous grade 2 cutaneous and ocular toxicities were observed with prolonged therapy

Keywords: Mesothelioma, FGF, AZD4547

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MA23.02 CDK4/6 INHIBITORS SHOW ANTITUMOR EFFECTS IN PRECLINICAL MODELS OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Novel therapeutic approaches are needed to improve the clinical outcome of patients with malignant pleural mesothelioma (MPM). In the current study, we investigate the antitumor activity of CDK4/6 inhibitors in preclinical models of MPM. **Method:** MPM cell lines (H28, H226, H2052, H2452, MSTO-211H) and primary cultures (ICO_MPM1, ICO_MPM2, ICO_MPM3) were treated with abemaciclib or palbociclib for 24 and 72 hours. Cell viability was evaluated by cell counting and crystal violet assays. Cell death and cell cycle distribution were analyzed by flow cytometry and senescence was quantified by β-galactosidase expression. For transcriptomic studies, mRNA expression was assessed through RNA sequencing analysis. Gene set enrichment analysis (GSEA) was used to identify signaling pathways deregulated in MSTO-211H cells treated with CDK4/6 inhibitors. MSTO-211H cells were implanted subcutaneously in athymic mice that were randomly assigned to the following cohorts (n=7): i) vehicle; ii) cisplatin + pemetrexed; iii) palbociclib alone and iv) palbociclib + gemcitabine. Tumors' size and mice weight was monitored during 4 weeks to evaluate efficacy. **Result:** Treatment with abemaciclib or palbociclib at 100nM induced a significant decrease in cell proliferation (mean 50.9% ± 7.6; mean 47.3% ± 9.9, respectively) in distinct MPM cell models, including cells derived from patients who progressed to prior cisplatin and pemetrexed. Both CDK4/6 inhibitors induced G1-phase cell cycle arrest, while cell death was slightly affected (up to 1-5%). At concentrations ranging from 250 to 500nM, the percentage of senescent cells was increased after abemaciclib (15-26%) and palbociclib (18-25%) treatment in all the analyzed cell models. GSEA revealed that CDK4/6 inhibitors promote interferon signaling pathway and MHC presentation. In the *in vivo* experiment, a significant reduction in tumor growth was observed in response to palbociclib alone or combined with gemcitabine for 4 weeks (vehicle = 1335.8±586.4 mm^3; cisplatin + pemetrexed= 726±573.5 mm^3; palbociclib = 479±235.7 mm^3; palbociclib + gemcitabine = 517±487.4 mm^3; $p< 0.05$). **Conclusion:** CDK4/6 inhibitors reduce cell proliferation in culture models of MPM mainly by blocking cell proliferation at G1 and by inducing senescence. Palbociclib alone or combined with gemcitabine reduces *in vivo* tumor growth of subcutaneously implanted MSTO-211H cells compared to chemotherapy.

Keywords: MPM, cancer therapy, CDK4/6 inhibitors

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
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MA23.03 BAP1 LOSS INDUCES GENOME INSTABILITY THROUGH BRCA1-DEPENDENT AND INDEPENDENT MECHANISMS IN MESOTHELIOMA

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Background: BRCA1 associated protein 1 (BAP1) is a tumor suppressor that is the most frequently mutated in the majority of mesotheliomas. We have previously reported that loss of BRCA1 expression in mesothelioma is a common event, and mediates resistance to spindle checkpoint activator vinorelbine, a drug with relevance to treatment of mesothelioma. However, the loss of BRCA1 is unknown in mesothelioma. The aim of this study is to determine the functional relationship between BAP1 and BRCA1 and examine their role in vinorelbine resistance in mesothelioma cells. **Method:** We conducted functional genetic analysis of BAP1 and BRCA1 in two MPM cell lines, MSTO and H2452, the latter carrying an inactivating A95D mutation in the UCH domain of BAP1. BAP1 knockdown was achieved by siRNA transfection, while BRCA1 knockdown was achieved by doxycycline induction of an integrated shRNA. Patient samples were processed for BAP1 and BRCA1 immunohistochemistry from MEDUSA cohort. **Result:** Loss of BAP1 expression led to reduced expression of BRCA1, whereas knockdown of BRCA1 did not affect BAP1 expression. Treatment with the proteasome inhibitor, MG132, restored BRCA1 expression in the absence of BAP1 indicating that BAP1 contributes to post-translational stabilization of BRCA1 protein and the stabilization of BRCA1 by BAP1 is independent of its de-ubiquitination activity. Knockdown of BAP1 induced SAC deficiency and vinorelbine resistance concurrent with reduced expression of BRCA1 and the SAC component, MAD2L1. We also identified a positive and significant correlation between BAP1 and BRCA1 expressionin patient samples. **Conclusion:** Our data demonstrates that BAP1 regulates BRCA1 expression through regulating its protein stability. Our findings suggest that BAP1 inactivation dysregulates the spindle assembly checkpoint via BRCA1 dependent and independent mechanisms, conferring resistance to vinorelbine. As such BAP1 may have potential as a predictive biomarker for spindle poisons, to underpin chemotherapy stratification. A hypothesis that would be tested in a multicentre randomised phase II VIM trial.

Keywords: Mesothelioma, BAP1, BRCA1

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
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MA23.05 A PHASE II TRIAL OF NINTEDANIB IN RECURRENT MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Background: Malignant pleural mesothelioma (MPM) is a disease that is resistant to chemotherapy and there remains an unmet need for better therapeutic options. Nintedanib (BIBF 1120) is an oral multikinase inhibitor impacting VEGF, FGF, PDGFR, and other kinase activity such as TGFß signaling pathways. VEGF, FGF, and TGFβ are commonly expressed in MPM. We conducted a phase II trial in patients with recurrent MPM after platinum-based chemotherapy. **Method:** Methods: Patients (pts) with MPM previously treated with platinum-based chemotherapy, performance status (PS) 0-1, adequate organ function, and no contraindications to anti-angiogenic therapy were eligible for treatment. Nintedanib 200 mg twice per day was administered until disease progression or unacceptable toxicity. The primary endpoint was the 4-month progression-free survival (PFS). A two-stage design was used and >4 pts had to have a PFS of ≥4 months to proceed to the second stage. **Result:** Twenty pts. were enrolled. The median age was 70 yrs. (32-81), 90% were male, and 80% were PS=1. The histology was 70% epithelioidal, 5% sarcomatoid, 10% biphasic, and 15% unknown. 15% had prior bevacizumab. The median follow-up is 16.4 mo. A median of 2 treatment cycles (range 1-18) were delivered. There were no responses but 40% had stable disease. The median PFS was 1.8 mo. (95% CI: 1.68, 3.55) and the PFS rate at 4 mo. was 13%. The median OS was 4.2 mo. (95% CI: 2.53, 8.74) and the OS rate at 4 mo. was 55%. Toxicities were usually grade 1-2 and included diarrhea, fatigue, edema, transaminase elevation, anorexia, nausea, vomiting and dyspnea. **Conclusion:** Conclusions: The activity of nintedanib in previously treated MPM pts. was modest. The trial did not meet the primary PFS endpoint. However, there was a small subset of pts. that had prolonged stable disease for >4 months thus potentially deriving some clinical benefit from treatment. Supported by Boehringer Ingelheim.

Keywords: Mesothelioma, Nintedanib

MA23.06 DEVELOPMENT OF A NOVEL GENETICALLY ENGINEERED MOUSE MODEL OF MALIGNANT PLEURAL MESOTHELIOMA

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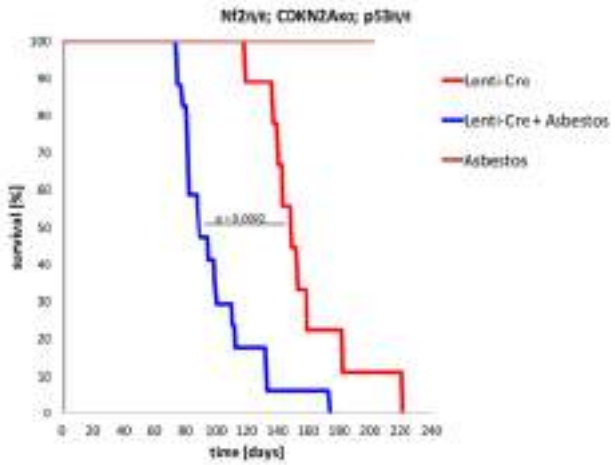
Background: Malignant pleural mesothelioma (MPM) is an aggressive neoplasm strongly associated with inhalation of asbestos. MPM is difficult to diagnose and typically occurs after long latency period. Most of the studies are restricted to the end-stage disease and little is known about pre-malignant disease. Efforts to develop targeted therapeutic strategies based on cell culture have largely failed. Our aim was to develop a novel genetically engineered mouse model that combines deletion of the major tumour suppressors lost in human MPM with intra-pleural injection of asbestos. This model will allow us to investigate how mutagenesis combines with fibre-induced inflammation to drive disease evolution. **Method:** We used genetic engineering to develop an accelerated mesothelioma mouse model combining pleural-restricted, CRE-mediated deletion of NF2, Tp53 (Tp53 is lost in c.10% of human MPM) and full-body knock-out of Cdkn2a with intra-pleural injection of asbestos recapitulating the disease-relevant inflammatory microenvironment. We used immunohistochemistry to analyse the tissue and the lesions. **Result:** Intra-pleural injection of asbestos dramatically accelerates mesothelioma development in mice triple deleted for NF2, Cdkn2a and Tp53, with all such mice succumbing to malignant disease within 3-4 months (Figure 1). These mice develop malignant lesions in the mesothelial lining of the thoracic cavity accompanied with pleural effusion showing high similarity with human malignant mesothelioma. IHC analysis shows positive staining for mesothelioma markers, e.g. pancytokeratin, vimentin and WT-1. Positive macrophage staining (F4/80) strongly indicates involvement of inflamatory component.



Conclusion: In our model, we combined conditional mouse genetics with dose-defined exposure to asbestos to mimic development of human MPM. Our system provides unique insights into the critical transition from pre-malignancy to MPM and will allow us to test emerging therapeutic interventions in the most physiologically relevant pre-clinical setting possible.

Keywords: asbestos, genetically engineered mouse model, Mesothelioma

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
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MA23.07 LOSS OF EXPRESSION OF BAP1 AND/OR MTAP AIDS IN THE DIAGNOSIS OF MALIGNANT MESOTHELIOMA METASTATIC TO LYMPH NODES

A.C. Roden[1], T. Peikert[1], J. Vrana[1], A. Hudson[1], D. Wigle[1], M.C. Aubry[1], A. Mansfield[2]

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Background: Stage and histology are the strongest prognostic parameters in malignant pleural mesothelioma and aid management of patients. However, the distinction between reactive intranodal mesothelial cells and metastatic malignant mesothelioma (MM) can be challenging. Loss of BRCA1 associated protein-1 (BAP1) and/or methylthioadenosine phosphorylase (MTAP) expression has been identified in a subset of MM but not in reactive mesothelial proliferation. We investigated the value of these markers in the distinction between reactive mesothelial cells and metastatic MM in lymph nodes. **Method:** Surgical files of Mayo Clinic Rochester (1996-2018) were searched for metastatic MM in lymph nodes. All cases and if available corresponding primary MM were reviewed by a thoracic pathologist (ACR) to confirm the diagnosis. Primary MM and lymph nodes were stained with BAP1 (clone C-4) and MTAP (2G4). Absence of nuclear staining of BAP1 and absence of nuclear and cytoplasmic staining of MTAP in essentially all tumor cells was considered as loss of expression. **Result:** Forty-four patients (25 males, 56.8%) had a median age of 64 years (range, 24-75) at time of surgery. Tissue was available from nodal metastases in all cases, either paired with the primary MM at time of nodal sampling (N=37) or at a different time (N=4) (time between tissue collections, range, 1day- 4 years, respectively), or without paired primary MM (N=3). Thirty-seven pleural, 6 peritoneal and 1 pericardial MM were of epithelioid (N=39) or biphasic (N=5) subtype. Patients underwent extrapleural pneumonectomy (N=17), pleurectomy (N=7), resection (N=9), debulking (N=2), biopsy (N=8), or autopsy (N=1). In nodal metastases, BAP1 and/or MTAP expression was lost in 29 (of 43, 67.4%) cases; specifically, BAP1 expression was lost in 28 (of 44, 63.6%), MTAP was lost in 14 (of 43, 32.6%), and both were lost in 12 (of 43, 27.9%) cases. Agreement in expression/loss of expression of BAP1 and/or MTAP in primary and metastatic MM occurred in all cases. During a median follow up of patients who underwent extrapleural pneumonectomy or pleurectomy (available in N=23) of 14.8 months (range, 1-119) 17 patients died within a median time of 16 months. **Conclusion:** BAP1 and MTAP immunostains are helpful in the distinction between metastatic MM and reactive mesothelial cells in lymph nodes when one or both markers lost expression in the mesothelial cells. Expression of both markers does not exclude the possibility of metastatic MM.

Keywords: malignant mesothelioma, BAP1, MTAP

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MA23.09 FUSION GENES IDENTIFIED FROM WHOLE GENOME AND WHOLE TRANSCRIPTOME SEQUENCING OF MALIGNANT PLEURAL MESOTHELIOMA TUMOURS

T.M. Chee[1], H. Oey[2], K. Fong[3], I. Yang[3], L. Krause[2], R. Bowman[3]

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Background: Malignant Pleural Mesothelioma (MPM) is an asbestos-related cancer without curative treatment. Fusion genes result from structural chromosomal rearrangements such as translocation, inversion, amplification and deletions, leading to erroneous apposition of components of two or more genes. Consequences include abolition of gene functions that protect against tumourigenesis, or increased activation of genes that promote cell proliferation. To identify fusion genes in MPM genomes, we executed whole genome sequencing (WGS) on eight MPM tumours, and validated the expression of putative fusion genes identified from WGS by whole transcriptome analysis (RNA-Seq). **Method:** Histology of eight MPM tumours was confirmed by two qualified anatomical pathologists,

prior to extraction of genomic DNA and RNA. Whole genome and whole transcriptome sequencing were performed using Illumina HiSeq platforms. Following stringent data processing and filtration, putative fusion variants were called using an in-house bioinformatics pipeline. Fusion events with potential functional consequences were then validated by whole transcriptome analysis, and annotated using TCGA Fusion Gene Data Portal and The Gene Ontology Resource. **Result:** A total of 592 and 321 putative fusion variants were called respectively from WGS data using Delly, and from RNA-Seq using STAR-Fusion computational tools. Expression of WGS putative fusion variants was confirmed in RNA-Seq data, resulting in twelve fusion genes being identified. Among 24 genes involved in fusion events, twenty-two were listed in TCGA Fusion Gene Data Portal with gene partners that were not identified in our cases. Two genes were novel to that database. Multiple functional processes that may lead to tumour development were attributable to these genes including protein polyubiquitination, protein deubiquitination, antioxidant activity, DNA repair, immune response, integrin-mediated signalling pathway, chromatin organization, transcription coactivator activity, angiogenesis, natural killer cell proliferation and DNA-binding transcription factor activity. **Conclusion:** In combination, WGS and RNA-Seq data analysis revealed several fusion genes that warrant further investigation as possible drivers of malignant mesothelioma, and which may serve as diagnostic and therapeutic targets.

Keywords: Mesothelioma, FusionGene, Genomics

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
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MA23.10 LOW NUMBER OF MUTATIONS AND FREQUENT CO-DELETIONS OF CDKN2A AND IFN TYPE I CHARACTERIZE MALIGNANT PLEURAL MESOTHELIOMA

A. Nastase[1], A. Mandal[1], S.K. Lu[1], S. Gennatas[1], H. Anbunathan[1], M. Edwards[1,2], D. Morris-Rosendahl[1,2], A. Newman Taylor[1], R.C. Rintoul[3,4], E. Lim[5], S. Popat[6], A. Nicholson[1,7], M. Lathrop[8], A. Bowcock[1], M. Moffatt[1], W. Cookson[1]

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumour with dismal prognosis and overall survival. To expand our understanding of molecular background of MPM and to identify novel targetable aberrations we report an integrated genomic analysis of 121 tumour samples. **Method:** Fresh-frozen tumour samples (obtained from Mesobank UK,the BLF funded Mick Knighton Mesothelioma Tissue Bank, Respiratory BRU Biobank Diagnostic Archive, Royal Brompton Hospital and an Imperial College London prospective study) were analysed by whole exome sequencing (WES, n=50), SNP genotyping (n=118) and targeted capture sequencing (n=119) for 57 genes. Sequencing libraries were prepared using Target Enrichment Systems for the Illumina Multiplexed Sequencing platform. Somatic mutations were called using VarScan after recalibration of alignments by Genome Analysis Toolkit (GATK). SNP genotyping was performed with the Human Infinium Omni-Express-Exome v1.3/1.4 Bead Chips arrays. Segmentation and copy number calling was performed using a combination of Allelic specific copy number analysis of tumour (ASCAT), DNACopy and GISTIC softwares. **Result:** Analysis of WES paired samples revealed a median of 31 non-synonymous somatic mutations per tumour, lower than melanoma (315 somatic mutations) or lung cancer (187.5 for squamous and 158 for adenocarcinoma), two types of tumours linked to known carcinogen exposure. Investigation of copy number showed significant frequent deletion (q-value>0.05) of 9p21 locus where *CDKN2A, MTAP* and *IFN* type I genes are located. Deletion of *CDKN2A* was seen in 71/121 patients with homozygous deletion in 58/71 patients. Homozygous co-deletion of *CDKN2A* and *IFN* type I was seen in 38/58 patients, homozygous codeletion with *MTAP* in 49/58 patients while 37 patients showed all three as homozygous co-deleted. Patients with *CDKN2A* and *IFN* type I deletions had worse overall survival compared with the *CDKN2A* wild type and patients *CDKN2A* only deleted patients (median 8.3 months vs 13.1 months, p-value=0.016). Deletion of 3p21.1 locus and mutations in *BAP1* were detected in 54.5% of the patients, making *BAP1* the second most commonly altered gene. *RB1* (13q14.2) was commonly altered mainly by deletion in 25.6% of the patients. *NF2* and *TP53* were affected by mutations in 19.8% and 7.4% of the patients, repectively. Patients with mutations in *TP53* had worse overall survival compared with *TP53* wild type patients (p-value=0.0005). **Conclusion:** Co-deletion of *CDKN2A*, *MTAP* and *IFN* type I genes could have therapeutic implications for the patients. Deletion of *IFN* type I may have direct implications for patient responses to immunotherapy. In the contex of multiple vulnerabilities, the presence of both *CDKN2A* and *RB1* loss might define an important group of patients susceptible to CDK4/6i targeted therapies.

Keywords: targeted capture sequencing, copy-number alterations

MA23 PRECLINICAL MODELS AND GENETICS OF MALIGNANT PLEURAL MESOTHELIOMA
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MA23.11 ANALYSIS OF IMMUNE PHENOTYPE COMPOSITION IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) USING BULK RNA SEQUENCING

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Background: Exploiting the immune status of the tumour microenvironment (TME) is increasingly being adopted for many cancer types. Investigation into immune phenotype composition of the TME is at present lacking for malignant pleural mesothelioma (MPM) but critically important in light of the cancer's overall poor prognosis and lack of targeted therapy as clinical standard of care. In this study, CD8+ve tumour infiltrating lymphocyte (TIL) level has been used as a starting point to compare differences in mutational patterns, histology and survival in MPM. **Method:** Bulk RNA sequencing of tumour tissue from 35 MPM patients (in-house cohort) was performed. Sequencing read alignment and gene count estimation were performed using STAR (v.2.5.2b). To increase the sample size, raw data from Bueno *et al.* (n=211 subjects) was accessed and gene count estimations performed. In addition, the TCGA-MESO cohort (n=86 subjects) count data was included from the GDC (Genomic Data Commons) website. All count data were normalized cohort-wise using the 'voom' method implemented in *limma* package. Deconvolution of constituent immune phenotypes in the TME from the bulk RNA-sequencing data was performed by applying CIBERSORT (v.1.04) on normalized count data sets. For assessing the genetic context of observed immune phenotypes, somatic mutations were profiled using targeted sequencing of a custom gene panel for the in-house cohort. For the Bueno *et al.* and the TCGA-MESO cohorts, somatic mutations were either available from an overlap of whole-exome sequencing (WES) and targeted gene panel, or from WES only. **Result:** A total of 27 samples (3 of 35 (8.6%), 21 of 211 (9.9%) and 3 of 86 (3.5%) from the in-house, Bueno *et al.* and TCGA-MESO cohorts respectively) were identified with immune phenotype enriched for CD8+ve TIL. Histological subtype distribution in the CD8+ve enriched samples was seen to be almost equivalently split between Epithelioid and Biphasic subtypes (51.85% and 48.15% respectively). Interestingly, *BAP1* mutation was found to be present in only 7.7% of the samples. Considering in addition the genes *NF2, SETD2, SETD6*, *SETDB1*, *TP53* and *LATS1/2*, mutations were only found to be present in 57.7% of the samples in total. As such >40% of samples with CD8+ve TIL do not have any mutations detected in known hotspot genes for MPM. Histological subtype is not significantly different between these 'wild-type' and hotspot gene(s) mutated samples. Median survival for the groups was found to be 1.85 and 0.73 years respectively. **Conclusion:** In the present study, approximately 3-10% of MPM samples were found to have enrichment for CD8+ve TIL. Nonetheless on closer

examination of the genetic context, mutation patterns emerge that warrant further investigation. For samples that have *TP53* (n=3) mutation or mutations in multiple hotspot genes (*BAP1*, *NF2*, *SETD2*, *LATS2*; n=1), survival understandably is lowest (0.27 years average). This raises a number of further questions including what sustains a tumour despite high CD8+ve TIL population? And more importantly with lack of tumour mutational burden what other TME signals draw effector immune cells? Further investigations, by comparing additional immune markers with copy number changes that might be present in hotspot genes, are therefore required.

Keywords: Mesothelioma, tumour-infiltrating lymphocytes, RNA sequencing

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.01 CHALLENGES IN LUNG CANCER CLINICAL TRIALS: A EUROPEAN PERSPECTIVE

A.-M. Baird[1], D. Villalón[2], A. Aguarón[3], C. Smitt-Plank[3], T. Björk[3], R. Deniel Ihlen[3], E. Szmytke[3], S. Vallone[3]

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This abstract is under embargo until September 10 10:45 CET

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.02 DEVELOPING REGIONAL ACTIVITY FOR A NATIONAL CHARITY: THE LUNG CANCER CANADA EXPERIENCE

P. Wheatley-Price[1,2,3], P. Robertson[3], M. Brennan[3], J. Hamer-Wilson[3], A. Redway[3], M. Bouris[3], D. Manii[3], J. Ricard[3], S. Singh[3]

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Background: Lung Cancer Canada (LCC) is the only national charity solely committed to the most common cancer in Canada. Its mission is to raise awareness; to advocate; and to provide support and educational resources for lung cancer patients and caregivers. At a strategic planning event the LCC Board held in 2017, the goal of building regional hubs was identified - to deliver the charities mandate within local contexts. **Method:** A group of key stakeholders (patients, caregivers, fundraisers, social workers, nurses and physicians) met to identify local priorities. Specific programs were developed, with other initiatives flowing from that initial effort. Here we describe the group's achievements. **Result:** From the initial stakeholder meeting two prime opportunities were identified. 1. Create a support group for women with lung cancer. 2. Take advantage of being in the national capital to more purposefully engage with Federal politicians. In addition to the stakeholder meeting, subsequent social gatherings of key individuals helped build momentum. Through partnership with a local charity (Ottawa Regional Cancer Foundation), marketing through LCC, recruitment through the cancer centre, and program development from a senior psychosocial oncology social worker, the support group was formed for an initial 12 week period, and has now grown to an established permanent fixture. The benefits have been previously reported, but out of this group further local initiatives have included: regular patient-led lung cancer information sessions in the cancer centre; a regional patient summit for all lung cancer patients to learn latest research, patient testimonies and psychosocial challenges; the funding and initiation of an LCC podcast series. Concurrently more individuals and families have become engaged in fundraising for lung cancer: events including quiz nights, makeovers, golf days, wine raffles and more, which in addition to raising funds also builds awareness and builds the local community. These individuals have partnered with physicians to stimulate the second goal, initiating regular meetings with municipal, provincial, federal and senatorial politicians, in addition to military leadership and indigenous groups. This itself helped the national organization to hone the advocacy message we share (lung cancer awareness, lung cancer screening, access to treatments, and the establishment of a national registry). **Conclusion:** Through identification of local champions who effectively work together, many initiatives have successfully developed. With funding and support from LCC, the charity's mandate is being delivered within the local context. This serves as a model for other centres across Canada to develop local programs.

Keywords: Podcast, Lung cancer, Advocacy

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.03 FACTORS IMPACTING PATIENTS' WORRIES (ACCESSING TREATMENT, TREATMENT TOXICITY, & EMOTIONAL BURDEN) ASSOCIATED WITH LUNG CANCER TREATMENTS

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Background: Understanding patient experiences with lung cancer can guide research, treatment, and policy decisions. Conducted as part of a larger study (Project Transform) that aimed to quantified patient experiences, we sought to study the primary concerns of lung cancer patients and their caregivers and to determine what demographic and clinical factors impact these worries. **Method:** Lung-cancer worries were identified from patient interviews and the literature. A novel an instrument assessing 13 potential worries on a 3-point importance scale was incorporated as part a national survey of lung cancer patients (inclusive of all types/stages of disease) and caregivers recruited through LUNGevity Foundation. Factor analyses was used to identify key constructs among the 13 worries. We then explored variation in the standardized factor scores across demographic and clinical indicators collected in the survey. **Result:** Of the 426 participants in the survey, there were 385 patients and 41 caregivers. The average age of respondents was 58.9 years, 54% earned less than $75,000 per year, and 67.6% had completed college. Three factors were identified associated with worrying: 1) "accessing treatments" (incorporating knowledge, communication, access); 2) "treatment toxicity" (incorporating both side-effects and financial impact); and 3) "emotional burden" (including worries about dying, emotional toll, and being a burden), with Cronbach's alphas of 0.89, 0.73, and 0.74 respectively. Worries about accessing treatment were lower among NSCLC (P=0.006), presence of MET mutations (P = 0.027) and those not currently receiving therapy (P=0.033). Worries about treatment toxicity were higher among non-white (P<0.001), non-retired (P<0.001), those earning less than $75,000 (P<0.001), younger patients (P<0.001), and those with ALK (P=0.026) or HER2 (P=0.041) mutations. Worries about treatment toxicity were lower among patients on Medicare or Medicaid during treatment (P = 0.023) and NSCLC patients (P=0.018). Worries about the emotional burden of treatment were lower among those >=60 years (P=0.002) and those who are retired (P=0.021) and higher among those having surgery (P=0.039). Table 1: Marginal effects of patient factors on standardized worry scores

Factor	Accessing Treatment	Treatment toxicity	Emotional burden
Patient	-0.052 (0.16)	-0.144 (0.16)	-0.224 (0.16)
Age >= 60	-0.1 (0.1)	-0.336 (0.1)***	-0.309 (0.1)**
Female	0.003 (0.12)	0.239 (0.12)	0.158 (0.12)
Non-white	-0.022 (0.16)	0.56 (0.16)***	0.048 (0.16)
Hispanic, Latino, or Spanish	-0.003 (0.22)	0.233 (0.22)	0.161 (0.21)
Primary Language - Spanish	0.116 (0.7)	0.879 (0.69)	0.423 (0.67)
Armed Forces	-0.103 (0.18)	-0.134 (0.18)	0.055 (0.18)
Marries	0.139 (0.11)	-0.177 (0.11)	0.073 (0.11)
Has children	0.004 (0.13)	-0.031 (0.13)	0.203 (0.12)
College or professional degree	0.208 (0.11)	-0.096 (0.11)	-0.104 (0.1)
Retired	-0.048 (0.1)	-0.488 (0.1)***	-0.233 (0.1)*
Household Income < $75,000	0.031 (0.11)	0.376 (0.11)***	0.025 (0.11)
Population < 2,500	-0.168 (0.22)	-0.099 (0.22)	0.193 (0.21)
Chronic conditions as diagnosis	-0.078 (0.12)	-0.021 (0.12)	0.146 (0.12)
NSCLC	-0.308 (0.11)**	-0.263 (0.11)*	-0.111 (0.11)
Private Insurance	0.084 (0.11)	0.139 (0.11)	0.057 (0.11)
Medicare or Medicaid	0.02 (0.1)	-0.235 (0.1)*	-0.079 (0.1)
Other Insurance	-0.092 (0.17)	-0.144 (0.17)	-0.128 (0.17)
No Insurance	0.363 (0.58)	0.56 (0.58)	-0.083 (0.58)
Participated in a clinical trial	-0.029 (0.12)	-0.134 (0.12)	0.077 (0.12)
ALK	0.143 (0.14)	0.295 (0.13)*	0.041 (0.12)
BRAF	-0.241 (0.56)	-0.663 (0.55)	-0.345 (0.52)
EGFR	-0.038 (0.13)	-0.109 (0.13)	0.121 (0.12)
HER2	0.689 (0.48)	0.973 (0.47)*	0.439 (0.45)
KRAS	-0.201 (0.21)	-0.067 (0.21)	-0.113 (0.2)
MET	-0.765 (0.34)*	-0.389 (0.34)	0.19 (0.32)
NTRK	0.767 (0.68)	0.467 (0.67)	0.101 (0.63)
RET	0.154 (0.4)	-0.47 (0.39)	-0.69 (0.36)
ROS1	0.149 (0.26)	-0.053 (0.25)	0.202 (0.24)
More than 2 lines of treatment	0.09 (0.1)	0.026 (0.1)	0.03 (0.1)
Chemotherapy	0.019 (0.16)	0.008 (0.16)	0.007 (0.16)
Radiation	0.197 (0.29)	0.339 (0.3)	0.101 (0.3)
Targeted therapy	0.143 (0.1)	0.038 (0.1)	0.129 (0.1)
Immunotherapy	0.124 (0.18)	0.188 (0.19)	-0.125 (0.19)
Surgery	0.454 (0.29)	0.407 (0.3)	0.612 (0.29)*
Angiogenesis inhibitors	0.081 (0.41)	0.101 (0.42)	0.268 (0.42)
No current treatment	-0.214 (0.1)*	-0.192 (0.1)	-0.163 (0.1)

Notes: Standard errors in parentheses, * p<0.05, ** p<0.01, ***p<0.001

Conclusion: Patients worry to differing extents about accessing treatment, treatment toxicity, and the emotional burden of lung cancer, yet caregivers and patients (on the whole) have similar worries. Lung cancer researchers, clinicians, and policymakers should make decisions in ways that address the heterogeneous experience of patients. Patients worries vary across a confluence of demographic, disease, and treatment factors, hence greater attention to the individual needs of the patient is needed.

Keywords: financial toxicity, Real-world data, side-effects

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.05 LUNG CANCER IN EUROPE: STRENGTHENING POLICY RESPONSES ONE COUNTRY AT A TIME

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Background: Despite diagnostic and treatment progress in lung cancer, outcomes remain poor and costs remain high. Prevalence and mortality rates in Europe are higher than the global average and five-year survival rates stand at a mere 11.2% for men and 13.9% for women. The Economist Intelligence Unit is conducting research to identify the impact of policy on lung cancer incidence and outcomes, sponsored by MSD. Recommendations stemming from our research will support countries to build improved systemic responses for lung cancer. **Method:** Our research centres on twelve countries: Austria, Belgium, Finland, Germany, Greece, Netherlands, Norway, Poland, Romania, Spain, Sweden, and the UK. Following an initial literature review using evidence from internationally-recognised sources (e.g. Globocan, OECD, and proprietary Economist Intelligence Unit sources), we organised our thinking into five domains. This is operationalised by quantitative and qualitative indicators to provide insight into how each country addresses cancer planning and guideline usage as well as how strategic thinking impacts behaviour and access. At a meeting with leading European experts, we presented our initial findings and validated our framework. The next step was to populate our scorecard to compare policy and practice in each country. Individual country profiles were developed from our findings, examining local barriers to progress in terms of service delivery, systems, access, financing and governance. Workshops were then held in each country. Meeting with a range of leading clinicians, patient organisations, and other key stakeholders ensured a detailed examination of our preliminary findings and, most importantly, enabled us to obtain further information on conditions within each country. This nuanced information provides us with a clearer grasp on approaches to the provision of lung cancer care to a greater degree than we could have obtained from desk research alone. **Result:** Preliminary results indicate patches of good practice, yet no country scores highly across all of our measurements and each country has several opportunities for improvement. For example, all but one country has a national cancer control plan: of eleven plans, nine are over five years old which means that they are not taking account of recent oncological innovations. Often, a country's national lung cancer clinical guidelines lack details regarding fast-tracking suspected patients for diagnosis as well as referral pathways for moving a patient to secondary/tertiary care, supportive/palliative care, shared decision-making, and provision of psychological support in specific time periods. Cancer registries exist in each country, yet clinicians report that clinically-focused cancer registries could provide useful information on patient care. Finally, reimbursement for all four commonly used biomarkers for lung cancer is available in only five countries. **Conclusion:** Significant room for improvement in lung cancer policy exists across all of the countries and domains we have studied. Our country-based workshops have ensured that our research focuses on the most important opportunities for improving the delivery of lung cancer care from the standpoint of each country. We are now entering the policy development phase of our research where our goal is to assist policy-makers to improve care for people living with lung cancer in Europe.

Keywords: lung cancer policy Europe, systemic responses to lung cancer in Europe

MINI ORAL SESSIONS

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.06 USING GLOBAL DATA AS AN ADVOCACY TOOL – THE GLOBAL LUNG CANCER COALITION'S E-ATLAS OF LUNG CANCER

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Background: The Global Lung Cancer Coalition is the international voice of lung cancer patients and is committed to improving disease outcomes for all. The Coalition's work includes activities to support lung cancer advocates in campaigning for actions that will improve research, information, treatment, and care for people living with lung cancer. Significant variations exist both between and within different countries in lung cancer incidence, mortality and survival. Advocates can use evidence of these variations to make the case for legislative, policy or regulatory change. In 2014 the GLCC brought together multiple, comparable, statistical sources about lung cancer's impact and outcomes in different nations in the first Global Lung Cancer E-Atlas. For the first time, national lung cancer data became easily accessible in a single place online. In 2019, a new edition was published incorporating more recent global data, breakdowns by gender and age, and features to make it easier for advocates to use. **Method:** Incidence and mortality data were drawn from GLOBOCAN 2018, which provides estimates, by age and gender, for 185 countries of the world. Survival data were drawn from: CONCORD-2, covering 67 countries; the EUROCARE-5 study, covering 29 European countries; and the International Cancer Benchmarking Partnership (ICBP), comprising Australia, Canada, Denmark, Norway, Sweden and the United Kingdom. The E-Atlas also details whether countries operate a cancer plan, have national cancer registries in place, or have implemented the WHO Framework Convention on Tobacco Control. GLCC members were invited to validate their country's data. Any more recent national data identified was included alongside the data from other sources. **Result:** The Lung Cancer E-Atlas is publicly accessible on the GLCC's website for anyone in the world to use. Data can be compared, turned into graphs and infographics, and shared via social media. It can also be downloaded ready for use in presentations. Clinicians have used the data in presentations to national and regional congresses. Patient advocacy groups are using it to support their engagement with national policymakers and media. **Conclusion:** Feedback from GLCC members confirms that the E-Atlas continues to be an essential resource in their campaigning and advocacy. Policymakers respond positively to being able to see how their country's national data compares to that of other countries. The GLCC is keen to increase the profile of the E-Atlas so that any lung cancer advocate – whether a clinician, patient, carer, researcher, advocacy group or journalist – is aware of it and able to use it. The GLCC is also keen to receive feedback on national data for inclusion or suggestions for further development.

Keywords: Policy, Advocacy, Digital

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.07 IMPACT OF RADIOLOGIST RECOMMENDATIONS ON TIMELINESS OF LUNG CANCER REFERRAL: BASELINE DATA TO GUIDE A QUALITY IMPROVEMENT INITIATIVE

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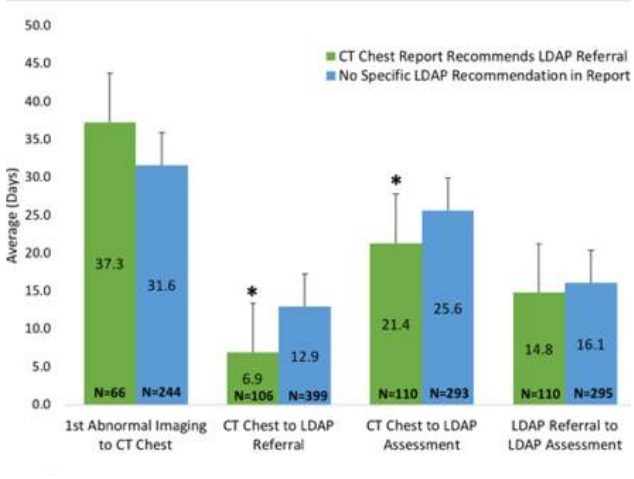
Background: Lung cancer (LC) diagnostic pathways are typically initiated following suspicious radiographic imaging. In southeastern Ontario, Canada, we identified delays from first thoracic imaging suspicious for LC to referral for evaluation at our regional LC rapid assessment clinic, the Lung Diagnostic Assessment Program (LDAP). Given that delays in diagnosis of LC are associated with worse patient outcomes, we sought to characterize local processes to guide Quality Improvement (QI) initiatives. **Method:** We retrospectively reviewed all patients referred to the LDAP between

January and October 2018. Collected data included dates of: first imaging suspicious for LC, first CT chest (if different from first suspicious imaging), LDAP referral, LDAP assessment, and details regarding Radiologist recommendations in the report. Data are reported as mean days (± standard error); unpaired t-tests were used to assess for significance. **Result:** Of 558 patients referred to the LDAP, 509 (91.2%) patients had a CT chest performed prior to LDAP referral. Of these, 110 (21.6%) had a CT chest report issuing a specific Radiologist recommendation for LDAP referral. When such a recommendation was made, time from CT chest to LDAP referral was significantly faster than if no recommendation was made (6.9 versus 12.9 days, p=0.017), as was time from CT Chest to LDAP assessment (21.4 versus 25.6 days, p=0.026). Of all patients with a Radiologist recommended LDAP referral, 38 (34.5%) were not assessed in the LDAP for reasons including: patient followed by the LDAP, a Respirologist, or an Oncologist, inpatient status, or patient refusing assessment. Data are presented in Figure 1.



Conclusion: We identified that a Radiologist recommendation for LDAP referral leads to significantly faster patient referral and assessment for evaluation of suspected LC. A QI initiative is underway, consisting of knowledge sharing and regional standardization of radiologist reporting recommendations for imaging suspicious for LC in order to expedite LDAP referral.

Keywords: Radiology, Quality Improvement, Timeliness of Care

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.09 STIGMA IN EARLY STAGE LUNG CANCER

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Background: Lung cancer stigma, arising from the causative relationship between smoking and lung cancer, can result in those with a lung cancer diagnosis being seen by themselves and others as responsible for and even deserving of their condition. Lung cancer stigma is linked to adverse outcomes for patients, including decreased quality of life and depression. Most studies have focused on stigma in patients with advanced lung cancer, whose experiences may differ from earlier stage, surgical patients with better prognosis. The objective of this study is to establish a baseline of stigma related experiences for patients presenting with early stage lung cancer. The overarching goal is to assist in determining appropriate interventions to decrease harmful stigma for patients with lung cancer. **Method:** This study is a descriptive cross-sectional design using the 25-item previously validated Lung Cancer Stigma Inventory (LCSI). The LCSI was self-administered by patients with newly diagnosed lung cancer at a tertiary referral thoracic surgical clinic to quantitatively measure their experience of lung cancer stigma. Statistical comparisons were performed with Student's t-test. **Result:** 128 patients were approached to participate and 53 completed the LCSI (response rate= 41.4%), 33 were women. All had resected early stage lung cancer except one patient staged pIIIA (I=41, II=11). 38 patients (71.7%) met the established threshold of a total LCSI score of 37.5, indicating a clinically meaningful level of stigma. Stigma was experienced predominantly on the Internalized Stigma subscale (mean 2.64/5), whereas scores on the Constrained Disclosure and Perceived Stigma subscales were lower (mean 1.84/5, 1.66/5). There was a trend towards higher overall stigma scores in current and former smokers compared to never smokers (mean 53.9 vs 39.8, p=0.12) There was no difference in stigma experience based on gender or stage, surgical approach or use of adjuvant chemotherapy. **Conclusion:** A surgical population of patients with early stage lung cancer experienced lung cancer stigma at a high rate, and at a level similar to previously studied populations with more advanced disease. Respondents experienced more internal stigma than stigma stemming from society or others. Exploratory analysis of this study's results have informed the development of a further study, currently underway, using patient interviews to better understand patients' experiences of lung cancer stigma, which may help to identify potential interventions to decrease lung cancer stigma and its impacts.

Keywords: Patient Reported Outcomes, patient experience, stigma

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.10 ESTIMATION OF DEATHS DUE TO LACK OF ACCESS TO IMMUNOTHERAPY FOR BRAZILIAN PATIENTS DIAGNOSED WITH ADVANCED NSCLC WITHOUT ANY DRIVER MUTATION

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Background: Lung cancer is a major cause of cancer worldwide. Despite efforts to curtail risk factors such as tobacco consumption, it remains both common and lethal. More recently novel targeted therapies and the development of immunotherapy provided a substantial increase in the expected survival of patients diagnosed with advanced lung cancer. Nonetheless, the lack of access to these medications, especially in low and middle-income countries, is a trending concern. Brazil is considered to be a middle-income country and its citizens have access to a universal healthcare system (Sistema Único de Saúde – SUS) – fully funded by the government. Around 75% of the population rely exclusively on this public system when treating their diseases. Many high-cost drugs, such as immunotherapy and TKI's, are not provided due to budget constraints. This study has the goal of estimating the impact in premature lives lost in the Brazilian population due to lack of access to the best currently available therapy for patients with advanced non-small cell lung cancer (NSCLC) without driver mutations. **Method:** Firstly, we searched for data regarding the incidence of lung cancer in the Brazilian population using INCA's (Brazilian National Cancer Institute) database, demographic data from the Brazilian Government and compiled staging and histologic data from different private and public oncologic centers. For analytic reasons, we compared the incidence data with the ones observed in the American Surveillance, Epidemiology, and End Results (SEER). Using survival data from the pivotal phase 3 studies for immunotherapy in NSCLC (PACIFIC, Keynote 189 and 407) we estimated the expected total number of patients alive one year after diagnosed with stage III or IV NSCLC (excluding those with driver mutations) considering they had received the best treatment available according to the NCCN guidelines. This number was compared with the expected survival for patients receiving the standard treatment in the Brazilian SUS (chemoradiation followed by observation for stage III NSCLC and palliative Carboplatin + Paclitaxel for stage IV NSCLC without driver mutations). **Result:** After compiling all data of interest, we estimated that 2.332 premature deaths would occur in Brazilian patients with advanced NSCLC one year after diagnosis, exclusively due to lack of access to immunotherapy. Comparing Brazilian incidence data with the American data from SEER, this number may actually be underestimated and can reach up to 11.193 premature deaths in a single year. **Conclusion:** The lack of access to immunotherapy is a major concern for countries in development and this can lead to an enormous impact on survival of patients with lung cancer. Further studies are needed to best estimate the economic impact and provide data to help decide when to adopt new technologies and drugs to treat these patients. Strategies may rapidly be implemented in order to avoid further unnecessary premature deaths of NSCLC patients.

Keywords: Lung cancer, Immunotherapy, access

MA24 INITIATIVES TO IMPROVE HEALTH IN LUNG CANCER PATIENTS
TUESDAY, SEPTEMBER 10 14:30–16:00

MA24.11 A PROJECT TO CONTROL PASSIVE SMOKING BY LUNG CANCER PATIENTS "DON'T SMOKE NEAR ME! DON'T BE LIKE ME!"

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Background: According to a survey of patient group members (n = 215, 2017), 31% of lung cancer patients who continue to work were exposed to passive smoking at workplaces. Once Japanese tobacco industry used to be a national monopoly, so Japan is one of the countries where a ban on indoor smoking has not been realized. Although education on smoke prevention in elementary and junior high schools tells the fact that smoking is one of the risks for lung cancer, it is unknown that lung cancer patients are living frightened of cancer relapse, especially with the fear of being exposed of passive smoking. Lung cancer patients encourage highly dependent smokers who cannot stop smoking despite they have colleagues or families suffering from lung cancer to visit smoking cessation clinics. **Method:** Intervention to close persons is difficult. In order to overcome the difficulties, we select ambassadors from each patient group. Then we provide training on education, action guidelines and tool development, have them participate in tool development, and have them become mentors when scaling up. The state of the activity is published on the Internet, and we spread media interview invitations in parallel. We let families, colleagues, community members, professionals, medical professionals, media and politicians know that lung cancer patients are frightened of passive smoking. The activities already done are as follows. -Granted Global Bridge grant of tobacco control personnel development department in Mayo Clinic, USA • Ambassador briefing session was held twice. (Kobe and Tokyo) • Selected 13 ambassadors from 11 lung cancer patient group and held 5 workshops. • Planned communication strategies • Communication tactics currently developing **Result:** [Activity (project) evaluation] • Won 13 ambassadors from all over Japan • No withdrawal of the ambassador • One of the ambassadors changed job to be in charge of tobacco control in a public administration. • One of the ambassadors was appointed as a member of patient information evaluation committee of National Cancer Center Japan. **Conclusion:** [Future plans] • Completion of Tool • Hold briefing session to member in each patient group • Campaign implementation • Campaign evaluation

Keywords: advocacy second hand smoke

MA25 PRECISION MEDICINE IN ADVANCED NSCLC
TUESDAY, SEPTEMBER 10 14:30–16:00

MA25.01 PEMBROLIZUMAB PLUS CHEMOTHERAPY FOR ADVANCED NSCLC WITHOUT TUMOR PD-L1 EXPRESSION: POOLED ANALYSIS OF KN021G, KN189 AND KN407

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[1]*Fox Chase Cancer Center, Philadelphia/United States of America,* [2]*University of Pennsylvania, Philadelphia/United States of America,* [3]*Hospital Universitario 12 de Octubre, Madrid/Spain,* [4]*Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria/Spain,* [5]*Montefiore Einstein Center for Cancer Care, Bronx/United States of America,* [6]*The University of Texas/MD Anderson Cancer Center, Houston/United States of America,* [7]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan/Italy,* [8]*Mid North Coast Cancer Institute, Port Macquarie Base Hospital, Port Macquarie/Australia,* [9]*Kansai Medical University Hospital, Osaka/Japan,* [10]*Jilin Cancer Hospital, Changchun/China,* [11]*Merck & Co., Inc., Kenilworth/United States of America,* [12]*University of Michigan, Ann Arbor/United States of America*

Background: Randomized studies have demonstrated that pembrolizumab plus chemotherapy improves OS, PFS, and ORR compared with chemotherapy alone in patients with advanced NSCLC regardless of tumor PD-L1 expression level. We present a post hoc pooled analysis of pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced NSCLC and no PD-L1 expression (ie, TPS <1%), representing an area of unmet need. **Method:** Patients enrolled in KEYNOTE-021 cohort G (nonsquamous; NCT02039674), KEYNOTE-189 (nonsquamous; NCT02578680), and KEYNOTE-407 (squamous; NCT02775435) were included. Patients with nonsquamous NSCLC were randomized to pemetrexed-platinum with or without pembrolizumab; those with squamous NSCLC were randomized to carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab. OS, PFS, and ORR were evaluated for the pooled intent-to-treat population. Response was assessed per RECIST v1.1 by blinded independent central review. Across studies, PD-L1 expression was assessed centrally using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA). Analyses were descriptive. **Result:** Of 1298 patients enrolled across the 3 trials, 428 (33%) had PD-L1 TPS <1% (pembrolizumab plus chemotherapy, n=243; chemotherapy alone, n=185) and were included in this analysis. 52% had nonsquamous histology, 63% had ECOG PS of 1. Median (range) follow-up at data cutoff was 10.2 (0.1-34.9) months. OS, PFS, and ORR were improved with pembrolizumab plus chemotherapy versus chemotherapy alone (Table). Grade ≥3 AEs (all-cause) occurred in 68% of patients receiving pembrolizumab plus chemotherapy versus 72% receiving chemotherapy alone. Immune-mediated AEs and infusion reactions occurred in 26% who received pembrolizumab plus chemotherapy versus 12% who received chemotherapy alone.

	Pembrolizumab + Chemotherapy n=243	Chemotherapy Alone n=185
Median (95% CI) OS, mo	19.0 (15.2–24.0)	11.0 (9.2–13.5)
Hazard ratio (95% CI)	0.56 (0.43–0.73)	
Median (95% CI) PFS, mo	6.5 (6.2–8.5)	5.4 (4.7–6.2)
Hazard ratio (95% CI)	0.67 (0.54–0.84)	
ORR, % (95% CI)	46.9% (40.5%–53.4%)	28.6% (22.3%–35.7%)
Difference (95% CI)	18.3% (9.0%–27.1%)	

Conclusion: Our results highlight the clinically meaningful efficacy benefit and acceptable safety profile of pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced NSCLC and no PD-L1 expression. Benefit was consistent with that observed in the overall study populations, suggesting pembrolizumab plus chemotherapy should be considered standard-of-care first-line therapy for all patients with NSCLC, irrespective of PD-L1 expression.

Keywords: Pembrolizumab, NSCLC, PD-L1

MA25 PRECISION MEDICINE IN ADVANCED NSCLC
TUESDAY, SEPTEMBER 10 14:30–16:00

MA25.02 ARRANGEMENT AND ARCHITECTURE OF TUMOR-INFILTRATING LYMPHOCYTE ON H&E SLIDES PREDICT OS IN NIVOLUMAB TREATED NON-SMALL CELL LUNG CANCER

X. Wang[1], C. Barrera[1], K. Bera[1], C. Lu[1], M. Feldman[1], K. Schalper[2], D. Rimm[2], V. Velcheti[3], A. Madabhushi[1]

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Background: Immune checkpoint inhibitors (ICI) are a promising and novel approach to treating chemotherapy refractory advanced NSCLC as well as first-line combination therapy in certain NSCLC. Nivolumab, a PD-L1 inhibitor is a promising ICI showing durable benefit with low toxicity in these patients. While PD-L1 positivity is an established tissue based biomarker for response to Nivolumab, studies have shown response rates ranging from 20-50%. Recent research has shown that TILs have been implicated in cancer aggressiveness as well as immune response. In this work, we go beyond simply counting TILs, and apply novel computer-extracted features characterizing the interaction and spatial co-localization of

TILs and cancer nuclei (SpaTIL) in stratifying patients based on OS following nivolumab therapy. **Method:** H&E tissue slides obtained from pre-treatment biopsies of 96 NSCLC patients treated with nivolumab were digitized and included for this study from 3 different institutions with the tumor region annotated by pathologists. Then 85 SpaTIL features related to TIL density, architecture and co-localization with tumor cells have been extracted to represent each patient. The most discriminative and uncorrelated features were selected by Elastic-Net regularized Cox-regression model to predict OS. The model was trained on D1 (n=25) and independently validated in D2 (n=32) and D3 (n=64). Multivariate analysis with clinico-pathologic factors was also performed. **Result:** The top features consisted of the abundance of TILs around tumor cells and the distribution of the TILs. On the validation set, SpaTIL classifier yielded a HR=3.03 (95%CI=1.1 -8.35; p=0.042) on D2 and HR=4.12 (95%CI=1.87-9.09; p=0.02) on D3 by a log-rank test. On multivariate analysis with stage, smoking, histologic type, total lymphocyte count (See Table 1) SpaTIL was independently prognostic of OS (HR=7.88; 95%CI=1.66 – 37.216; p=0.009).

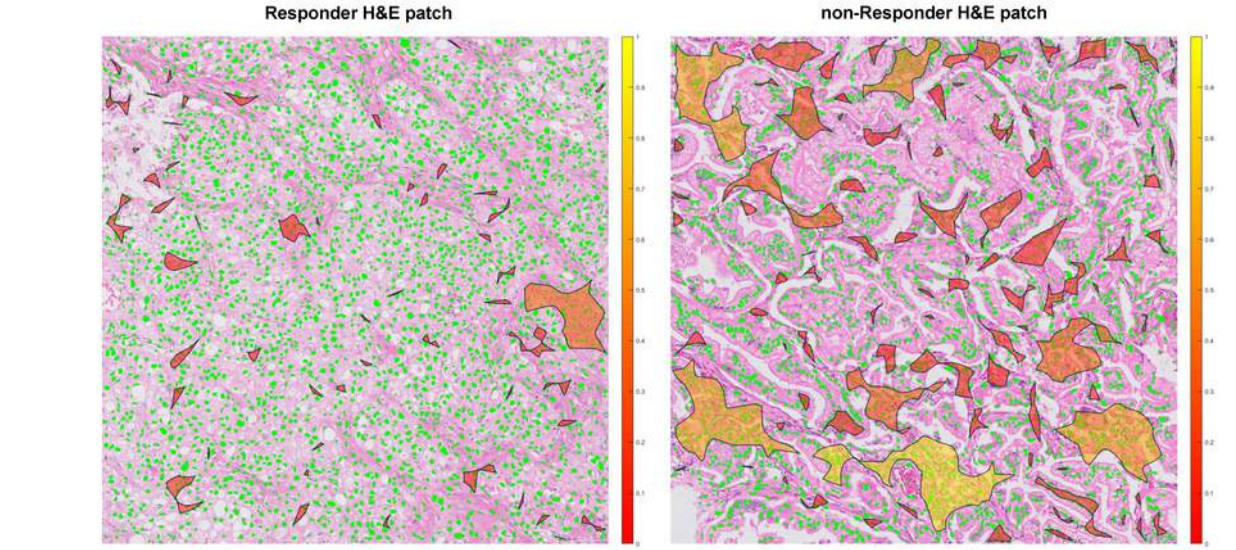

Table 1. Multivariate analysis for overall survival on the validation sets D2 and D3

Variables	HR(95% CI)	*p* value
Age (>65 vs <=65 yrs)	0.99(0.97-1.03)	0.67
Gender (Male vs Female)	1.05(0.75-2.79)	0.88
Smoking Status (Former vs Never smoker)	3.19(0.92-11.061)	0.07
Histological Subtypes (Adeno vs Squamous)1	1.06(0.13-8.54)	0.95
EGFR status	1.32(0.49-3.52)	0.58
ALK status	0.63(0.36-1.10)	0.10
Total lymphocyte count	0.99(0.99-1.00)	0.33
SpaTIL Classifier	7.88(1.66-37.216)	0.009

CI = confidence interval; HR = Mantel-Haenszel Hazard ratio. Values in bold are statistically significant, p<=0.05.

Conclusion: Spatial interaction of TILs and cancer are independently prognostic of OS in nivolumab treated NSCLC. Further validation needs to be done to evaluate its utility.

Keywords: predictive image signatures, TILs, response to immunotherapy

MA25.03 TUMOR-INFILTRATING LYMPHOCYTES (TIL) AND OUTCOMES WITH IMMUNOTHERAPY (ICI) OR CHEMOTHERAPY IN ADVANCED NSCLC (ANSCLC) PATIENTS

L. Mezquita[1], I. Gataa[1], C. Rossoni[1], E. Auclin[1], M. Kossai[1], F. Aboubakar[1], S. Le Moulec[2], J. Massé[2], M. Masson[3], N. Radosevic-Robin[3], M. Rouanne[1], M. Bluthgen[1], C. Caramella[1], L. Hendriks[1], A. Gazzah[1], D. Planchard[1], J.-P. Pignon[1], B. Besse[4], J. Adam[1]

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Background: Tumor infiltrating lymphocytes (TIL) morphologically assessed is prognostic in early stages in several tumors. We previously reported the correlation of TIL with immune checkpoint inhibitors (ICI) outcomes in 98 advanced (a) NSCLC patients treated with ICI. We aimed to assess the role of TIL in a larger cohort treated with ICI, and in patients exclusively treated with chemotherapy (CT). **Method:** aNSCLC patients with treated with single-agent ICI, with H&E stained sample available, were included between 11/2012 and 02/2017 in 3 cancer centers (immuno-cohort). Patient's characteristics, biological data were retrospectively collected. The CT-cohort was extracted from the prospective MSN study (NCT02105168), between 06/2009 and 10/2016, enrolling aNSCLC patients treated with platinum-based CT, and tissue available. TIL in the stroma was evaluated in archival samples. High-TIL was defined as ≥10% density. Multivariate Cox model was used to study its prognostic values on overall and progression-free survival (OS, PFS). **Result:** A total of 221 patients were included in the immuno-cohort: 142 (64%) male, with median (m) age of 63, 182 (84%) smokers, 161 (77%) PS≤1, 162 (63%) adenocarcinoma; 125 (57%) received ICI as second-line. High-TIL was observed in 49/221 (28%), non-assessable in 46. High-TIL had independent impact on OS and PFS (HR 0.40; 95% CI 0.25-0.63, *P*<0.0001). The mPFS and OS were 3.1months (mo.) (2.5-4.9) and 11mo. (7.0-13.2) respectively. The high-TIL group had mPFS of 13mo. (5.0-NR) vs. 2.2mo. (1.7-3.0) in low-TIL group (*P*<0.0001). High-TIL group had mOS not reached (NR) (12.2-NR) vs. 8.4 mo. (5.0-11.6) in low-TIL (*P*=0.007). The CT-cohort (N=189) had high-TIL in 103/189 (54%). The mPFS and mOS were 5.7mo. (4.9-6.7) and 11.7mo. (9.3-13.0) respectively, with no association with TIL.

	OS, Immuno-cohort (n=221)		OS, Chemo-cohort (n=188)	
	Hazard ratio (HR) 95% confidence interval (CI)	P-value	HR 95% CI	P-value
TIL ≥10% (high)	0.46 (0.28-0.81)	0.006	1.03 (0.76-1.41)	0.84
Age ≥65 y	0.86 (0.50-1.46)	0.57	0.99 (0.72-1.38)	0.99
Line of treatment* ≥ second line	0.69 (0.44-1.09)	0.11	0.84 (0.60-1.16)	0.29
N# metastatic sites >2	1.40 (0.88-2.20)	0.16	1.50 (1.07-2.12)	0.02
Performance status ≥2	2.75 (1.73-4.37)	<0.0001	1.94 (1.23-3.04)	0.004
Histology Squamous	1.13 (0.70-1.81)	0.62	1.09 (0.65-1.83)	0.75

*Line of treatment: lines of immunotherapy for the Immuno-cohort; lines of chemotherapy for the Chemo-cohort.

Conclusion: High-TIL (≥10%) is a simple and accessible marker associated with better ICI outcomes, but not with CT. This suggests a potential predictive value that must be validated in larger prospectively studies.

Keywords: tumor infiltrating lymphocytes, Biomarker, Immunotherapy

MA25.04 BLOOD-BASED TUMOR MUTATION BURDEN AS A PREDICTIVE BIOMARKER FOR OUTCOMES AFTER PEMBROLIZUMAB BASED FIRST LINE THERAPY IN METASTATIC NSCLC

C. Aggarwal[1], J. Thompson[1], A. Chien[1], K. Quinn[2], M. Lefterova[2], R. Nagy[2], S. Yee[1], M. Lariviere[1], C. Ciunci[1], A. Singh[1], J. Bauml[1], R. Cohen[1], C. Langer[1], E. Carpenter[1]

[1]*University of Pennsylvania, Philadelphia/United States of America,* [2]*Guardant Health, Redwood City/United States of America*

Background: PD-1 blockade with pembrolizumab (P) as monotherapy in patients with PD-L1 TPS ≥ 50% or in combination with platinum based chemotherapy (PC) is the current standard front-line therapy for metastatic non-small cell lung cancer (mNSCLC). We explored the correlation of blood (b) based tumor mutational burden (TMB) using circulating tumor DNA (ctDNA) with outcomes after front line P and PC therapy. **Method:** Patients with newly diagnosed metastatic NSCLC starting standard of care front line P-based therapy were enrolled. Plasma was prospectively collected at baseline prior to initiation of P or PC therapy for mNSCLC. A 2.145 megabase (Mb) next-generation sequencing panel was used to assess bTMB. A bTMB cutoff of ≥16 mut/Mb was selected based on previously published data (*Gandara et al, Nature 2018*). Response was assessed using RECIST 1.1. Durable clinical benefit (DCB) was defined as complete response/ partial response/ stable disease that lasted > 6 months. Correlations were made for patient demographics, tumor characteristics, DCB, progression free survival (PFS), and overall survival (OS) using logistic regression and Cox proportional hazards models. Significance was determined at the 0.05 level. **Result:** 66 pts with mNSCLC were enrolled, median age 67 years (range 47-89), current or ex-smokers (n=61, 92%). Thirty-one patients (47%) received P (all PD-L1>50%); 35 received platinum-pemetrexed based PC. At the time of data cut off, median OS for P was 14.8 months, and not reached for PC. bTMB was evaluable for 52 patients (n=26 P, 26 PC), median bTMB was 16.8 mutations per Mb (mut/Mb, range 1.9-52.5). There was no correlation between bTMB and tumor PD-L1 (p=0.28). Median bTMB for patients achieving DCB was higher than for those with no clinical benefit, 21.3 mut/Mb vs. 12.4 mut/Mb, p=0.004. For patients with bTMB ≥ 16 mut/Mb, median PFS was 13.8 vs. 4.7 months for patients with bTMB <16 mut/Mb (HR 0.27 [0.13-0.55]). Median OS was not reached for bTMB ≥ 16 mut/Mb (HR 0.47 [0.20-1.1]). Loss of function mutations in *STK11, KEAP1,* or *PTEN,* or *ERBB2* exon 20 insertion were enriched in patients with no clinical benefit. Combined score using bTMB ≥ 16 mut/Mb and mutations in *STK11, KEAP1,* or *PTEN,* or *ERBB2* exon 20 insertions resulted in improved prediction for DCB; PFS HR of 0.18 [0.08-0.41] and OS HR of 0.27 [0.10-0.73]. **Conclusion:** Our early results suggest that bTMB using plasma ctDNA may predict therapeutic outcomes after first line P-based therapy in mNSCLC. Loss of function mutations in *STK11/KEAP/PTEN* and *ERBB2* exon 20 insertion mutations appear to be negative predictors of benefit. As the sample size is limited and findings are reported on a pooled group of P and PC patients, the role of bTMB and response to P and PC based therapy separately should be validated in a larger prospective study.

Keywords: Blood based TMB, pembrolizumab, chemo-immunotherapy

MA25.07 GENOMIC PROFILING OF LUNG ADENOCARCINOMA BY TARGETED NGS USING EXTRACELLULAR VESICLE-DERIVED DNA IN BRONCHOALVEOLAR LAVAGE FLUID

S. Lee[1], K.Y. Lee[2], J.Y. Hur[3], H. Kim[3], W.S. Kim[3], I.A. Kim[2], H.Y. Park[4]

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Background: Extracellular vesicles (EV) are membrane-bound and nanometer-sized particles shed from most types of cells in our body and found in circulation, containing double-stranded genomic DNA reflecting mutational status of the parental tumor cells. Recently, we demonstrated that EVs successfully isolated from bronchoalveolar lavage fluid (BALF) in non-small cell lung cancer (NSCLC) patients. Several studies also have shown that EV-derived DNA is superior to cfDNA in plasma for detection of mutations in NSCLC and pancreatic cancer. We identified that liquid biopsy for *EGFR* genotyping using EV-derived DNA in BALF showed almost 100% sensitivity with tissue typing in advanced NSCLC patients. Therefore, we hypothesized that targeted next–generation sequencing (NGS) using EV-derived DNA in BALF may correlate with results using tissue in patients with *EGFR*-mutated lung adenocarcinoma. **Method:** To address this hypothesis, we compared with the targeted NGS profile using between BALF EV-derived DNA and tissue DNA in 20 patients with *EGFR*-mutated lung adenocarcinoma. Four types of somatic variants (SNVs, small indels, CNVs and gene fusions) of BALF-EV or FFPE tissue samples were analyzed by CancerSCAN™, a capture-based targeted sequencing platform, which targets 375 genes covering about 2.5-megabase genomic regions including full CDSs of 374 genes, selected intronic regions of 23 genes for fusion detection, and 1kb *TERT* promoter region. **Result:** Targeted sequencing resulted in over 99% of the target regions covered at a mean depth of 190-750× except one sample. DNA yields were higher in tissue DNA than EV-derived DNA (827.02ng vs 89.10ng). Depth of coverage (753x vs 379x) and estimated tumor purity (53% vs 23%) were also higher in tissue DNA than EV-derived DNA. However, estimated library size was not significantly different between tissue DNA and EV-derived DNA (50G vs 47G) and fragment size of DNA were longer in EV-derived DNA than tissue DNA (175.5bp vs 169.5bp). These findings support that EV-derived DNA has sufficient quality and quantity for NGS. By using mutations detected in tissue DNA as a reference, we achieved 83% sensitivity for somatic and clinically significant variants in EV-derived DNA. Clinically significant mutations in *EGFR*, *TP53*, *PTEN*, *APC*, JAK3 and PIK3CA were identified with an overall concordance of 81% in matched tissue DNA and EV-derived DNA. Variants in *EGFR* and *TP53* were most common, with concordance of 80% and 100%, respectively. Variant allele frequencies of *EGFR* and *TP53* were most abundant in range of 10-25% in tissue DNA, while much lower (<5%) in EV-derived DNA. Tumor mutation burdens (TMB) of EV-derived DNA showed correlation with tissue DNA (R^2=0.21). **Conclusion:** To our knowledge, this is the first of study of comprehensive clinical NGS panel using EV-derived DNA of BALF and matched tumor tissue biopsies in patients with lung adenocarcinoma. Although EV-derived DNA demonstrated comparable results to tissue DNA, it is needed much higher sequencing coverage and optimization of NGS-pipeline to detect low-allele frequency variants of EV-derived DNA. This study demonstrates the feasibility and clinical utility of BALF EV-derived DNA for patients with lung adenocarcinoma.

Keywords: Extracellular vesicles (EV), Targeted NGS, lung adenocarcinoma

MA25.08 CHARACTERISATION OF TUMOR AETIOLOGY USING MUTATIONAL SIGNATURES FROM THE NON-SMALL CELL LUNG CANCER GENOME

C. Lindsay[1], S. Rafee[1], P. Nicola[1], A. Wallace[2], G. Burghel[2], H. Schlecht[2], K. Baker[1], E. Baker[2], L. Priest[1], J. Rogan[3], S. Moghadam[3], M. Carter[1], W. Newman[2], F. Blackhall[1]

[1]*The Christie NHS Foundation Trust, Manchester/United Kingdom,* [2]*Manchester Centre for Genomic Medicine, Manchester/United Kingdom,* [3]*Manchester Cancer Research Centre Biobank, Manchester/United Kingdom*

Background: Somatic genome and exome analyses in cancer are currently dominated by a search for actionable mutations that inform new treatments for stage IV patients. Tumour mutational signatures, originally described by the Sanger centre, offer the potential to understand cancer cure and prevention strategies by using the genome/exome to define aetiological contributions to cancer from both environmental and endogenous sources. **Method:** 132 NSCLC samples were resected from 131 Greater Manchester patients and submitted to the UK 100,000 Genomes Project (Genomics England). A 5×5×5 mm fresh tumour sample was taken from the surgical specimen and stored at -80°C before undergoing genomic testing. To determine the neoplastic cell count, an additional tumour biopsy was taken for routine histological assessment. Germline DNA for comparable whole genome analysis was extracted from peripheral blood lymphocytes from a paired whole blood sample.Whole genome sequencing (WGS) was performed on tumor specimens and matched blood samples. Through the 100,000 Genomes Project pipeline, coverage was calculated from high-quality, non-overlapping bases present on well-mapped reads, as defined by SAMtools v1.1. Whole genome sequencing analysis was undertaken with the Illumina North Star pipeline v2.6.53.23. Data were then mined for tumour mutational burden (TMB) and mutational signature profiles. Signatures were extracted if they accounted for >5% of the mutations per sample. Clinical characteristics including tumor size, nodal status and stage were documented. Mann-Whitney and Fisher's exact tests were used for statistical comparisons. **Result:** Signature 8 (unknown aetiology) was the most prevalent mutational process overall (122/132 samples, 92.4%), while smoking signature 4 was the main mutational process in 86/131 (65.6%) of NSCLC cases. SIgnature 4 contributed as a principal or secondary mutational process to a total of 105/131 (80.2%) cancers; 104/105 (99%) of these patients were annotated as smokers or ex-smokers. Signature 5 (unknown aetiology) was the second most common driving signature (24/131, 18.3% cancers), contributing to an additional 19 cancers as a secondary mutational process (43/131, 32.8% of cancers overall). Median number of signatures contributing to signature 4 NSCLC was four, whilst non-smoking mediated NSCLC had contributions from a median of 5.5 mutational signatures (range 2-8). A median of four signatures contributed to both adenocarcinomas and squamous cancers, with 61/88 (69.3%) adenocarcinomas and 25/41 (61%) squamous cancers associated with signature 4 as their main mutational process. More results will follow on duration of signature 4 persistence following discontinuation of smoking, as well as prevalence of each signature according to common molecular subtypes of NSCLC. **Conclusion:** Tumor mutational signatures have the potential to inform cancer prevention by offering a new level of genetic detail that reflects environmental and endogenous carcinogenesis. As expected, signature 4 offers the main contribution to NSCLC although a number of other aetiological factors are involved in its carcinogenesis. In particular, signatures 5 and 8, both currently of unknown aetiology, significantly contribute to the NSCLC genome. Along with that reported by the Sanger centre, this work lays the foundations for characterisation and identification of new carcinogens.

Keywords: mutational signatures, Non-Small Cell Lung Cancer, prevention

MA25.09 NAVIGATING ANLOTINIB PRECISION THERAPY THROUGH THE GENETIC PROFILING OF CIRCULATING DNA IN NON-SMALL CELL LUNG CANCER PATIENTS

J. Lu[1], H. Zhong[1], J. Wu[2], T. Chu[1], L. Zhang[1], H. Li[3], Q. Wang[4], R. Li[1], Y. Zhao[1], A. Gu[1], C. Shi[1], L. Xiong[5], X. Zhang[1], W. Zhang[1], Y. Lou[1], B. Yan[1], Y. Dong[1], Y. Zhang[1], B. Li[6], L. Zhang[7], X. Zhao[3], K. Li[8], B. Han[1]

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Background: Anlotinib is an oral multi-targeted anti-angiogenic drug, and its clinical predictor for non-small cell lung cancer (NSCLC) patients is still elusive. The aim of this study is to screen predictor for anlotinib via non-invasive genetic profiling of plasma cell free DNA and circulating tumor DNA (cfDNA & ctDNA). **Method:** Tumor-specific target capture to profile the circulating DNA of ALTER0303 (Evaluating NSCLC clinical anti-tumor efficacy through anlotinib therapy) study participants. Acquired mutations were screened out via comparing genetic profiling between baseline (BL) and progression disease (PD), and were used for anlotinib stratification. Based on the sequencing data at BL, tumor mutation index (TMI) was established from three independent predictors germline and somatic mutation burden (G+S MB), nonsynonymous and synonymous mutation burden (N+S MB) and unfavorable mutation score (UMS), and was used for predicting anlotinib responders. In addition, TMI combined with *IDH1*^{Exon4} mutation status also be examined for serving as predictor for anlotinib stratification. **Result:** Our data firstly indicated no benefit (NB, PFS $\leq$ 45 days) patients can be mainly excluded via analysis of *ARID1A* and *BRCA2* genetic profiling. Secondly, for the no durable benefit (NDB, 45 days < PFS $\leq$ 130 days) and durable clinical benefit (DCB, PFS > 130 days) patients, harboring lower mutation burden (G+S MB, N+S MB, and UMS) received more benefit from anlotinib therapy. Subsequently, we found the predictor-TMI can predict anlotinib responders upon discovery cohort (Median PFS: 210 days vs 126 days; p = 0.0238; AUC = 0.77), and validation cohort (Median PFS: 210 days vs 127 days; p = 0.0352) and all patients (Median PFS: 210 days vs 127 days; p = 0.0044) more effectively. Furthermore, the *IDH1*^{Exon4} mutation was identified as an unfavorable factor to anlotinib therapy under TMI-based stratification. Lastly, the TMI plus *IDH1*^{Exon4} mutation status predict response to anlotinib significantly (Median PFS: 210 days vs 127 days, p < 0.0001, AUC = 0.90; Median OS: 423 days vs 162 days, p < 0.0001, AUC = 0.80). **Conclusion:** This study provides circulating DNA sequencing-based stratification for underlying anlotinib responders via non-invasive approach, and thus potentially improve clinical outcome for NSCLC patients at 3rd line.

Keywords: Precision therapy, Anlotinib, Non-small cell lung cancer

Posters

P01.01 ADVANCED NSCLC
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.01-01 CLINICAL RELEVANCE OF TARGETING PROTEINS REQUIRED FOR MITOTIC PROGRESSION TO IMPROVE CHEMOTHERAPY RESPONSE IN NON-SMALL CELL LUNG CANCER

M. Adams, J. Burgess, D. Richard, K. O'Byrne

Institute of Health and Biomedical Innovation, Queensland University of Technology Translational Research Institute, Woolloongabba/Australia

Background: Lung cancer is the leading cause of cancer-related mortality worldwide with a ~14% 5-year survival rate. Patients with non-small cell lung cancer (NSCLC), may undergo surgery followed by platinum-based chemotherapy for resectable disease, chemoradiotherapy for locally advanced disease, systemic treatment for advanced disease and palliative care. The primary issue with chemotherapy is that only 20-40% of patients have responsive disease. Although combinations with immunotherapy can enhance drug response in advanced disease, new strategies are needed to (1) identify which patients are most likely to benefit from platinum based therapy and (2) enhance the effectiveness of the current drug strategies. Herein we describe cell division cycle associated protein-3 (CDCA3) and CDCA8 as a novel prognostic factors and therapeutic targets to delay or prevent platinum resistance in NSCLC. Both CDCA3 and CDCA8 are key regulators of the cell cycle mediating mitotic entry and progression. CDCA3 functions to enable cell entry into mitosis through degradation of the mitosis inhibitory factor WEE1. Whereas, CDCA8 promotes mitotic progression functioning in concert with the chromosomal passenger complex to ensure accurate chromosomal segregation. **Method:** Tissue microarray (TMA), immunohistochemistry, Bioinformatics, Western blot, siRNA library, CRISPR-Cas9 knockout, cell viability, mass spectrometry. **Result:** Our preliminary data point to CDCA3 and CDCA8 as novel therapeutic options in NSCLC. CDCA3 and CDCA8 protein are markedly elevated in NSCLC cases with heterogeneous staining associated with Ki67+ cases and strongly prognostic in adenocarcinoma cases. Bioinformatics analysis of clinical trial data (UT Lung SPORE cohort; observation arm vs adjunct chemotherapy arm) indicated that NSCLC patients with elevated CDCA3 and CDCA8 and treated with adjuvant chemotherapy had a poorer outcome than $CDCA3^{low}$/$CDCA8^{low}$ patients. Accordingly, *in vitro* analysis of CDCA3 and CDCA8 expression in NSCLC cell lines identified a strong correlation with cisplatin sensitivity whereby $CDCA3/CDCA8^{high}$ cell lines have greater cisplatin IC50 values. Consistently, silencing of either CDCA3 or CDCA8 significantly enhanced cisplatin sensitivity. As a means to reduce either CDCA3 or CDCA8 levels in tumours, we identified that, for CDCA3 in particular, cisplatin induces phosphorylation of CDCA3 (Ser222) which is dependent upon casein kinase 2 (CK2). Inhibition of CK2 with the small molecule CX-4945 (Senhwa Biosciences) abrogated CDCA3 phosphorylation and consequently suppressed CDCA3 levels. CK2 inhibition also suppressed CDCA8 levels whereby CDCA8 protein stability is dependent upon CDCA3. The sensitivity of cisplatin was enhanced by CX-4945 across a panel of 11 NSCLC cell lines, particularly in $CDCA3/CDCA8^{low}$ cell lines. Cisplatin efficacy was further enhanced in CDCA3 or CDCA8 depleted NSCLC cells. **Conclusion:** Our data highlight CDCA3 and CDCA8 as novel factors mediating NSCLC cell proliferation and sensitivity to cisplatin. Our data also suggest that novel strategies to suppress CDCA3/CDCA8 protein levels, using agents such as CX-4945, might ultimately benefit NSCLC patient outcome by delaying or preventing cisplatin resistance.

Keywords: Platinum-based chemotherapy, cell cycle, Chemotherapy response

P1.01-02 PEMETREXED-CARBOPLATIN VERSUS PACLITAXEL (WEEKLY)-CARBOPLATIN AS FIRST LINE CHEMOTHERAPY IN ADVANCED NON-SQUAMOUS NSCLC

P. Malik, A. Yadav, D. Jain, S. Pathy, A. Mohan, S. Khurana, S. Kumar

All India Institute of Medical Sciences, New Delhi/India

Background: Platinum doublet chemotherapy has been standard of care in treatment naïve advanced non-small cell lung cancer (NSCLC) without targetable driver mutation until recent approvals of first line immune check point inhibitors. Pemetrexed-platinum combination has been preferred over other combinations in non-squamous NSCLC (ns-NSCLC). However there has been no direct comparison to Paclitaxel-carboplatin. **Method:** This open label randomized control trial was designed to compare Pemetrexed-Carboplatin versus Paclitaxel (weekly)-Carboplatin combination in treatment naive advanced/metastatic ns-NSCLC without driver mutations and ECOG PS 0-2. The study was powered to detect superiority of Pemerexed-Carboplatin over Paclitaxel-Carboplatin by 15% in terms of 6 months PFS rates (primary outcome) and total 182 events were required for the same. Patients received either Pemetrexed 500 mg/m2 and Carboplatin AUC 5 every 3 weekly cycle for 4 cycles (with standard vitamin supplementation) or Paclitaxel 80 mg/m2 day 1, day 8 and day 15 with Carboplatin AUC 5 every 4 weekly cycles for 4 cycles. Patients in both arms were allowed to receive Pemetrexed maintenance in absence of progressive disease after 4 cycles. Patients, in whom EGFR mutation or ALK rearrangement were detected after randomization, were allowed to receive appropriate targeted therapy after 4 cycles or earlier as per physician's discretion. The trial was approved by institute ethics committee and registered with CTRI (CTRI/2016/12/007605). **Result:** A total of 180 patients were enrolled between April 2016 and January 2019. The study was terminated early due to slow accrual, however at the time of analysis (31stMarch 2019) total 129 events (70.8% of required) had occurred. Finally, 164 patients were evaluable, 83 in Pemetrexed-Carboplatin arm and 81 in Pacitaxel-Carboplatin arm. After a median follow up time of 15 months, PFS rates at 6 months were not different in two treatment arms (43.3% vs 43.2%; p=0.98). Median PFS were 5.63 months (95%CI 3.73-7.3) in Pemetrexed-Carboplatin arm and 5.03 months (95%CI 2.63-7.43) in Paclitaxel-Carboplatin arm (p=0.61; HR 1.09(95%CI 0.77-1.54). Median overall survival wasn't different, 13.4 months (95%CI 8.6-17.63) and 10.13 (95%CI 7.6-19.7) respectively (p=0.11; HR 1.07(95%CI 0.71-1.61). All grade toxicities were similar except for alopecia and peripheral neuropathy, which were significantly higher in the Paclitaxel arm.

Baseline Characteristics of the patients

Characteristics	Pemetrexed arm N (%)=83	Paclitaxel arm N(%)= 81	p
Median Age	52 years (29-65)	52 years (28-65)	0.6
Gender Males Females	56 (67.47%) 27 (32.5%)	58 (71.6%) 23 (28.4%)	0.61
Smoking Status Non smokers Smokers	45 (54.22%) 38 (45.78%)	39 (48.15%) 42 (51.85%)	0.5
ECOG PS 0 1 2	9 (10.84%) 51 (61.45%) 23 (27.71%)	3 (3.7%) 57 (70.37%) 21 (25.9%)	0.18
Histology Adenocarcinoma NSCLC- NOS	83 (100%) 0	76 (95%) 4 (5%)	0.039
EGFR mutation Positive Negative Not available	20 (24.39%) 47 (57.32%) 16 (19.2%)	18 (22.2%) 48 (59.26%) 15 (18.52%)	0.94
ALK rearrangement Positive Negative Not available	08 (9.76%) 50 (60.98%) 25 (30.12%)	07 (8.64%) 50 (61.73%) 24 (29.61%)	0.66
Stage (AJCC 7th) Stage 3B Stage 4	02 (2.41%) 81 (97.59%)	03 (3.7%) 78 (96.3%)	0.59
Pleural/Pericardial Effusion Present Absent	32 (38.55%) 51 (61.45%)	27 (33.33%) 54 (66.67%)	0.48
Brain metastasis Present Absent/ Not evaluated	16 (19.28%) 67 (80.7%)	16 (19.75%) 65 (80.2%)	0.93

Conclusion: Pemetrexed-Carboplatin is not superior to Paclitaxel (weekly) -Carboplatin as first-line regimen in advanced ns-NSCLC in terms of 6 months PFS rates.

Keywords: non squamous non small cell lung cancer, firstling chemotherapy, pemetrexed

P1.01-03 EFFICACY AND SAFETY OF BIOSIMILAR QL1101 COMPARED WITH AVASTIN IN PATIENTS WITH NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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Background: QL1101 is a biosimilar molecule of bevacizumab (BEV, Avastin®), a monoclonal antibody (mAb) that binds and inhibits vascular endothelial growth factor (VEGF).The main purpose of the study is to evaluate whether the effectiveness of QL1101 is bioequivalent to that of Avastin®, and the secondary purpose is to evaluate the bioequivalence on safety and immunogenicity between QL1101 and Avastin®. **Method:** Total 512 patients with locally metastatic or recurrent non-squamous cell non-small cell lung cancer were planned to recruit in the study (NCT03169335). The patients were divided into QL1101 (test group) or Avastin® (control group) at 1:1 ratio in combination respectively with paclitaxel/carboplatin (paclitaxel 175mg/m^2, carboplatin AUC=5). QL1101 or Avastin was given every 3 weeks as one treatment cycle for 6 cycles with the same dose of 15mg/kg per time, then followed by QL1101 single-drug maintenance treatment. The primary endpoint was the best objective response rate (ORR) at week 18 as evaluated by the blind independent imaging review committee, and the secondary endpoints include DOR, PFS and OS. **Result:** A total of 675 subjects were screened and 532 were finally enrolled and treated including 266 in the trial group and 266 in the control group. At week 18, the ORR of the QL1101 group and Avastin group were 52.26% (CR: 0, PR: 139) and 56.02% (1 cases CR, 148 PR), respectively, and risk ratio (RR) value and 90% CI was 0.933 (0.818-1.064), which met the pre-specified equivalence margins (0.75-1.33). The mDOR in QL1101 group and Avastin group was 5.88 and 6.93 month (P=0.5044)respectively, and mPFS were 7.88 and 8.34 months (P=0.2760) accordingly, the 12-month OS in the two groups was 69.18% and 75.10% respectively. The incidence of CTCAE≥ grade 3 adverse events was 31.20 % in QL1101 group and 24.06 % in Avastin group, respectively (P = 0.0808). The immunogenicity (ADA and Nab tested) of the two groups was similar. **Conclusion:** QL1101 and Avastin are equivalent in clinical efficacy, and the safety profile (including immunogenicity) is quite similar in patients with non-squamous cell non-small cell lung cancer. There are no unexpected serious adverse reactions were found during the study.

Keywords: QL1101, Bevacizumab, biosimilarity

P1.01-04 A PHASE II TRIAL OF WEEKLY NAB-PACLITAXEL IN THE SALVAGE SETTING FOR ADVANCED NON-SMALL CELL LUNG CANCER: RESULTS OF NICE SALVAGE STUDY

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Background: The optimal treatment in patients with advanced non-small cell lung cancer (NSCLC) after failing second- or third-line chemotherapy, i.e. NSCLC in salvage setting, has yet to be established. A small study reported that solvent-based paclitaxel (sb-P) monotherapy was safe and efficacious and could be a treatment option for NSCLC in salvage setting (Anticancer Res 2005). Nanoparticle albumin-bound paclitaxel (nab-P) showed a higher overall response rate (ORR) and better tolerability than sb-P when combined with carboplatin (CBDCA) as a first-line chemotherapy (J Clin Oncol 2012). These results suggest that nab-P monotherapy could be better therapeutic option than sb-P monotherapy for NSCLC in salvage setting. We therefore planned NICE Salvage study aiming to assess the efficacy and safety of nab-P monotherapy for NSCLC patients in salvage setting. **Method:** NICE Salvage study was a multicenter single arm phase II study. Eligibility criteria included patients aged >= 20 years, with PS 0-2 and adequate organ function, and who have failed two or three prior lines of chemotherapy including at least a platinum-containing regimen for pathologically-proven advanced NSCLC. Patients who had treatment history with sb-P or nab-P, or had tumors harboring *EGFR* mutation or *ALK* fusion gene were excluded. Nab-P was administered at a dose of 80 mg/m^2 on days 1,8 and 15 of a 28-days cycle and repeated until progressive disease, unacceptable toxicity, or patient's refusal. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), ORR, disease control rate (DCR), efficacy according to prior use of docetaxel, quality of life, and safety. The study is powered to detect a 1.5-month improvement in median PFS in the investigational arm beyond the 2.0-month median PFS estimated from historical data. Assuming a one-sided 0.10 level of Type I error and 80% power, target sample size is calculated at 35. (UMIN000016173). **Result:** Thirty-eight patients were enrolled and a patient was excluded from efficacy and safety analysis. Patient's characteristics (n = 38) were as follows: median age = 68 years, male/female = 31/7, adenocarcinoma/squamous cell carcinoma /others = 20/15/3. Median PFS and OS was 3.5 month (95% confidence interval (CI), 1.7-3.8), and 13.4 month (95%CI, 9.1-25.1), respectively. ORR and DCR were 10.8% (95%CI, 2.9-24.8) and 56.8% (95%CI, 38.3-71.3), respectively. Grade 3 or 4 treatment-related adverse events were neutropenia (10.8%), anemia (2.7%), hepatotoxicity (2.7%) and diarrhea (2.7%). One treatment-related death (pulmonary infection) was observed. **Conclusion:** This study failed to meet predefined primary endpoint. However the results showed that nab-P monotherapy was moderately efficacious and well-tolerated, suggesting the need for further investigation for NSCLC in salvage setting.

Keywords: NSCLC, nab-Paclitaxel, salvage setting

P1.01-05 PHASE I STUDY OF INHALED 5-AZACYTIDINE (5-AZA) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Our previous study in an endo-bronchial NSCLC murine model suggested that aerosolized 5-Aza could inhibit cancer growth, prolong survival, and induce re-expression of methylated tumor suppressor genes. This is the first in human phase I study of 5-Aza delivered by inhalation in pts with advanced NSCLC. **Method:** Main inclusion criteria: Stage IV or recurrent NSCLC with predominantly lung involvement, ≥1 prior systemic therapy, ECOG PS 0-1, and good pulmonary function. Pts were treated with inhaled 5-Aza daily, D1 to D5 and D15 to D19 of a28-day cycle. Initial dose escalation used an accelerated titration scheme, followed by a 3 + 3 dose escalation and de-escalation design. The starting dose was 15mg/m^2 (derived from preclinical studies that showed it to be a safe and DNA demethylating dose), followed by 30 and 45 mg/m^2. The primary objective was to determine the MTD and toxicity (especially pulmonary toxicity). Secondary objectives included PK, methylation profiles pre and post 5-Aza (bronchoscopy), efficacy (RECIST 1.1), PFS and OS. **Result:** From 3/2015 to 12/2017, 8 pts were treated with 3 escalating doses of inhaled 5-Aza, including 2 at the highest level of 45mg/m^2. Median follow up: 15m. Median age 70, 62.5% female, 62.5% blacks, all PS=1, 87.5% adenocarcinoma with 1 *EGFR* and 2 *KRAS* mutants, 62.5% active/former smoker, mean number of prior therapies: 3 lines. Mean treatment cycles: 3.4 (1-12). No treatment related adverse events were reported. No DLTs were observed. Preliminary PK study indicated no detectable 5-Aza in the blood. No objective response was observed, 37.5% (3/8) had stable disease (SD). Median PFS and OS were 2 m and 12 m respectively. One pt had SD > 17 m and received a total of 2 cycles, whereas another KRAS-

mutant pt had SD >29 m and received a total of 12 cycles. **Conclusion:** Inhaled 5-Aza was well-tolerated with no treatment-related toxicity. The administration of 5-Aza by inhalation was feasible for multiple cycles in pts with advanced NSCLC without any significant pulmonary toxicity. The methylation studies in bronchial epithelium are ongoing and will be presented. Our results suggest that inhaled 5-Aza may represent a novel and safe therapeutic strategy for patients with lung-confined malignant and/or premalignant lesions. Clinical trial information: NCT02009436. Supported by NIH CA154755

Keywords: 5-Aza, inhaled therapy, NSCLC

P1.01-06 COMPARATIVE EFFECTIVENESS OF FIRST LINE (1L) THERAPIES FOR ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC): A SYSTEMATIC LITERATURE REVIEW (SLR)

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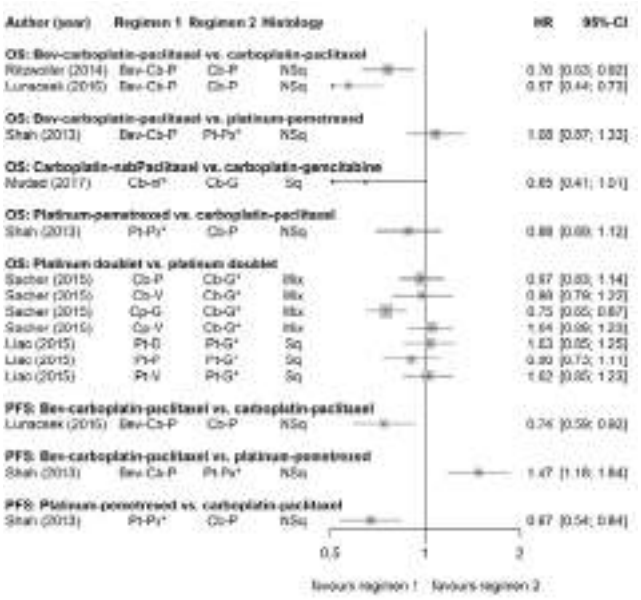
Background: The therapeutic landscape for aNSCLC has shifted in recent years. Novel therapies, including immunotherapies, have been tested in clinical trials but less is known about their effectiveness and safety in real-world (RW) settings. Our primary objective was to quantify the relative effectiveness and safety of 1L therapies for aNSCLC in a RW setting. **Method:** An SLR was conducted using EMBASE and MEDLINE (2012-2018), alongside searches of conference proceedings (2015-2018). Two reviewers assessed eligibility and included observational studies involving at least two chemotherapy or immunotherapy-based 1L therapies for aNSCLC. EGFR+, ALK+, and KRAS+ mutation-targeting therapies and sub-populations were excluded. Effectiveness and safety endpoints were extracted; relative effects were presented using forest plots. Pooled estimates were not generated due to study design heterogeneity and limited number of studies per treatment comparison. Risk of bias was assessed using ROBINS-I. **Result:** From 4,307 abstracts, 18 RW chemotherapy-based studies were included; no immunotherapy-based studies were identified. Of the 18 studies, only seven used methods to balance patient characteristics across treatments. Of these seven, relative effect estimates trended toward improved overall survival (OS) and progression-free survival (PFS) associated with chemotherapy doublets involving pemetrexed, nab-paclitaxel, or the addition of bevacizumab, relative to older platinum-based chemotherapy doublets (Figure 1). Significantly higher objective response rates (ORR) were observed for pemetrexed-based doublets relative to paclitaxel- and gemcitabine-based doublets reported in one multi-group study. There were no significant differences in non-hematologic and few significant differences in hematologic adverse event rates.



Conclusion: This SLR provides complementary evidence showing relative effect sizes of 1L chemotherapies in the RW setting, which were broadly consistent with those observed in clinical trials. Comparative RW evidence for immunotherapies in 1L aNSCLC is lacking and is expected to emerge in the future; however, this research provides a benchmark against which new evidence can be compared.

Keywords: Systematic literature review, Comparative effectiveness, Real world evidence

P1.01-07 REAL WORLD DATA OF DOCETAXEL PLUS NINTEDANIB FOR PRETREATED NSCLC PATIENTS: 4 YRS UPDATE COMPASSIONATE USE PROGRAM SINGLE INSTITUTION IN MEXICO

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Background: Nintedanib is an oral, potent, tyrosine kinase inhibitor that simultaneously targets vascular endothelial growth factor receptors 1-3, platelet-derived growth factor receptors α and β, and fibroblast growth factor receptors 1-3, as well as FLT3 and Src. Currently, the molecule has proved benefit for second-line in non-small cell lung cancer patients. Previous we report the results of a cohort of NSCLC patients receiving nintedanib within a compassionate-use program (CUP) in México demonstrated significant improvement in progression-free survival. **Method:** Patients with advanced NSCLC progressing after one line of chemotherapy were enrolled. Eligible patients received docetaxel 75 mg/m(2) (day 1) plus nintedanib 200 mg twice daily; days 2-21) in 21-day cycles. Data collection was monitored. Treatment continued until disease progression or unacceptable drug-related AEs. The intention of this CUP was to provide controlled access to nintedanib. Here, we report a 4-year update, representing the longest follow-up of a real world study evaluating nintedanib docetaxel in combination therapy. **Result:** From February 2014 to April 2015, 24 patients (54.2% female 45.8% male; median age: 61 years [range: 29-83 years]) were enrolled. ECOG performance status 0-1 in 100% of patients. Patients received nintedanib 200 mg BID (n=16). Median PFS was 15 months (range, 5-24). OS median, 16 months [95% CI = 9.59–22.4]. Among 24 evaluable patients, 20 (83%) had a partial response and 3 (12.5%) had stable disease by Response Evaluation Criteria In Solid Tumors criteria. The most frequent drug-related adverse events (all grades) were diarrhea (32%), fatigue (58%), nausea (37%), vomiting (8.2%), neutropenia (12.5%), anemia (24.9%) and elevations in alanine aminotransferase (37.5%) and aspartate aminotransferase (31.2%). Dose-limiting toxicities (all grade 3 hepatic enzyme elevations) occurred only in 2/24 patients (8.3%). All hepatic enzyme elevations were reversible and manageable with dose reduction. No new safety signals were observed compared with the 2015 first analysis **Conclusion:** Based on cohort result update, continuous treatment with second-line nintedanib combined with docetaxel was well tolerated and showed efficacy in Mexican patients with advanced non-small-cell lung cancer.

Keyword: Advanced Lung Cancer, nintedanib, second line

P1.01-08 RANDOMIZED PHASE II TRIAL OF CBDCA+NAB-PTX VS CDDP+GEM IN PATIENTS WITH CHEMO-NAÏVE SQUAMOUS CELL LUNG CANCER: NJLCG1302

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Background: The subset analysis of CA031 trial showed a significant improvement of overall response rate (ORR) for carboplatin (CBDCA) plus weekly nab-PTX versus CBDCA plus PTX in patients (pts) with

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squamous cell histology (41% vs 24%). We conducted a phase II study comparing CBDCA plus weekly nab-PTX (CnP) to cisplatin plus gemcitabine (CG), one of the standard regimens in pts with squamous cell lung cancer (SCC). **Method:** Chemo-naïve stage IIIB/IV or postoperative recurrent SCC pts were randomly assigned to receive either cisplatin (80 mg/m^2) on day 1 plus gemcitabine (1000 mg/m^2) on days 1, 8 every 3 weeks or CBDCA (area under the curve [AUC] 6 mg/ml/min) on day 1 plus nab-PTX (75 mg/m^2) on days 1, 8, 15 every 3 weeks. The primary endpoint was ORR. Secondary endpoints were progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and toxicity. Assuming that an ORR of 40% in eligible pts indicates potential usefulness and ORR of 20% is the lower limit of interest, the estimated accrual was 32 pts in each arm. Allowing for dropouts, the accrual goal was determined to be 35 pts in each arm (alpha, 0.05; beta, 0.20).Thisstudy was planned to enroll 70 pts in total. **Result:** Between June 2013 and October 2018, 71 pts were enrolled and assigned to CG arm (n=35) and CnP arm (n=36). The median follow-up time was 10.8months. At data cutoff (March 31, 2019), ORR was 43% (95% confidence interval [CI]: 27.3-58.5) in CG arm and 47% (95%CI: 31.7-62.7) in CnP arm. DCR was 77% in CG arm and 80% in CnP arm. Median PFS was 4.6 months in CG arm and 4.1months in CnP arm. Median OS was 15.2months in CG arm and 10.2months in CnP arm. Of the grade 3 or higher adverse events, anemia was more common in CnP arm (CG, 17% and CnP, 53%). There was one treatment-related death in CG arm and no treatment-related death in CnP arm. **Conclusion:** In this study, CBDCA plus weekly nab-PTX was likely to be equivalent to cisplatin plus gemcitabine despite carboplatin-based regimen. CBDCA plus weekly nab-PTX could be a promising regimen for SCC.

Keywords: Squamous Cell Lung Cancer, Chemotherapy, chemo-naïve

P1.01-09 RANDOMIZED TRIAL COMPARING MAINTENANCE PEMETREXED WITH OBSERVATION FOLLOWED BY PEMETREXED AT PROGRESSION IN ADVANCED NSCLC

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Background: Previous placebo-controlled studies show that maintenance treatment with pemetrexed prolongs progression free survival (PFS) and overall survival (OS) in advanced non-squamous non-small-cell lung cancer (NSCLC) patients who do not progress on induction platinum-doublet chemotherapy. There were, however, a few limitations of these studies: Few on the control arms received pemetrexed at progression, few patients >70 years were enrolled, and patients with performance status 2 (PS2) were ineligible. **Method:** In this open phase III trial, patients with stage IIIB/IV non-squamous NSCLC ineligible for curative treatment who had PS 0-2, and non-progression after four courses of carboplatin (AUC=5) day 1 + vinorelbine (25 mg/m^2 IV day 1 and 25 mg/m^2 IV or 60 mg/m^2 PO day 8) were randomized to receive immediate pemetrexed maintenance therapy or observation followed by pemetrexed at progression. There was no upper age limit. The primary endpoint was OS, secondary endpoints were PFS and toxicity. To demonstrate an improvement in median OS from 6 to 8 months (from the time of randomization) with an α=0.05 and β=0.20, 198 patients were required on each arm. Accounting for a drop-out of maximum 10%, we aimed to randomize 436 patients. **Result:** 105 patients were randomized between May 2014 and September 2017 at 19 hospitals in Norway (maintenance: n= 54, observation: n=51). Inclusion was stopped prematurely due to poor recruitment after immunotherapy became available. Median age was 67 years (range 46-83), 34% were >70 years, 14% had PS 2, 93% stage IV, and 54% were women. 75% of the patients received pemetrexed at progression. The median number of pemetrexed courses were 4 (maintenance: 3, observation: 4; p=0.265). Patients in the maintenance-arm had a significantly longer PFS (median 3.1 vs. 1.9 months; p=0.02), and a 2 months longer median OS (12.0 vs. 10.0 months; p=0.10). In a Cox regression analysis adjusting for baseline patient and disease characteristics (gender, stage of disease, PS), there was a trend towards a statistically significant difference in OS (HR 0.67 95% CI 0.436-1.030; p=0.068). There were no significant differences in toxicity between those who received maintenance therapy and those who received pemetrexed at progression. **Conclusion:** Maintenance pemetrexed therapy prolongs PFS and with a trend towards improved OS in non-squamous NSCLC compared with observation followed by pemetrexed at progression in a cohort including more elderly patients than previous studies of maintenance pemetrexed therapy and when allowing PS2 patients.

Keywords: pemetrexed, palliative, Maintenance chemotherapy

P1.01-10 IMPACT OF ANTI-COPD SUPPORT TREATMENT IN ADVANCED NSCLC PATIENTS WITH COPD UNDERGOING CHEMOTHERAPY AS FIRST-LINE TREATMENT

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Background: To investigate the impact of standardized anti-COPD support treatment of advanced NSCLC patients complicate with COPD undergoning chemotherapy as the first-line treatment, which without driver mutations. And putting forword the new concept of "simultaneous treatment of cancer and lung itself". **Method:** The clinical data of advanced NSCLC patients complicated with COPD were analyzed retrospectively. And patients were divided into observation group and control group according to whether the patients received standardized anti-COPD support treatment. Compared the survival statistics of the two groups. **Result:** The study consisted of 76 patients, only 31 patients received standardized anti-COPD support treatment. The courses of first-line chemotherapy in observation group were more than that of control group (4.8vs.3.8, p<0.05), and patients in observation group were more likely to received second-line chemotherapy (95.7%vs.75.0%,p<0.05). Progression-free surival (PFS) and overall survival(OS) of observation group were significantly higher than control group (6.0 months vs.3.5 months,p<0.05;18.0 months vs.15.0 months,p<0.05).

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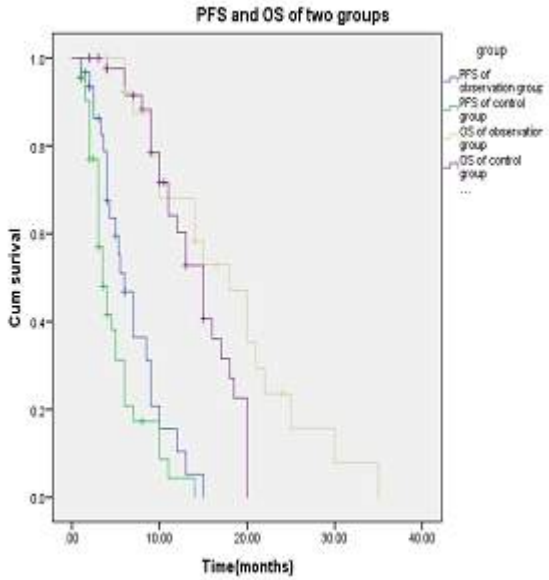
Baseline data of two groups of patients				
Baseline data	**Observation group**	**Control group**	**Test value**	**P value**
Sex (Male/Female)	30/1	44/1	χ^2=0.072	0.789
Age	67.0±7.2	67.8±7.8	t=0.501	0.667
Smoker	29	43	χ^2=0.148	0.700
Smokeing index	880.0±52.5	991±68.6	t=0.76	0.387
Stage			χ^2=0.473	0.492
IIIB	10	18		
IV	21	27		
PS	(1.97±0.48)	(1.93±0.54)	-0.285	0.42
Pathological type			χ^2=0.794	0.373
Adenocarcinoma	14	25		
Squamous	17	20		
Non-special type	1	2		
Pulmonary fuction				
FEV1%PRED(%)	61.32±6.95	63.49±6.23	t=1.421	0.159
FEC%PRED(%)	58.81±5.73	60.82±4.69	t=1.682	0.097
FEV1/FVC(%)	61.81±5.11	62.89±4.74	t=0.947	0.347
DLCO(%)PRED)(%)	46.42±9.36	47.16±9.73	t=0.329	0.743
Chemotherapy				
TP	6	12		
GP	8	9		
DP	8	5		
PP	7	16		
PP+bevacizumab	2	4		
Average courses	4.8	3.8	t=2.589	0.012
Second-line	22	24	χ^2=4.170	0.041

The outcome of two groups of patients				
Curative effect idex	**Observation group**	**Control group**	**Test value**	***P* value**
PR	7	10		
SD	11	16		
PD	13	19		
DCR	58.1%	57.8%	χ^2=0.02	0.889
ORR	22.6	22.2	χ^2=0.01	0.971
PFS	6.0 month	3.5 month	χ^2=3.947	0.047
OS	18.0 month	15.0 month	χ^2=4.083	0.043



Conclusion: Advanced NSCLC patients complicate with COPD, which without driver mutations, received standardized anti-COPD support treatment can complete the courses of chemotherapy more smoothly, prolong PFS and OS.

Keywords: chronic obstructive pulmonary disease, management of comorbidities, Non-Small Cell Lung Cancer

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P1.01-11 QUALITY OF LIFE IN NSCLC PATIENTS TREATED WITH DOCETAXEL AND EITHER PLINABULIN OR PEGFILGRASTIM FOR PREVENTION OF NEUTROPENIA

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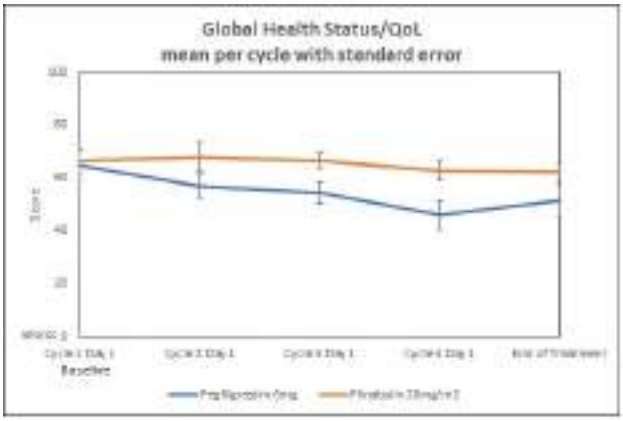
Background: Plinabulin is a novel small molecule, in development for the prevention of chemotherapy-induced-neutropenia (CIN). Plinabulin has anticancer activity and is separately developed through a global 3 trial (NCT02504489) for 2nd and 3rd line NSCLC patients. In contrast to pegfilgrastim, plinabulin does not produce bone pain, a chief complaint of patients taking pegfilgrastim. As part of the Phase 2 CIN protocol we measured patient quality of life (QoL) comparing pegfilgrastim and plinabulin. **Method:** In the Phase 2 portion of the Phase 2/3 Study 105 (NCT03102606), patients received docetaxel 75 mg/ m2 on Day 1, and were randomly assigned to either one of three plinabulin doses: 5 mg/m2 (n=14), 10 mg/m2 (n=13), 20 mg/m2 (n=14) mg/m2 on Day 1 (30 minutes after docetaxel infusion) over 4 cycles or no plinabulin and pegfilgrastim on Day 2. QoL was assessed with the validated health related questionnaires EORTC QLQ-C30 on D1 of each of the 4 cycles prior to study drug, and end of treatment. Day 1 Cycle 1 was baseline QoL. The data was analyzed using the standard methodology from the EORTC QLQ-C30 scoring manual which converts the 30 questions into three categories: global health status / QoL, functional scales, and symptom scales. The individual scores as well as the combined quality of life status, functional scales, symptoms scales, and the overall summary EORTC QLQ-C30 scores were analyzed. The difference between the treatment arms was analyzed using a linear mixed model for repeated measures with baseline and treatment arms as covariates. **Result:** Plinabulin 20mg/m^2 (clinically effective dose for CIN) demonstrated a significant improvement in QoL over 4 treatment cycles in three of the four parameters measured: global health status (p-value >0.0001), symptom scales (p-value 0.0093), and summary score (p-value 0.0195). In addition, there were significant improvements in three symptom scales: fatigue (p-value 0.0317), pain (p-value 0.0274), and insomnia (p-value 0.05).



Conclusion: Although these results are preliminary, they are significant and indicate improvements in QoL in patients being treated for advanced NSCLC with docetaxel and the addition of plinabulin for CIN prevention. This trend will be further investigated in ongoing Phase 3 trials for both NSCLC (NCT02504489), and CIN (NCT03102606 and NCT03294577).

Keyword: NSCL Neutropenia QoL

P1.01-12 TRENDS IN THE NATIONAL CANCER INSTITUTE (NCI) SPONSORED LUNG CANCER CLINICAL TRIALS PRE AND POST NCI'S NATIONAL CLINICAL TRIALS NETWORK (NCTN)

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Background: On March 1, 2014, NCI launched the new NCTN, transforming NCI's longstanding Cooperative Group Program. The NCTN coordinates and supports cancer clinical trials at more than 3,000 sites across the United States and Canada providing the infrastructure for NCI-funded trials to improve the lives of people with cancer. **Method:** We reviewed 10 years of lung cancer treatment trials accrual data that included 5 years pre-NCTN trial activations and accruals to these trials between3/1/2009-2/28/2014 and 3/1/2014-2/28/2019 for post-NCTN.More than 3,800 patients were enrolled to lung cancer treatment clinical trials that activated pre-NCTN during the pre-NCTN period, while more than 2,300 were enrolled in the post-NCTN period. Histology identifiers of small cell vs. non-small cell and Phase II vs. Phase II/III or III were sorted. **Result:** Table 1 Histology and Phase

Trial Information		PRE-NCTN	POST-NCTN
Number of trials		**19**	**23**
Lead disease	Non-small cell lung cancer	15	22
	Small cell lung cancer	4	1
Phase	Phase II	13	11
	Phase III (including II/III)	6	12

Table 2 Trial Status

		PRE-NCTN	POST-NCTN
Trial status	**Active**	**1**	**9**
	Closed	18	14
Closed trials	Completed	8	6
	Premature closure	10	8
Among Prematurely Closed Trials			
Reasons for premature closure	Interim monitoring	4*	5
	Drug supply/ external information		1
	Unacceptable toxicity	2	
	Inadequate accrual rate	4	2

While there is a 20% increase in activated trials in post NCTN era, the number of phase III trials has doubled. A decrease in small cell lung cancer clinical trials due to lack of active new drugs is noted. Enrollment of non-whites and females improved in post NCTN era and there was an increase in ethnicity and gender data capture. Additional demographic data will be available to report at the meeting and a discussion of evolving treatment trends. **Conclusion:** In this era of precision medicine trials, the total treatment trial patient numbers have deceased, however; the screening part of the NCI master protocol trials were excluded from this analysis. ALCHEMIST enrolled patients 3264 patients that were screened but not enrolled in the treatment arms of ALCHEMIST. All the patients screened on ALCHEMIST will be followed for a total of 10-years and their tumor will also undergo genomic analysis. Similarly, LungMap screening trial included 1278 patients that did not get assigned to any treatment protocol.

Keywords: Clinical Trials in Lung Cancer, National Cancer Trials Network, Lung Master protocols

P1.01-13 EFFICACY AND SAFETY OF CONCURRENT ANTI-TUBERCULOSIS TREATMENT AND CHEMOTHERAPY IN LUNG CANCER PATIENTS WITH CO-EXISTENT TUBERCULOSIS

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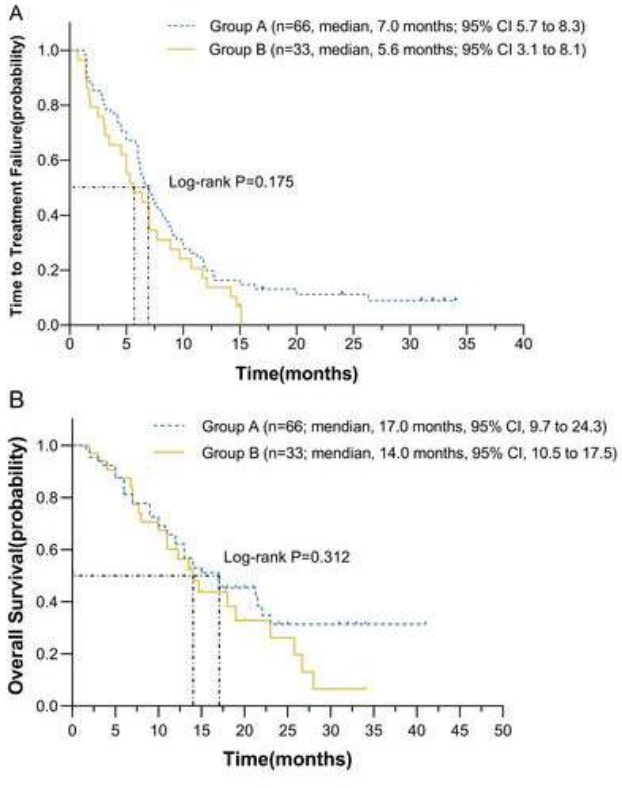
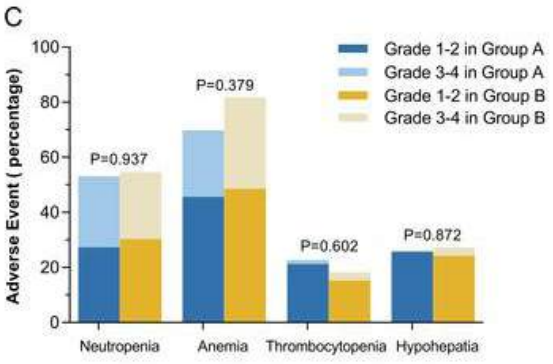
Background: This study evaluated the safety and efficacy of concurrent anti-tuberculosis (TB) and chemotherapy in patients with advanced lung cancer and active tuberculosis in a large sample size. **Method:** We retrospectively analyzed treatment naïve patients with advanced lung cancer diagnosed at Guangzhou Chest Hospital from 2015 to 2017. These patients were categorized into two groups: lung cancer patients without a history of TB treated with first-line standard anti-cancer chemotherapy (group A) and lung cancer patients with active TB treated concurrently with anti-TB and first-line chemotherapy(group B). Patients in group A were matched (2:1) to patients in group B with similar age, stage and tumor histology. Adverse events (AEs) and objective response rate (ORR) were tested using Chi-square test or Fisher's exact tests. Time to treatment failure (TTF) and overall survival (OS) were evaluated with Kaplan-Meier method and compared with the log-rank test. **Result:** A total of 99 patients were eligible (group A, n=66; group B, n=33). Grade≥3 treatment-related AEs (TRAEs), primarily hematologic toxicity, occurred in 41% and 48% of patients, for the A versus B groups, respectively. The hepatic insufficiency in two groups was generally grades 1 or 2, and their incidences were similar (26% and 27%, respectively). After two cycles of chemotherapy, ORR was 42.4% in group A and 33.3% in group B, which did not show any significant difference (P = .383). There were also not statistically significant in TTF (median, 7.0 vs 5.6 months for groups A and B, p= .175) and OS (median, 17.0 vs 14.0 months, p= .312). Among group B patients, rates of sputum negative conversion and lesion absorption were 100% within 3 months, and no recurrence was observed within 1 year.





Conclusion: Compared with chemotherapy alone in lung cancer patients, the combination of anti-TB treatment and chemotherapy did not increase hematological toxicity and hypohepatia of chemotherapy in lung cancer patients with pulmonary TB, which was safety and feasibility.

Keywords: Lung cancer, Pulmonary tuberculosis, Chemotherapy

P1.01-14 THE IMPACT OF SYSTEMIC TREATMENT ON BRAIN METASTASIS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER: A NATIONWIDE POPULATION-BASED COHORT STUDY

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Background: We performed a large-scale, retrospective, nationwide, cohort study of the incidence of brain metastasis in patients with advanced non-small-cell lung cancer (NSCLC) according to the systemic treatment administered. **Method:** The data were extracted from the Health Insurance Review and Assessment Service of Korea database from January 1, 2011 to November 30, 2016. Of the 29,224 patients newly diagnosed with stage IIIB or IV NSCLC who received first-line cytotoxic chemotherapy (CC group) or targeted therapy (TT group), 22,508 patients without brain metastasis were analyzed. **Result:** In total, 1,131 (5.0%) patients subsequently developed brain metastasis. The overall cumulative incidence of brain metastasis was significantly higher in the TT group than in the CC group (1-year cumulative incidence: 8.7 ± 0.6% vs. 3.8 ± 0.3%; 3-year: 17.2 ± 0.7% vs. 5.0 ± 0.3%, respectively; P < 0.001), despite the higher rate of brain metastasis in the CC group at < 3 years after diagnosis. Younger age, female sex, living in a rural area, anticoagulant use, and first-line TT (relative risk, 2.17 ± 0.03; 95% confidence interval, 1.92–2.50, P < 0.0001) retained significant associations with subsequent brain metastasis after adjusting for all variables. **Conclusion:** In the Korean population, the overall cumulative incidence of brain metastasis was significantly higher in patients in the TT group than in those in the CC group; the former could be regarded as having mutations in the EGFR or ALK gene.

Keywords: Population-based cohort study, Non-Small Cell Lung Cancer, brain metastasis

POSTERS

P1.01-15 MULTICENTER, SINGLE-ARM PHASE II STUDY OF NAB-PACLITAXEL/CARBOPLATIN IN UNTREATED PS2 PATIENTS WITH ADVANCED NSCLC: TORG1426

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Background: Performance Status (PS) has been shown to predict survival in patients with advanced non-small cell lung cancer (NSCLC). To date, PS2 patients have been underrepresented in clinical trials due to concerns about tolerability. Consequently, no standard of care exists for these patients. In CA031 trial, nab-paclitaxel/carboplatin (nab-PTX/CBDCA) demonstrated significantly higher response rate (RR) compared with PTX/CBDCA in PS0-1 patients with advanced NSCLC. Furthermore, in elderly subgroup, nab-PTX/CBDCA tended to show superior progression-free survival (PFS) and overall survival (OS) based on better tolerability compared with PTX/CBDCA. Therefore, this phase II trial was designed to characterize the efficacy, safety, and tolerability of nab-PTX/CBDCA in untreated PS2 patients with advanced NSCLC. **Method:** Chemotherapy-naive PS2 patients with stage IIIB/IV NSCLC were treated with nab-PTX (70 mg/m^2 on day1, 8, and15, q4w) and CBDCA (AUC 5 on day1, q4w) up to 6 cycles if they did not have uncontrolled brain metastasis or pleural effusion. The primary endpoint was PFS rate at 6 months. Its achievement of more than 50% was considered worthy of further development of this regimen, whereas that of less than 30% was considered insufficient for further investigation. The estimated power was 80% with type I error of 0.05, resulting in 35 patients needed. Concurrently, Symptom Score and Charlson Comorbidity Index (CCI) were evaluated. **Result:** This trial was terminated due to slow accrual. Between September 2015 and August 2018, 17 patients (median age, 68 years [range, 50-73]) were enrolled and received a median of 3 cycles. The reasons for PS2 were tumor progression (71%), comorbidities (12%), or both (17%). The PFS rate at 6 months was 20.8% (95% confidence interval, 0%-41.6%). The median PFS, OS, RR, and disease control rate (DCR) were 3.0 months, 9.5 months, 17.4%, and 70.6%, respectively. Grade 3-5 adverse events (AE) included fatigue (24%), lung infection (24%, including 6% of grade 5), neutropenia (18%), and anemia (18%), resulting in trial withdrawal rate of 24%. The median PFSs of 11 patients with and 6 patients without 2nd line chemotherapy were 5 months and 1.7 months, respectively (p = 0.009). Symptom Score was improved by chemotherapy (p = 0.004), whereas comparison between lower and higher CCI values demonstrated no difference regarding chemotherapy cycles administered (p = 0.5) and regarding chemotherapy efficacy (p = 0.268). **Conclusion:** Nab-PTX/CBDCA did not meet its primary endpoint, but could be a feasible treatment option for untreated PS2 patients with advanced NSCLC. Clinical trial information: UMIN000019458

Keywords: NSCLC, performance status, nab-Paclitaxel

P1.01-16 EVOLUTION OF SYSTEMIC THERAPY UPTAKE IN NSCLC OVER TIME: THE IMPACT OF NEW THERAPIES

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Background: Non-small cell lung cancer remains the most common cancer worldwide, and the leading cause of cancer deaths, partly because half of all patients are diagnosed at stage IV. Due to comorbidities or poor functional status many never receive systemic therapy. In previous research, we reported only 55% of advanced NSCLC patients received systemic therapy between 2009-2012 following out-patient oncology consultation (Brule et al. Lung Cancer 2016). Since then there has been broader emergence of rapid diagnostic assessment pathways, targeted therapies and immunotherapy, so we explored whether treatment rates have increased. **Method:** With ethics approval, we reviewed all cases of de novo stage IIIB/IV NSCLC seen in out-patient medical oncology consultation between 10/2015 and 09/2017. Patients treated with curative intent were excluded. The primary endpoint was the proportion of patients who received any line of systemic therapy. Further descriptive analysis looked at rates of targeted therapy and immunotherapy uptake. **Result:** In the study period, 461 patients met eligibility for analysis. Of these, 205 (44%) women; 425 (92%) stage IV, 343/82/36 adenocarcinoma/squamous/other. Median age was 69 years. Median time from pathological diagnosis to medical oncology consult was 13 days. Overall, 286 patients (62%) received at least one line of systemic therapy (155 patients received one line only, 90 received two lines, 34 received three lines and four patients received >=four lines). Among the 175 patients who did not receive any systemic therapy, the most common stated reasons were; poor PS (104, 59%), patient choice (48, 27%) or comorbidities (7, 4%). From 379 non-squamous NSCLC patients, 314 (83%) had a documented EGFR test (42/245/27 positive/negative/inconclusive) and 339 (89%) had a documented ALK test (12/311/13 positive/negative/inconclusive). Among the 42 EGFR+ patients, 90% received systemic therapy and among the 12 ALK+ patients, 92% received systemic therapy. For the non-EGFR, non-ALK patients, the proportion who received systemic therapy was 61%. Immunotherapy was prescribed in 87 patients: 3 in first line, 72 in second line and 12 in three+ line. **Conclusion:** In our academic centre between 2009-2012 only 55% of patients seen in out-patient oncology consultation received any line of systemic therapy. With more widespread molecular testing and the emergence of immunotherapy this has climbed to 62%. With an increase in first-line immunotherapy and more widespread molecular profiling, this should continue to improve, giving more patients the option of effective therapy.

Keywords: Non-Small Cell Lung Cancer, systemic therapy

P1.01-17 CHANGES IN PULMONARY FUNCTION DURING PLATINUM-DOUBLET CHEMOTHERAPY FOR LUNG CANCER

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Background: Lung cancer treatments, including checkpoint inhibitors, tyrosine kinase inhibitors, chemotherapy and multimodal treatments, may cause pulmonary side effects. Clinical trials document pulmonary toxicity but rarely include mandatory serial pulmonary function testing. As such, little is known about the changes in pulmonary function during systemic treatments, in particular in patients without manifest pulmonary toxicity. We present a longitudinal analysis of platinum-based chemotherapy for lung cancer and examine the effect of different chemotherapies on pulmonary function. **Method:** We retrospectively analyzed lung cancer patients treated with platinum-doublets and correlated lung function (FEV1, vital capacity, total lung capacity and diffusion) changes with the type of chemotherapy received. **Result:** We included 838 patients at the Munich Lung Cancer Centre from January 2013 until April 2019. The average patient age was 66,8 ± 9,79 years. 510 patients were male (60,9%). Histology was as follows: 410 adenocarcinoma, 153 small cell neuroendocrine carcinoma, 147 squamous cell carcinoma and 128 cases with other histologies. Platin was paired with pemetrexed (n=279), vinorelbine (n=205), etoposide (n=190), taxanes (docetaxel, paclitaxel, nab-paclitaxel; n=93) or gemcitabine (n=53). Lung function tests performed before and after chemotherapy were analyzed. During treatment, lung function parameters often improved. Pneumonitis was rare. There were chemotherapy-subgroup differences in lung function during treatment. **Conclusion:** Platinum doublets are associated with clinically relevant changes in lung function. Pneumonitis during chemotherapy is rare, and many patients experience improvements in pulmonary function during chemotherapy. The choice of chemotherapeutic agents may affect pulmonary outcomes. Larger studies of the effect of individual chemotherapeutic agents on pulmonary function in this setting and combined with immunotherapies are warranted.

Keywords: Lung function, Lung cancer, Chemotherapy

P1.01-18 INTEGRATED GENOMIC AND DNA METHYLATION ANALYSES OF NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES

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Background: Brain metastases (BM), with a dismal prognosis, are a common and lethal complication of non-small cell lung cancer. Approximately, 10% patients present with BM at their initial diagnosis. Although, surgery and/or radiation therapy remain to be the mainstay treatment, targeted therapies are finding increasing application in treating BM. However, due to the very limited accessibility of brain lesions, its genomic and epigenomic landscape remain elusive. **Method:** Capture-based targeted sequencing for somatic mutation profiling was performed on 27 treatment-naïve advanced NSCLC patients with paired lung primary and BM lesions using a pane consisting of 520 cancer related genes. DNA methylation analyses was performed on same samples using a DNA methylation panel consisting of 100,000 CpG sites. **Result:** Collectively, we identified 370 (291 SNVs+Indels, 78 CNVs and 1 rearrangement) and 574 (245 SNVs+Indels, 327 CNVs and 2 rearrangements) mutations from lung primary lesions and BM, respectively. Among them, 242 mutations were shared; 128 were lung primary-specific and 332 were BM-specific. Among the BM specific mutations, a majority of them (82%, 272/332) were copy number variations (CNVs). Only 16% of CNVs were shared by lung lesions and BM. The concordance for SNVs and indels were much higher-54% between the two sources of tissues. Furthermore, we observed a much higher concordance rate (79%) in *TP53* and classic lung cancer driver genes than other genes (p<0.001), indicating that they might be stem mutations. Next, we performed pathway analysis of genes that were only mutated in BM and revealed an enrichment of genes participating in PI3K-AKT and focal adhesion pathways. We also compared tumor mutation burden (TMB) between them and revealed comparable TMB (p=0.1). Our DNA methylation analysis revealed distinct methylation patterns with 268 blocks that are significantly differentially methylated between primary lung lesions and BM. Among them, 211 blocks were hypermethylated in BM and the remaining 57 blocks were hypermethylated in lung lesions. These blocks were enrichment in genes participating in cell adhesion, Rap1 signaling and calcium signaling pathways. **Conclusion:** We revealed diverse somatic mutation and DNA methylation profiles between lung primary lesions and BM. BM had significantly more unique CNVs. A great concordance was observed for classic lung cancer driver genes and *TP53*. Our study provided a comprehensive view of genomic and DNA methylation profiling for lung primary lesions and BM, paving the avenue for the development of targeted therapies for treating BM.

Keywords: DNA methylation analyses, Non-Small Cell Lung Cancer, Brain metastases

P1.01-19 PREDICTIVE AND PROGNOSTIC VALUES OF CTDNA CLEARANCE IN OSIMERTINIB TREATED ADVANCED NON-SMALL CELL LUNG CANCER COHORT

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Background: Although growth advantage of certain clones would ultimately translate into a clinically visible disease progression, radiological imaging does not reflect clonal evolution at the molecular level. Circulating tumor DNA (ctDNA), validated as a tool for mutation detection in lung cancer, reflects dynamic molecular changes. Here, we evaluated the potential of ctDNA in monitoring molecular changes and predicting clinical outcomes of *EGFR* T790M-positive osimertinib treated NSCLC patients. **Method:** This prospective multicenter study, enrolled 72 T790M positive osimertinib-treated advanced NSCLC patients who progressed on prior EGFR-TKI to evaluate the potential of ctDNA in monitoring, is part of the ongoing ASTRIS study (NCT02474355). Longitudinal plasma samples, collected from 52 patients, were subjected to sequencing using a panel consisting of 168 lung cancer-related genes. **Result:** Genomic profile prior to the initiation of osimertinib revealed that mutations participating in cell cycle (14 patients, p=0.004) and P53 pathways (43 patients, p=0.032) were associated with shorter OS (*p53* was excluded from analysis due to high mutation frequency). Interestingly, patients with undetectable ctDNA at first follow-up (within 50 d, n=41) were correlated with longer PFS (p=0.009) and OS (p=0.022). With a median follow-up of 168 d (ranged from 40 - 550 d), 32 patients experienced radiological disease progression. Among them, 11 (34%) experienced molecular progression reflected by emergency of new mutation or increased allelic frequency of existing mutation prior to radiological progression, with an average leading time of 74 days. Patients with molecular PD prior to radiological PD were more likely to harbor any gene copy number amplification (CNA, p=0.035) and *p53* (p=0.023) mutations at radiological PD. In addition, patients with CNA at radiological PD had shorter PFS (p=0.002) and OS (p=0.052). **Conclusion:** This clinical trial study demonstrates that ctDNA clearance at first follow-up can serve as a predictive and a prognostic marker for patients undergoing osimertinib treatment. Furthermore, it revealed the potential of ctDNA in early detection of disease progression, preceding imaging modalities with an average lead time of 74 days.

Keywords: Osimertinib, Non-Small Cell Lung Cancer, ctDNA clearance

P1.01-20 THE ASSOCIATION BETWEEN BRAF MUTATION CLASS AND CLINICAL FEATURES IN BRAF-MUTANT CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: BRAF mutations, occurring in 2-4% NSCLC patients, can be classified into 3 classes based on signaling mechanism and kinase activity: V600-mutant RAS-independent kinase activating monomers (class I), RAS-independent kinase activating dimers (class II) and RAS-dependent kinase inactivating heterodimers (class III). The association between functional classes and clinical features of Chinese NSCLC patients remain elusive. **Method:** Sequencing data of either plasma or tissue samples obtained from 8,405 Chinese (Stage I-IV NSCLC) patients were retrospectively analyzed to screen for *BRAF* mutations. Of the patients with *BRAF* mutations, 79% (188/238) were diagnosed with adenocarcinoma,7.6% with squamous cell carcinomas (SCC) and the remaining patients were either adenosquamous carcinoma or large cell carcinoma. **Result:** *BRAF* mutations were detected in 238 patients, revealing a prevalence of 2.8%. Among them, 32% (75/238), 21% (51/238) and 13% (31/238) had class I, II and III mutations, respectively. The remaining 35% (81/238) had other *BRAF* mutations. V600 (32%, 75/238) and G469 (13%, 32/238) were the 2 most predominant mutations. *BRAF* mutations, when considered collectively, including non-class I-III mutations, were more likely to occur in males (p<0.01). However, class I mutations have a female predominance (p=0.003); whereas, class II mutations showed a trend of male predominance (p=0.09) and class III had no gender preference (p=0.22). We also revealed no association between histology types and the class of *BRAF* mutations. Next, we investigated co-occurring classic lung cancer driver mutations in this cohort and revealed that patients with class II and III mutations were more likely to have concurrent *KRAS* mutations (p=0.001). We also compared the overall survival (OS) of chemotherapy-treated patients and revealed comparable OS among the 3 groups. **Conclusion:** Our study revealed a 2.8% *BRAF* mutation rate in Chinese NSCLC patients. Our data also showed a male predominance when all *BRAF* mutations were considered collectively, and a female predominance for class I mutations. Furthermore, patients with *BRAF* V600E is less likely to have concurrent *KRAS* mutations.

Keywords: Chinese, braf, NSCLC

P1.01-21 SPUTUM CAN SERVE AS AN ALTERNATIVE SOURCE FOR LIQUID BIOPSY IN PATIENTS WITH LUNG CANCER

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Background: With the advancements in the development of targeted therapy, the detection of actionable mutations has become routine practice in diagnosing lung cancer, especially in non-small cell lung cancer (NSCLC). Due to its non-invasiveness and great accessibility, plasma-based mutation profiling, with a sensitivity of approximately 70%, is widely used in clinical settings. Profiling using other body fluids have been actively explored. In this study, we investigated the potential of sputum obtained from non-small cell lung cancer (NSCLC) patients for mutation profiling. **Method:** We performed capture-based ultra-deep targeted sequencing on matched Falin-Fixed Paraffin-Embedded (FFPE), plasma and sputum samples of 11 treatment-naïve NSCLC patients using a panel consisting of 168 lung cancer-related genes. Among the 11 patients, with a median age of 57, 8 were diagnosed with adenocarcinoma and 3 with squamous cell carcinoma. In addition, 4 patients were classified with central types and the other 7 were classified with peripheral types. Five of them were non-smokers and the remaining were smokers. Three of them were females and 8 were males. All patients were diagnosed with advanced disease (stage III or IV). **Result:** Collectively, we identified 52, 40 and 33 mutations from FFPE, plasma and sputum samples, respectively. Using FFPE samples as a reference, both plasma and sputum had an overall concordance rate of 61.5%. If only actionable classic driver mutations were considered, the concordance rate increased to 91% for sputum and 82% for plasma. Profiling of sputum revealed 8 patients with classic lung cancer driver genes: 4 patients with *EGFR* mutation, 1 with *ALK* rearrangements, 2 with *KRAS* mutation, and 1 with *ERBB2* mutation. The *ERBB2* mutation revealed by sputum was not detected from the corresponding plasma sample. Furthermore, our study revealed that the allelic fractions (AFs) from sputum were significantly higher than AFs from plasma samples (p=0.039). For smokers, the difference of AFs between sputum and plasma was more significant (p<0.001). Furthermore, among the mutations which were detected from both sputum and plasma, 92% mutations had higher AF in sputum. In contrast, for non-smokers, only 29% of mutations had higher AF in sputum. Our data revealed for non-smokers, two media had comparable AFs (p=0.273). **Conclusion:** Our study demonstrated that sputum from advanced stage NSCLC patients is an alternative media for mutation profiling. Potentially, it may serve as a better source for mutation profiling than plasma in smokers. Larger studies are needed to confirm our findings.

Keyword: sputum, genomic profiling, liquid biopsy

P1.01-22 INVESTIGATION OF ACQUIRED RESISTANCE FOR EGFR-TKI PLUS BEVACIZUMAB AS 1ST LINE TREATMENT IN PATIENTS WITH EGFR SENSITIVE MUTANT NSCLC

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Background: The progression-free survival (PFS) advantage of EGFR-TKI plus Bevacizumab (A+T) over standard TKI monotherapy (T) in the 1st line treatment of *EGFR* mutant non-small cell lung cancer (NSCLC) has been confirmed in prospective clinical trials. However, the acquired resistance mechanism which impacts the subsequent management was poorly understood. We did the first analysis to unveil it using next generation sequencing (NGS). **Method:** 256 *EGFR* sensitive mutant (*EGFR* 19del and L858R) NSCLC patients received NGS of 168 genes panel of tumor tissue in baseline from Jan, 2015 to Aug, 2018 was enrolled in this study. 60 patients treated with A+T were recognized as cohort A. Using Propensity Score Matching (Ratio of 1:2), 120 patients treated with single T were chosen as cohort B. Clinical outcomes and resistance mechanism (also by the 168 genes NGS panel) were evaluated. **Result:**

Newly present alterations in cohort A	%	N
EGFR amp	3.2%	1
MET amp	3.2%	1
MET amp+EGFR amp+TP53	3.2%	1
RB1	3.2%	1
RB1+TP53	3.2%	1
RB1+TP53+EGFR amp	3.2%	1
SMAD4	3.2%	1
T790M	22.6%	7
T790M+BRAF V600E	3.2%	1
T790M+EGFR exon 18 p.V834L+TP53	3.2%	1
T790M+TP53	6.5%	2
TP 53	16.1%	5
unknown	25.8%	8
Total	**1**	**31**

Newly present alterations in cohort B	%	N
EGFR amp	6.8%	7
EGFR exon 7 p.T263P	1.0%	1
EGFR exon18 p.G724S	1.0%	1
ERBB2 amp	1.0%	1
KRAS	1.0%	1
MET amp	4.9%	5
MET skipping	1.0%	1
RET+KRAS	1.0%	1
SCLC	2.9%	3
T790M	37.9%	39
T790M+BRAF V600E	1.0%	1
T790M+EGFR amp	8.7%	9
T790M+MET amp	1.9%	2
T790M+TP53	1.9%	2
TP53	4.9%	5
TP53+RB1	1.0%	1
unknown	22.3%	23
Total	**1**	**103**

There was no different for clinical characteristics between Cohort A and B. Comparing with single T, A+T significantly prolonged the medium PFS (16.5m *vs.*12.0m, HR=0.7, p=0.001). A+T significantly increased the overall response rate (95% *vs* 74.2%, *p*<0.05). Until Jan 2019, 31 patients in cohort A, 103 patients in cohort B were evaluated with progressed disease and received tissue re-biopsy for NGS with the same 168 genes panel. In cohort B, T790M was defined as the domain acquired resistance mechanism, contributing to 51.5% (53/103) of progressed patients, followed by *EGFR* amplification 15.5% (16/103), *MET* amplification 6.8% (7/103), *TP53* mutations 6.8% (7/103) and small cell lung cancer transformation 2.9% (3/103). However, in cohort A, although T790M was also defined as the domain acquired resistance mechanism, the mutation ratio was decreased to 35.5% (11/31), followed by *TP53* mutations 29.0% (9/31), *RB1* mutations 9.7% (3/31), *EGFR* amplification 9.7% (3/31), *MET* amplification 6.5% (2/31), and novel *SMAD4* mutations 3.2% (1/31), *EGFR* uncommon mutation (p.V834L) 3.2% (1/31). **Conclusion:** Treatment of 1st line A+T significantly extends the time to progression and increases the response rate with acceptable safety profile. The dominant acquired resistance mechanism retained in T790M but with lower probability. *SMAD4* mutation and *EGFR* p.V834L were considered as novel resistant mechanism to A+T.

Keywords: Bevacizumab plus EGFR-TKI, resistance mechanism, Next generation sequencing

P1.01-23 RETROSPECTIVE ANALYSIS OF REAL-WORLD CLINICO-GENOMIC DATA FOR CLINICAL IMPACT OF GENOMIC PROFILING OF CTDNA IN NSCLC

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Background: Liquid biopsy (LBx) and comprehensive genomic profiling (CGP) of circulating tumor DNA (ctDNA) is a minimally-invasive approach that is increasingly used for detection of targetable genomic alterations (GA) in patients with NSCLC. To determine the clinical utility of LBx-based CGP in routine clinical practice, we evaluated responses to targeted therapy post-LBx in the real-world setting. **Method:** The Flatiron Health-Foundation Medicine Clinico-Genomic Database included 475 NSCLC patients with LBx CGP results (FoundationACT): clinical characteristics and real-world tumor response (rwTR) were obtained via technology-enabled abstraction of clinician notes and radiology/pathology reports and linked to CGP data. Targetable GAs were defined as genomic alterations with a matched FDA-approved targeted therapy or in NCCN guidelines (Table). Patients with a targetable GA were evaluated for rwTR to matched targeted therapy. Real-world overall response rates (rwORR: fraction of patients with partial or complete response) to matched targeted therapy after LBx versus tissue-based CGP (TBx, [FoundationOne/FoundationOneCDx, N=3,956]) were compared. **Result:** At the time of LBx, 61% of patients had ≥1 line of prior therapy (vs 49% for TBx). Median ctDNA fraction was 1%. There was evidence of ctDNA in 86% (408/475) of LBx cases; among these 24% (96/408) had a targetable GA (vs 21% for TBx). Post-detection of a targetable GA, 35% (34/96) of LBx patients received matched targeted therapy (vs 38% for TBx). 21 patients with targetable GAs were evaluated for LBx-based rwTR to matched targeted therapy (Figure): rwORR was 76.2% (vs 62.8% for TBx; p=0.25), including 76.5% (13/17) for FDA-approved matched targeted therapy and 75.0% (3/4) for NCCN targeted therapies (Table).

Table: rwORR to matched targeted therapy for LBx vs TBx

Targetable GAs	Class of targeted therapy	# evaluated for response (LBx v TBx)	rwORR to matched targeted therapy (%, LBx v TBx)
EGFR exon 19del/L858R	Approved	8 v 115	75% v 69%
EGFR G719X/S768I/L861Q	Approved	0 v 12	NA v 50%
EGFR T790M	Approved	1 v 22	0% v 73%
ALK rearrangement	Approved	8 v 43	88% v 70%
ROS1 rearrangement	Approved	0 v 11	NA v 64%
BRAF V600E	Approved	0 v 9	NA v 44%
MET exon 14 skipping and/or high-level amplification	NCCN	3 v 16	67% v 50%
RET rearrangement	NCCN	0 v 2	NA v 100%
HER2 activating mutation	NCCN	1 v 12	100% v 8%
	rwORR (% LBx v TBx)		
All targetable GAs	76.2% v 62.8%; p = 0.25		
GAs with approved therapies	76.5% v 66.8%; p = 0.59		
GAs in NCCN guidelines	75.0% v 35.5%; p = 0.28		

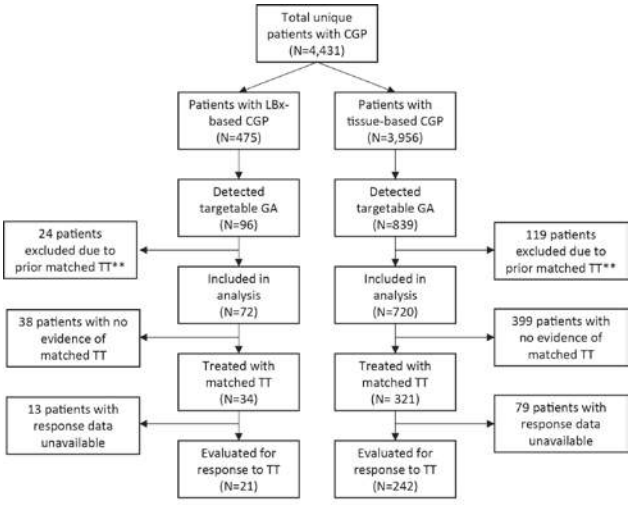

Figure: Diagram showing how patients were selected for analysis of response to matched targeted therapy (TT). **Responses were evaluated for first-line TT. Subsequent line TT was excluded from the analysis, except for approved second-line TT including osimertinib or ALK inhibitors post-crizotinib.

Conclusion: Retrospective analysis of real-world clinico-genomic data from a large series of NSCLC cases demonstrated that the frequency of detected targetable GAs and rwTR to matched targeted therapy was similar for LBx and TBx CGP.

Keywords: Real-world data, ctDNA, liquid biopsy

P1.01-24 PRECLINICAL PROTEOMIC EVALUATION OF ALTERNATING ALK TKI THERAPY VERSUS CONTINUOUS DOSING IN ALK NSCLC TO INFORM THE ALKTERNATE CLINICAL TRIAL

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Background: Despite recent advances in the management of advanced *ALK*-rearranged NSCLC, with high objective response rates to ALK TKI therapy and survival gain, resistance to TKIs is inevitable. Mechanisms of *ALK*-dominant and non-dominant resistance are being increasingly recognized, although in many patients the underlying cause of drug resistance is unexplained. ALKternate is a clinical trial recruiting pre-treated patients, testing the hypothesis that with fixed alternating TKI therapy, the emergence of ALK resistant clones can be suppressed through applying variable selection pressure compared to continuous treatment with a TKI. This has been tested pre-clinically with a human cell line to complement the clinical trial in progress, ALKternate (Abstract #2043). Genetic profiling to complement these data are presented in #2074. **Method:** ALK TKI treatment was conducted on resistant *ALK*-rearranged cell lines (methods in Abstract #2074). Protein profiling was performed using the SWATH-MS 2.0 algorithm, conducted on the Sciex 6600 TripleTOF on cell pellets collected prior to treatment and at cycles (C) 5, 11 and 17 of both alternating lorlatinib with crizotinib (ALT) and continual lorlatinib (CONT) treatment arms. **Result:**

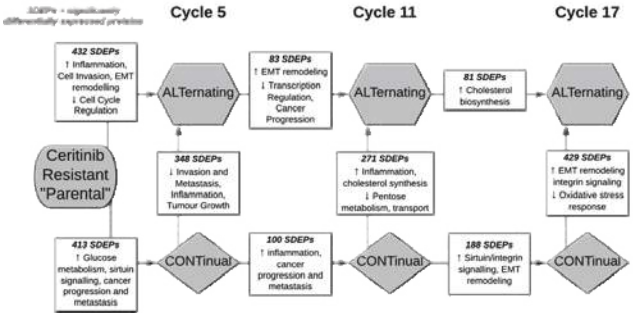

Figure 1: Significantly different proteins and pathways identified by proteomic profiling Overall, LC-MS/MS data was extracted for 3850 proteins. Significantly differentially expressed proteins (SDEPs) identified between CONT/ALT cell lines (FC>1.5, p<0.05) are shown in Figure 1. There was significant enrichment of a number of pathways between the treatment arms. At cycle 5, the EIF pathway, which helps to drive tumour invasion and progression, was the most dysregulated. At C11, elevated activity of cholesterol biosynthesis was observed in the ALT treatment arm. It is notable that hypercholesterolemia is a known side effect of lorlatinib treatment. At the end of C17, the top dysregulated pathways in the CONT line involved sirtuin/integrin signalling, EMT remodelling, while all of the dysregulated pathways for the ALT line were related to cholesterol biosynthesis. **Conclusion:** This study represents the first of proteomics used to identify resistance mechanisms to ALK TKIs. Data from this *in vitro* work will inform the ALKternate clinical trial.

Keyword: NSCLC, ALK, proteomic

POSTERS

P1.01-25 REAL-WORLD OUTCOMES OF ADVANCED NSCLC PATIENTS WITH COMMON AND UNCOMMON/COMPLEX EGFR MUTATION PROFILES

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Background: In patients with advanced non-small cell lung cancer (aNSCLC) with non-squamous histology, the evaluation of EGFR mutations is standard of care and informs treatment selection. EGFR mutations are well-defined and can be classified into common, uncommon/complex mutation subtypes that are known to have different response rates to approved EGFR tyrosine kinase inhibitors (TKIs). **Method:** We used data from the nationwide Flatiron Health electronic health record-derived database in this study. Our retrospective cohort included patients diagnosed in the US from Jan-2014 to Mar-2018 who had a positive EGFR test at time of first-line (1L) therapy initiation. Patients with baseline EGFR T790M mutations (n=44) or variants of unknown significance were excluded. Demographics, clinical characteristics, 1L treatment duration, and overall survival outcomes were compared between patients with common (Exon 19 E746-A750 del, Exon 19 del other, or Exon 21 L858R) vs. uncommon/complex EGFR mutations (all other EGFR mutations [i.e. Exon 18 G719X, Exon 20 insertions, Exon 21 L861Q], and/or concomitant mutations [KRAS, BRAF]). Minimum follow-up after initiation of 1L therapy was 4 months. **Result:** 23,321 patients had non-squamous or NOS histology. 1,315 patients had EGFR mutations detected prior to or during 1L treatment. Of those, 1,000 (82% common, 18% uncommon/complex mutations) had 1L EGFR TKI therapy initiated (median age 70 years, 70% women, 57% Caucasian, 47% smokers). In this population, 1L median treatment duration was longer for patients with common mutations than for those with uncommon/complex mutation profiles (11 vs 7 months; p<0.0001). Median overall survival was also affected by mutation status (24 vs 15 months; unadjusted HR 1.6; 95% CI 1.3–2.1; p<0.001). Among 315 patients (59% common, 41% uncommon/complex mutations) who initiated 1L treatment with non-EGFR TKI systemic therapies (median age 68 years, 59% women, 57% Caucasian, 53% smokers), median overall survival also improved with common vs uncommon/complex mutations (30 vs 17 months; unadjusted HR 1.7; 95% CI 1.3–2.4; p<0.001). However, there were no significant differences in median 1L (non-EGFR TKI) treatment duration (4 months common vs 6 months uncommon/complex mutations). Notably, 60% of patients with a common mutation treated with other 1L systemic therapies went on to receive a 2L EGFR TKI. **Conclusion:** Uncommon/complex mutations were present in over 20% of aNSCLC patients with any EGFR mutations. Increased overall survival and 1L treatment duration with EGFR TKI therapy were observed in patients with common mutation subtypes vs. uncommon/complex mutation subtypes.

Keywords: EGFR mutation, Tyrosine Kinase inhibitors

P1.01-26 TP53 MUTATIONS IN EGFR MT+ NSCLC IV: STRONG INDEPENDENT PREDICTIVE FACTOR FOR ORR, PFS AND OS IRRESPECTIVE OF T790M

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Background: The impact of TP53 mutations in EGFR mt+ pts on PFS and OS is controversial, and different classifications of TP53 mt+ with respect to functional and potential predictive impact have been published. Therefore, we retrospectively analyzed the impact of TP53 aberrations on ORR, PFS and OS in a cohort of EGFR mt+ NSCLC IV pts (UICC 7) using different classifications of TP53 mutations. **Method:** 75 EGFR mt+ NSCLC IV pts were analyzed for TP53 co-mutations. TP53 mt+ were classified according to Poeta et al. into (1) disruptive vs. non-disruptive, according to structural prediction and biophysical characteristics into (2) pathogenic vs. non-pathogenic and finally into (3) exon 8 vs. non-exon 8 mutations according to Crino et al. The endpoints ORR according to Recist 1.1, PFS and OS were calculated by Kaplan Meier. **Result:** 69 of the 75 EGFR mt+ pts (92%) had a common mutation in EGFR E19/21. In 59/75 pts (79%) material was sufficient for successful TP53 analysis. TP53 mt+ were found in 29/59 pts (49%), 16/59 (27%) had a TP53 disruptive mt+, 13/59 (22%) a TP53 non-disruptive mt+ and 30/59 a TP53 WT configuration. Using the structural/biophysical classification, 7/59 (12%) had a TP53 non-pathogenic and 22/59 (37%) a TP53 pathogenic mt+. Of the 29 mutated pts, 6 had a TP53 Exon 8 mt+. Median PFS on 1st line TKI was 12 vs. 18 months for non-disruptive/disruptive mt+ vs. WT (p<0.004), 11 vs. 17 months for pathogenic vs. non-pathogenic/WT (p<0.0001), and 7 vs. 12 vs. 18 months for exon 8 vs. non-exon 8 vs. WT (p<0.006). Median OS was 24 vs. 42 months in non-disruptive/disruptive mt+ vs. WT (p<0.0009), 23 vs. 42 months in pathogenic vs. non-pathogenic/WT (p<0.001) and 12 vs. 28 months for TP53 exon 8 vs. non-exon 8 mt+ (p<0.024). Additionally ORR was significantly impacted by TP53 mt+. In rebiopsy samples on acquired resistance, no new TP53 mutations were observed and there were no correlations of TP53 mutations with clinical factors and the EGFR mt+ type including T790M. **Conclusion:** TP53 seems to be a frequent co-mutation in EGFR mt+ NSCLC and has a strong impact on all clinical endpoints on TKI therapy. These data might have an impact on the management and follow up of pts with TP53 mt+. Furthermore, there is an urgent need for further therapeutic approaches in this patient group.

Keywords: advanced NSCLC, EGFR, TP53

P1.01-27 SERIAL CIRCULATING TUMOR DNA (CTDNA) ANALYSIS OF BLOOD AND SALIVA PREDICTS OSIMERTINIB RESPONSE AND RESISTANCE IN EGFR-MUTANT NSCLC

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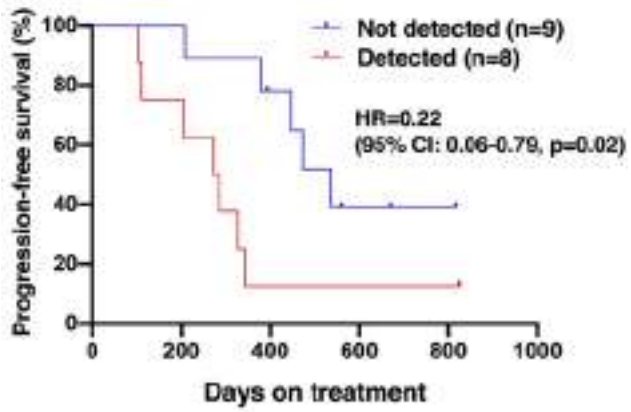
Background: ctDNA has emerged as a promising non-invasive tool to detect lung cancer associated genomic alterations. We assessed whether serial ctDNA monitoring of plasma and saliva correlates with tumor burden and predicts response, resistance, and progression free survival to osimertinib, the 3rd generation EGFR TKI during treatment of EGFR mutated NSCLC. **Method:** Plasma and saliva samples were collected at every clinic visit from patients with metastatic EGFR mutant NSCLC enrolled in a clinical trial of local ablative therapy (LAT) upon oligoprogression (5 or less sites of progression) on osimertinib (NCT02759835). Plasma ctDNA was analyzed by droplet-digital PCR (ddPCR) *EGFR* mutation detection and InVisionSeq Tagged-Amplicon next-generation sequencing. Saliva ctDNA was analyzed by Electric Field-Induced Release and Measurement (EFIRM) liquid biopsy (eLB) assay. Tumor burden was assessed by volumetric CT scoring of all target lesions and other soft tissue lesions ≥10 mm. ctDNA-level changes were correlated with clinical response. **Result:** We analyzed 389 plasma samples from 20 patients by ddPCR, 126 plasma samples from 16 patients by NGS and 298 saliva samples from 18 patients by eLB. A high correlation between ddPCR and NGS allele frequencies (AFs) was found (Spearman g=0.96; p<0.001). Plasma ddPCR and NGS also correlated with saliva eLB assay for mutant *EGFR* detection (Spearman g=0.42 and 0.45, respectively; p<0.001 for both). Among 14 patients who progressed, ctDNA progression (AFs increased two consecutive times by ddPCR) predated RECIST progression by a median of 87 days (range: 28-216 days) in 8 patients. Of 6 patients without ctDNA progression, 2 patients had increase in *EGFR* mutation-level by eLB and 1 patient by NGS. ctDNA clearance on day 42 or 56 (2 cycles of osimertinib treatment) predicted PFS (HR=0.22, 95% CI=0.06-0.79, p=0.02; figure 1). Both baseline sensitizing *EGFR* mutation AF and copy number, but not baseline tumor volume, were significantly associated with PFS. Acquisition of *MET, EGFR,* and *ERBB2* amplifications and the *EGFR* C797S mutation were identified as key resistance mechanisms by NGS in this cohort of patients.



Conclusion: Serial assessment of plasma and saliva ctDNA is clinically useful for monitoring the therapeutic response to osimertinib and for early detection of resistance mechanisms for clinical decision making. Three assays used in this study, the ddPCR and NGS for plasma ctDNA detection, and eLB for saliva ctDNA detection are complementary with each having unique advantages.

Keywords: ctDNA, Osimertinib, EGFR-mutant NSCLC

P1.01-28 MUTATIONAL HETEROGENEITY BETWEEN PRIMARY PULMONARY CANCER LESIONS AND MATCHED BRAIN METASTASES

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Background: Brain metastasis (BM) is a severe and common lethal condition in non-small cell lung cancer patients. A few data have been reported about the molecular landscape of genomic alterations in BM of non-small cell lung cancer (NSCLC). Yet little is known about molecular heterogeneity and evolution process during the cancer metastases from lung to brain. We seek to profile the genomic alterations in paired specimens of primary lung lesions (PL) versus brain metastasis (BM). **Method:** Paired specimens of thirteen patients with BM were collected. MassARRAY LungCarta (26 genes) and Next Generation Sequencing (NGS, 285 genes) assays were performed to generate genomic profiles. **Result:** Thirteen patients were aged mean 58 (range 40-74), 10 adenocarcinoma and 2 squamous carcinoma and 1 small cell lung cancer, 9 males and 4 females, 5 smokers and 8 non-smokers, 7 stage IV, 3 stage III, 2 stage II and 1 stage I. By LungCarta test, we detected 6 *EGFR*m (1 concurrent *STK11*, 1 concurrent *TP53*), 2 *KRAS*m, 1 *STK11*m cases and 4 wild type primary lung cancers. All corresponding BM lesions harbored the same mutations of *EGFR, KRAS*, *TP53* and *STK11,* and additional *EGFR* T790M in 1 *EGFR* mutated case. By NGS test, in 9 patients all above mutations were detected along with additional genomic alterations. There were average mutated 9 genes in primary lung lesions and 13 mutated genes in BM. Common altered genes in PL included *EGFR, KRAS, TP53, STK11, NF2, ARID1B* and *ATM*. Shared mutated genes between PL and BM had *EGFR, KRAS, TP53, KMT2C* and etc. BM specific altered genes included *ARID1A, SMARCA4, ATM, ATR, EPHA5, RB1, KMT2C, LRP1B*, and *SETD2,* etc. Notably, genes involved in the chromatin remodeling or modification and cell cycle pathways were enriched in BM. **Conclusion:** There were heterogeneous molecular alterations between PL and BM of NSCLC. Differential genes involved in the chromatin remodeling and modification and cell cycle checkpoint may be highly related to the process of BM, suggesting future therapeutic development on these potential molecular targets.

P1.01-29 MLPH PROMOTES EPITHELIAL–MESENCHYMAL TRANSITION AND BRAIN METASTASIS VIA CDC42/PAK1 SIGNALING IN NON-SMALL CELL LUNG CANCER

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Background: Brain metastasis (BM) is associated with poor prognosis, recurrence, and death in patients with non-small cell lung cancer (NSCLC). Therefore, a better understanding of molecular mechanisms underlying NSCLC development and progression could provide helpful insights for NSCLC prevention and effective treatment. Melanophilin (MLPH), an actin-based transport binding partner, involves in cancer progression. However, the role of MLPH in NSCLC remains unclear. Here we elucidated the functional significance, molecular mechanisms and clinical impact of MLPH in NSCLC. **Method:** RNA-Sequencing was performed to identify differentially expressed genes in lung tissues of NSCLC patients with (BM+) and without BM (BM-). The expression of MLPH was examined in the serum of BM+ and BM- patients by PCR. Integrative database analysis was used to examine MLPH levels in NSCLC tissues and analyze the relationship between MLPH levels and patient survival. Lentivirus containing small hairpin (sh) RNA targeting MLPH or empty vector was designed to explore its role in NSCLC. The cell counting kit-8 assay, wound healing assay, transwell assay, flow cytometry analysis, Phalloidin staining, xenografted tumor model and brain metastasis model were used to determine the effects of MLPH on the proliferation, migration, invasion, EMT, tumorigenesis and brain metastasis of NSCLC. Western blot analysis was used to explore the underlying mechanism. **Result:** High-throughput sequencing showed that MLPH mRNA was significantly differentially expressed in lung tumors between BM+ and BM- NSCLC patients. MLPH was frequently overexpressed in NSCLC tissues and cells, and high levels of MLPH correlated with poor prognosis of NSCLC patients. Silencing MLPH by shRNA suppressed NSCLC cell proliferation, migration, invasion and TGF-β-induced EMT, and triggered cell cycle arrest and apoptosis. Being in consistent with the *in vitro* findings, the *in vivo* experiment exhibited that knockdown of MLPH inhibited xenograft tumorigenesis and brain metastasis in nude mice. Mechanically, we identified TGF-β as a key downstream effector of MLPH. MLPH silencing attenuated Cdc42/PAK1 signaling activation at least in part through the downregulation of TGF-β. Furthermore, EMT phenotypes changes caused by MLPH knockdown were partially dependent on TGF-β inhibition. **Conclusion:** Our findings uncovered the role of MLPH in NSCLC progression and provided evidence for MLPH positively modulating the Cdc42/PAK1 signaling pathway to promote EMT and metastasis via TGF-β in NSCLC cells. MLPH may have the potential as a therapeutic target against metastatic NSCLC.

Keywords: brain metastasis, Non-Small Cell Lung Cancer, MLPH

P1.01-30 NON-SMALL CELL LUNG CANCER (NSCLC) NEXT GENERATION SEQUENCING (NGS): INTEGRATING GENOMIC SEQUENCING INTO A PUBLICLY FUNDED HEALTH CARE MODEL

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Background: Standard of care (SOC) molecular diagnostics for stage IV NSCLC patients in Ontario, Canada includes publicly reimbursed *EGFR/ALK,* and *BRAF/ ROS-1* testing in selected cases. Other genomic alterations are not tested routinely at all institutions; however, enhanced molecular testing may broaden treatment options for patients by identifying actionable targets. This study evaluated costs, identified actionable targets, and determined clinical trial eligibility as a result of using the Oncomine Comprehensive Assay v3 (OCA v3, ThermoFisher) NGS in stage IV NSCLC patients at a single institution. **Method:** This prospective study of stage IV NSCLC out-patients at Princess Margaret Cancer Centre (Toronto) began in February 2018 and recruitment is ongoing (NCT03558165). NSCLC patients without *EGFR/ALK/KRAS/ BRAF* alteration (unless failure of prior targeted therapy and tissue rebiopsy), had diagnostic samples tested by OCAv3 (ThermoFisher; 161 genes: hotspots, fusions, and copy number variations). Primary endpoints were identification of incremental actionable targets and clinical trial opportunities as a result of broader OCAv3 testing.

Secondary endpoints include feasibility and cost from the Canadian public healthcare perspective. **Result:** From Feb 2018- Jan 2019 65 patients were enrolled [62% (N=40) completed/ 21% (N=14) screen fail/ 17% (N=11) pending], median age of completed cohort was 65, 60% (N=24) female, never/light smokers 68% (N=27), Asian 38% (N=15), previously treated 33% (N=13). Actionable targets beyond SOC were identified in 33% (N=13): *ERBB2* (N=8), *BRAFV600* (N=3), *NRG* fusion (N=1), *MET* exon 14 (N=1). Failure of NGS was secondary to insufficient tissue. 91% (N=10) of screen failures was secondary to tissue exhaustion from prior sequential SOC molecular testing. New clinical trial options were identified in 70% as a result of OCA v3 testing. Incremental costs per case beyond *EGFR/ALK* are estimated at $540 CAD. If *ROS-1* and *BRAF* testing were publicly reimbursed at current rates, the incremental profiling cost with OCAv3 would be $90 CAD per case. **Conclusion:** The OCAv3 consolidates genomic testing, identifies additional actionable targets, and substantially increases clinical trial eligibility for patients at a small incremental cost. Sample failures are reflective of exhausted diagnostic tissue as a result of prior sequential genomic testing. The key barrier to implementation of NGS remains funding in the Canadian health care system.

Keywords: Next generation sequencing, NSCLC

P1.01-31 EVALUATING ENGINEERED HEME-SEQUESTERING PEPTIDES FOR TREATING NON-SMALL CELL LUNG CANCER ORTHOTOPIC TUMOR MODEL USING MULTI-MODALITY IMAGING

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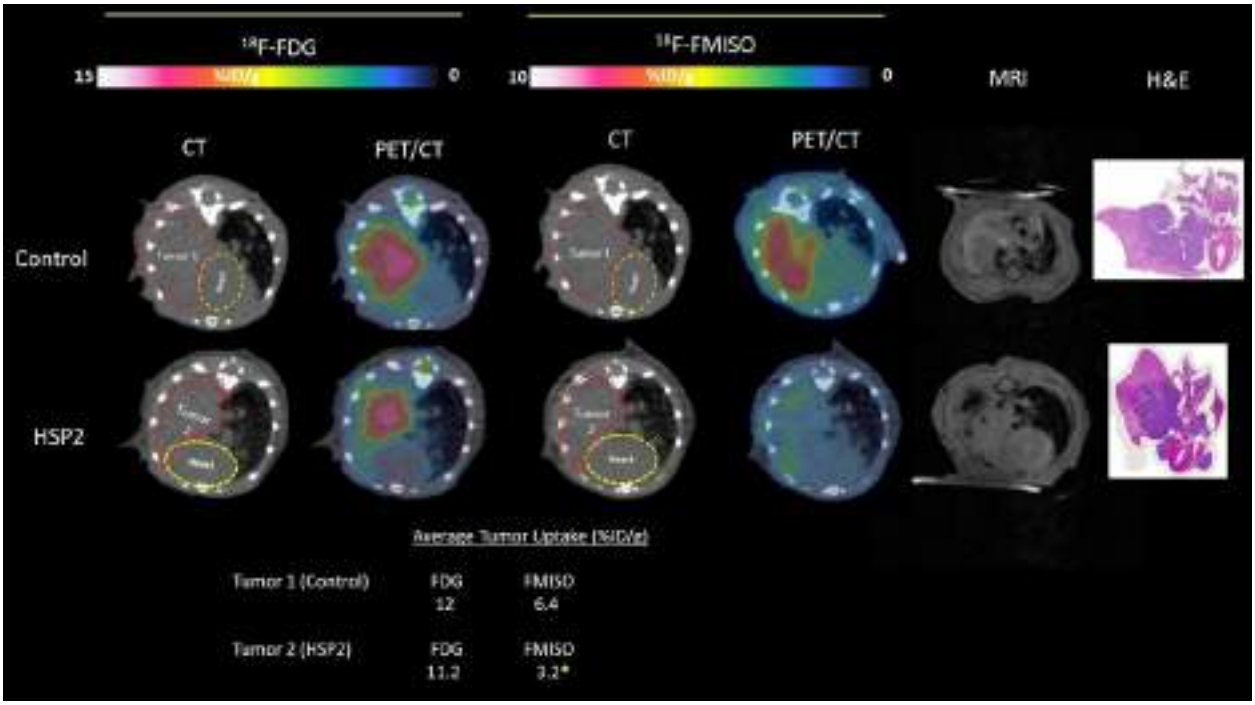
Background: There is still an urgent need to develop novel strategies to treat lung cancer. Lung cancer is the leading cause of cancer-related death in the US. About 85-90% of cases are classified as non-small cell lung cancer (NSCLC). Despite the advent of targeted therapies and immunotherapies, an effective treatment or cure for lung cancer remains an unlikely outcome for most patients. The five-year survival rate remains 10-20%, lower than many other cancers, such as breast (90%) and prostate (99%) cancers. Clearly, novel strategies are still needed for dramatic improvement in the overall survival rate of NSCLC patients. **Method:** NSCLC H1299-Luc cells in serum-free medium containing 50% Matrigel were implanted orthotopically in 8 weeks old NOD/SCID mice (n=6 for each treatment group) by surgery. BLI was carried out to monitor tumor growth and treatment. Treatments with HSP2 started 3-4 weeks after tumor implantation and BLI signal was reached to $1x10^5$. Anatomical T1-weighted MRI was performed with a 9.4T small animal MRI system. Two radiolabeled tracers, ^{18}F-FDG and^{18}F-fluoromisonidazole (^{18}F-FMISO), were selected for PET-CT scanning. FDG and FMISO-PET imaging data were correlated with MRI and histology. About 120μCi of ^{18}F-FMISO or ~100μCi of ^{18}F-FDG was injected via tail vein, 7 minutes list-mode PET at 1 hour post-injection of radio-tracer. CT imaging parameters used 360 projections at 80kV, 500μA and 140ms exposure. The mean radioactivity of ^{18}F-FDG and ^{18}F-FMISO tumor uptake were calculated using a decay correction from the entire ROI, and were compared between mice with or without treatment. After PET/CT imaging, mice were administered intravenously with pimonidazole to evaluate the extent of hypoxia within the tumor by immunohistochemistry (IHC) staining. **Result:** FDG uptake was identical in treated and control tumors. However, tumors treated with HSP2 revealed less hypoxia than control tumors as evidenced by less FMISO uptake within the tumor region. When comparing the ratio of FMISO and FDG uptake in treated versus control tumors, tumors treated with HSP2 had significantly less FMISO/FDG uptake compared to control tumors (p=0.003). **Conclusion:** Together, these results provided a solid foundation for further studies to determine the degree to which HSP2 influences tumor vasculature and oxygenation. Furthermore, we demonstrate the potential of HSP2 to increase treatment efficacy when used in combination with chemotherapy or radiotherapy in lung tumor models.

Keyword: Lung cancer, 18F-FDG, 18F-FMISO PET/CT



P1.01-32 BRONCHOALVEOLAR LAVAGE AS AN ALTERNATIVE TO REBIOPSY FOR DETECTION OF T790M MUTATION IN NSCLC PATIENTS WITH ACQUIRED RESISTANCE TO EGFR-TKIS

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Background: Rebiopsy is current standard to detect T790M mutation, but has limited value due to inaccessibility in significant number of patients. Plasma liquid biopsy using ctDNA has been adopted, but the sensitivity is not satisfactory. Extracellular vesicles (EVs) have been proven to contain double-stranded genomic DNA reflecting mutational status of the parental tumor cells in non-small cell lung cancer (NSCLC). Accordingly, EVs can be translated into clinically useful liquid biopsy for EGFR genotyping using bronchoalveolar lavage fluid (BALF) obtained from the tumor site. We investigated the role of BALF for detecting T790M mutation in the patients who developed acquired resistance to EGFR-TKI by comparing with standard tissue rebiopsy and liquid biopsy using plasma ctDNA. **Method:** Forthy-eight EGFR mutation-positive NSCLC patients with acquired EGFR-TKI resistance were evaluated respectively. EVs were isolated from BALF by ultracentrifugation and EVs DNA extracted after eliminating free-floating DNA. PNA clamping-assisted fluorescence melting curve analysis (PANAMutyper™) were used to assess the EGFR mutation status in rebiopsy tissue, plasma and BALF. **Result:** Median age of 48 patients was 63.5 years (range, 44-87 years); 26 (52.1%) were women; and 27 (56.3%) were never-smokers. Thirty-three of 48 patients (62.5%) underwent a repeated biopsy with results as follows: there was insufficient tissue in 3 of 33 (9.1%) and T790M mutation in 12 of 30 patients who were pathologically confired as NSCLC (40.0%). Fifteen of 48 patients (31.3%) did not undergo a repeated biopsy at progression for the following reasons: patient with target lesion less than 10 mm in 6 cases; and no lesion amenable to biopsy such as leptomeningeal seeding, distant metastasis to bone or adrenal gland and lung nodules which is difficult to agmqccess in 9 case. The EGFR mutation-positive rate from BALF (37.5%) was higher than that determined from plasma or tissue at 16.7% and 25.0%, respectively. Interestingly, out of the 36 patients who were not able to undergo a repeated biopsy, whose biopsy results were insufficient for diagnosis or who did not have T790M mutation, five (10.4%) and three (6.3%) samples were additionally positive from the BALF and plasma test, respectively. **Conclusion:** Less invasive genotyping by PNA clamping-assisted fluorescence melting curve analysis with EVs DNA extracted from BALF is a promising approach to the detection of T790M mutation during EGFR TKI treatment.

Keywords: T790M mutation, Extracellular vesicles, Bronchoalveolar lavage fluid

P1.01-33 GENETIC VARIANTS IN FIG4 AND IGF1R IN THE ENDOSOME-RELATED GENES ARE ASSOCIATED WITH NON-SMALL CELL LUNG CANCER SURVIVAL

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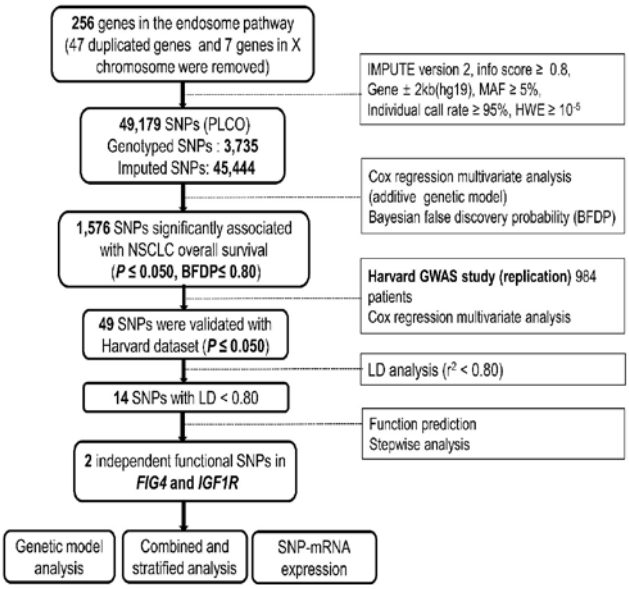
Background: The endosome is a membrane-bound organ inside most eukaryotic cells and is known to play an important role in the adaptive immunity of mammals. The endocytosed antigens in the antigen presenting cells are delivered to both MHC class I and MHC class II pathways via the endosome. **Method:** In the present study, we performed a two-phase analysis of two independently published genome-wide association studies (GWASs) to evaluate associations between genetic variants in the endosome-related gene-set and overall survival (OS) of patients with non-small cell lung cancer (NSCLC). In the discovery GWAS dataset, we performed multivariate Cox proportional hazards regression with Bayesian false-discovery probability (≤ 0.80) for multiple testing corrections and evaluated associations between 49,179 (3,735 genotyped and 45,444 imputed) single-nucleotide polymorphisms (SNPs) in 256 genes and survival of 1,185 NSCLC patients. After further validation in the Harvard Lung Cancer Susceptibility study, we performed linkage disequilibrium, functional prediction and a multivariate stepwise Cox model. **Result:** We found that two independent, potentially functional SNPs in two genes (*FIG4* rs6899506 C>A and *IGF1R* rs3743254 C>T) were significantly associated with NSCLC survival, and their meta-analysis showed an adjusted hazards ratio (HR) of 1.16 [95% confidence interval (CI) =1.06–1.26, P_m =0.001] and 0.78 (0.67-0.91, P_m =0.002); respectively. A genetic score of unfavorable genotypes of these two SNPs revealed a decreased OS in a dose–response manner (P_{trend} = 0.007). Further expression quantitative trait loci (eQTL) analysis showed significant associations between the genotypes and mRNA expression levels. It was found that the survival-associated *FIG4* rs6899506C allele, but not the *IGF1R* rs3743254T allele, was significantly associated with decreased mRNA expression levels of *FIG4* in 373 lymphoblastoid cell lines.



Conclusion: Taken together, the genetic variant of the *FIG4* rs6899506A allele and *IGF1R* rs3743254T allele from the endosome pathway genes may be a promising predictor of survival in NSCLC patients via *FIG4* and *IGF1R* expression alteration.

Keywords: single-nucleotide polymorphism, Non-Small Cell Lung Cancer, endosome pathway

P1.01-34 EARLY ASSESSMENT OF THERAPY RESPONSE IN NON-SMALL CELL LUNG CANCER (NSCLC) VIA LONGITUDINAL CTDNA ANALYSIS

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Background: Quantifying circulating tumor DNA (ctDNA) is an emerging method to non-invasively assess treatment effect for solid tumors. Despite disease heterogeneity in NSCLC, we set out to identify a broadly applicable ctDNA-based method for disease monitoring. By employing plasma taken during early treatment cycles, we tested whether early response assessed by ctDNA level could predict treatment effect. **Method:** Using a 197-gene NGS assay, the AVENIO ctDNA Surveillance Kit (For Research Use Only, not for use in diagnostic procedures), we measured ctDNA levels in post-treatment plasma samples based on variants identified at baseline. We used samples from an observational German Lung Cancer Multi-Marker Study. In a cohort of 83 stage IV lung adenocarcinoma treated with first-line chemo or chemoradiation therapies, we evaluated the association between survival and ctDNA levels in the first available post-treatment plasma sample (median number of days after start of treatment = 23). We used a ctDNA-based monitoring algorithm, and applied it to an independent set of 22 late stage lung squamous cell carcinoma that also underwent chemo or chemoradiation therapies

to further evaluate the algorithm in different histology subtypes. **Result:** We divided the 83 adenocarcinoma cohort into training (n=53) and test (n=30) sets. We found that subjects with longer progression free survival (PFS) had mean allele fraction (AF) < 1% in the training set. We applied the classifier to our adenocarcinoma test set and found that subjects with mean AF < 1% had longer PFS (HR 0.35; 95% CI 0.12 - 0.93; log-rank P = 0.028) and overall survival (OS) (HR 0.29; 95% CI 0.09 - 0.89; log-rank P= 0.021). Using cutoffs identified in adenocarcinoma, we applied the same algorithms to the squamous cell carcinoma cohort. Subjects with mean AF < 1% had longer PFS (HR 0.26; 95% CI 0.10 - 0.71; log-rank P = 0.005) and OS (HR 0.12; 95% CI 0.05 - 0.51; log-rank P= 0.001). **Conclusion:** Even in heterogeneous diseases such as NSCLC, changes in ctDNA levels in response to treatment may prove to be a valuable way of identifying subjects who may not benefit, before current standard of care methods like computed tomography (CT) scan. Future prospective studies to confirm these results are warranted.

Keywords: ctDNA quantification, CAPP-Seq, disease monitoring

P1.01-35 REAL WORLD CHARACTERIZATION OF ADVANCED NON-SMALL CELL LUNG CANCER IN NEVER SMOKERS

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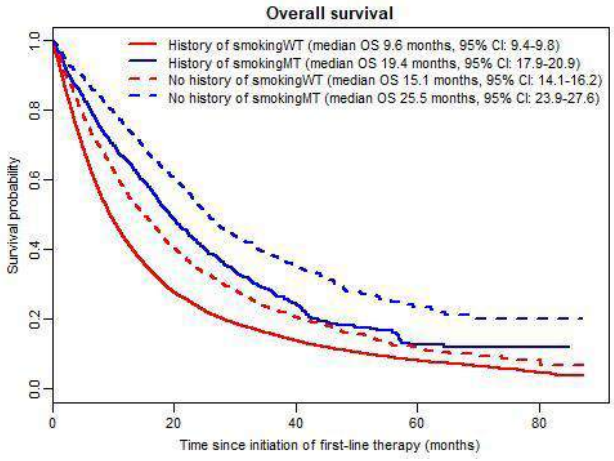
Background: NSCLC in never smokers is vastly different from those with a history of smoking in terms of etiology, driver-mutations and response to immunotherapy. We have previously demonstrated a hereditary contribution in never smokers which is not identified in smokers[1]. This study compares the real-world survival of NSCLC in never smokers to those with a smoking history by mutation status. **Method:** The study included patients in the Flatiron Health nationwide electronic health record-derived database who were diagnosed with NSCLC, received biomarker testing results (EGFR, BRAF, ALK, and ROS1), and initiated therapy between 2011-2017 with follow-up through June 2018. Overall survival (OS) of patients by smoking and driver mutation groups was summarized via Kaplan-Meier survival estimates, and compared in the context of a multivariate Cox proportional hazard model adjusted by age at stage IV diagnosis, gender, state of residence, histology, smoking status, and race/ethnicity, stratified by categories of advanced diagnosis date within practices. **Result:** The study included 30,310 patients with median age of 68.8 years, 46.7% female, 76.8% non-Hispanic white, and 12.6% never smokers. Actionable mutations were reported in 9.0%, differentially as 34.2% in non-smokers and 5.5% in smokers. OS differed by smoking and driver-mutation categories (adjusted and stratified p<0.001). The median OS for patients with wild-type mutation status and history of smoking was 9.6 months, for mutated smokers was 19.4 months (adjusted and stratified hazard ratio [HR] relative to WT smokers 0.65 (95% CI 0.60-0.71)), for wild-type never-smokers was 15.1 months (0.78 (0.73-0.83) relative to WT smokers), and for mutated never-smokers was 25.5 months (0.52 (0.48-0.58) relative to WT smokers).



Conclusion: Never-smokers with NSCLC survived longer than those with smoking history, in both groups of wild-type and mutation-positive patients. Findings highlight that in patients with NSCLC, a smoking history may have similar effect on hazard of death as actionable mutation status.

Keywords: never smokers, lung cancer, real world data, advanced NSCLC

P1.01-36 CLINICAL POTENTIAL OF TISSUE TUMOR MUTATIONAL BURDEN (TTMB) AND BLOOD TMB (BTMB) AS A BIOMARKER IN NON-SMALL CELL LUNG CANCER

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Background: Higher tissue TMB (tTMB) or blood TMB (bTMB) levels are associated with better response of immunotherapy in patients with non-small cell lung cancer (NSCLC). The clinical utility of bTMB and tTMB for clinical indications remain to be determined. **Method:** Comprehensive genomic profiling were performed on 28 paired tissue and plasma samples using 520-gene panel, which has been validated to accurately reflect the actual tTMB and bTMB using in-house validation. The max allelic fraction (max.AF) of 5% in tissue and 0.5% in plasma were defined as the detection limit for TMB assessment, and samples with max.AF < 5% (n=1) in tissue and 0.5% in plasma (n=6) were excluded. Union-TMB represents the union of tTMB and bTMB, and union-TMB-class-10 denotes union-TMB of 10 is used as the cutoff for grouping. **Result:** Correlation analysis revealed that bTMB and tTMB diaplayed significant consistency with each other (R^2=0.953). Next, associations of clinical characteristics and TMB status were analyzed. Older patients were significantly associated with higher tTMB (p=0.009) than younger ones, but slightly correlated with TMB-max (p=0.055) and TMB-union (p=0.079). We also found that male patients more commonly had higher tTMB (p=0.001), bTMB (p=0.011), max-TMB (p<0.001), union-TMB (p<0.001) and union-TMB-class-10 (p=0.018) than female ones with statistical significance, while smokers usually had higher tTMB (p=0.003), max-TMB (p=0.011), union-TMB (p=0.004) and union-TMB-class-10 (p=0.044) than non-smokers. Next, the correlation between TMB and clinical response were investigated in 19 patients who received nivolumab treatment. We found patients who had partial response to nivolumab commonly had higher bTMB than those experienced stable disease or progression (p=0.076); patients with bTMB>=10 or bTMB>=16 achieved higher objective response rate (ORR) than that with bTMB<10 (42.9% vs 0.0%) or bTMB<16 (66.7% vs 10.0%); patients with squamous cell carcinoma achieved significantly favorable progression-free survival than those with adenocarcinoma (p=0.019). **Conclusion:** We revealed that tTMB and bTMB were strongly correlated with each other for TMB assessment. Higher tTMB was strongly correlated with smokers and males compared with non-smokers and females. Higher bTMB predicted better response and ORR to nivolumab, indicating that bTMB could function as a biomarker for prognosis prediction. Prospective studies are necessary to investigate the clinical implications of tTMB and bTMB in a larger cohort of patients.

Keywords: bTMB, NSCLC, tTMB

P1.01-37 RADIOTHERAPY CHANGED THE SUBCLONAL COMPOSITION OF BRAIN METASTASIS FROM NON SMALL CELL LUNG CANCER: NGS-BASED ANALYSIS OF CEREBROSPINAL FLUID

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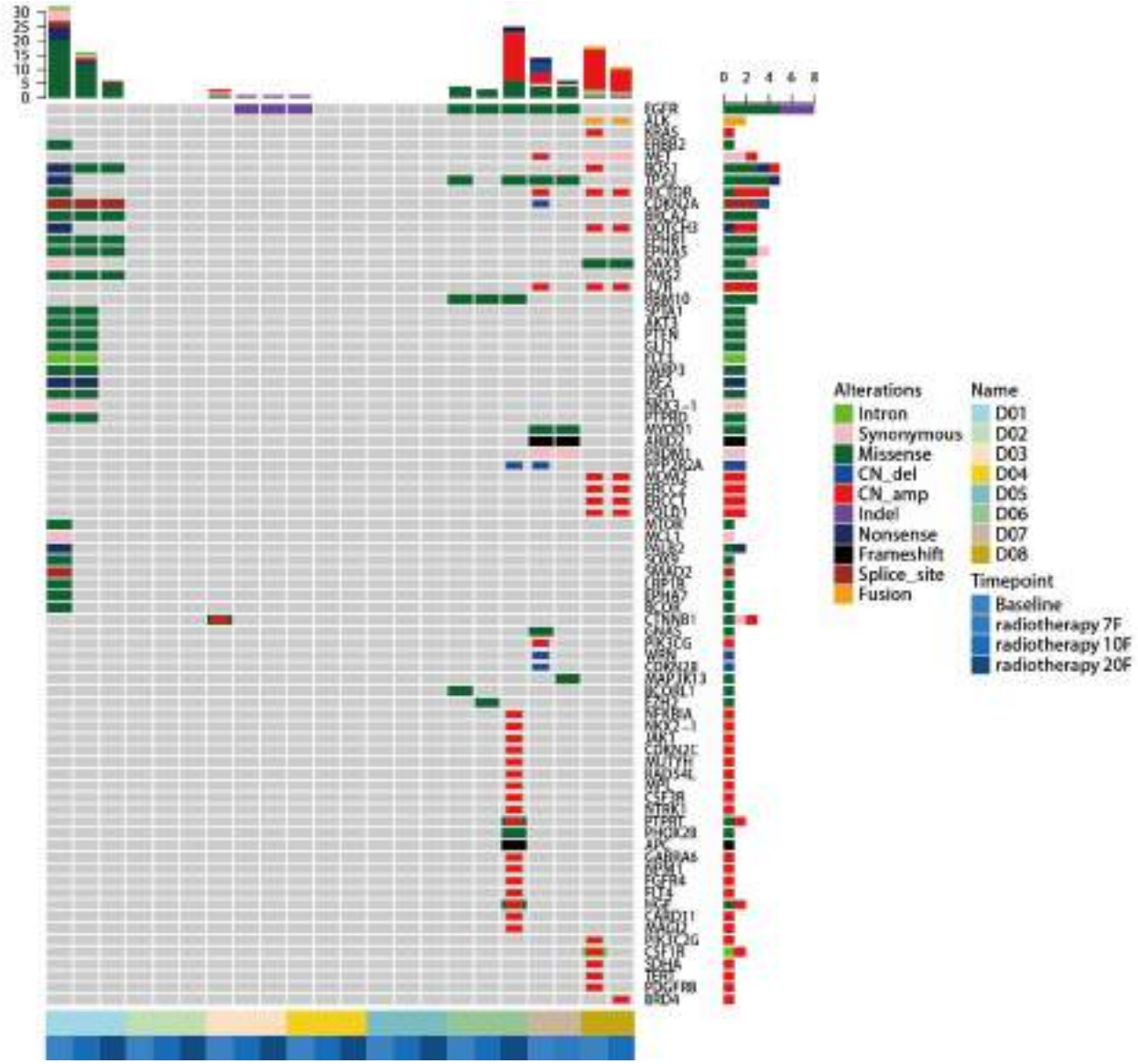
Background: Radiotherapy(RT) is an effective treatment for brain metastasis (BM) of non-small cell lung cancer (NSCLC). Cerebrospinal fluid (CSF) can be used for dynamic monitoring the oncogenic mutations of BM from NSCLC. **Method:** A total of 22 CSF samples from 8 patients with BM from NSCLC were collected at three time points(before the start, in the middle and at the end of RT)and analyzed using NGS. **Result:** Five patients (D01, D03, D04, D07, D08) exhibited a significantly decreased mutation number after RT, and new mutation was detected in two patients (D03, D07). A large number of new copy number variations (CNVs) were detected after RT in one patient (D06), and the mutation abundance of the primary clone also increased significantly. One patient (D08) showed a slight increase in mutation abundance of the primary clone after RT. Mutation detections at all time points were negative in two patients (D02, D05).

Patients	Gender	Pathology	Baseline mutation status (Sample type)	Radiotherapy regime	concurrent systematic treatment	Brain metastasis	Changes of CSF mutation status			
							Pre-radiation	Post-radiation		
							Common driven mutation	mutation abundance	mutation number	New mutations
D01	Male	Squamous cell carcinoma	Unknown	SIB-IMRT: WBRT 40Gy/20F, GTV 56Gy/20F	No	Newly diagnosed	No	↓	↓	No
D02	Female	Adenocarcinoma	C-MET(+++) (Tissue from BM)	SIB-IMRT: WBRT 40Gy/20F, GTV 56Gy/20F	Pem+Cis	Newly diagnosed	No	—	—	—
D03	Male	Adenocarcinoma	EGFR 19-Del (Tissue from lung lesion)	SIB-IMRT: WBRT 36Gy/20F, GTV 54Gy/20F	Erlotinib	Newly diagnosed after TKI	No	↓	↓	EGFR 19del
D04	Male	Unknown	Unknown	3D-CRT: WBRT 40Gy/20F	No	Newly diagnosed	EGFR 19-Del	↓	↓	No
D05	Female	Adenocarcinoma	EGFR 19-Del (Tissue from lung lesion)	SIB-IMRT: WBRT 36Gy/20F, GTV 56Gy/20F	Erlotinib	Progressed after TKI	No	—	—	—
D06	Male	Adenocarcinoma	EGFR 21 L858R(+) (Tissue from lung lesion)	WBRT 40Gy/20F SRS 16Gy	Erlotinib	Progressed after TKI	EGFR 21 L858R(+)	↓ at first and then ↑	↑	CNVs
D07	Female	Adenocarcinoma	EGFR 21 L858R(+) (Blood plasma)	3D-CRT: WBRT 30Gy/10F	No	Newly diagnosed after TKI	EGFR 21 L859R(+) MET amp	↓	↓	MAP3K13 p.R585Q
D08	Female	Adenocarcinoma	ALK(+) (Tissue from lung lesion)	SIB-IMRT: WBRT 40Gy/20F, GTV 56Gy/20F	Crizotinib	Newly diagnosed after TKI	ALK(+)	slightly ↑	↓	No

M:Male, F: Female, SCC:Squamous carcinoma, AD: Adenocarcinoma, NO: Unknown, ND:Newly diagnosed, PD: Progressed, N: No, E: Erlotinib

POSTERS

Figure 1.Mutation profiling of CSF



Conclusion: RT changed the subclonal composition of BM from NSCLC. Further timing mutational process during RT may provide insight into the optimization of the combination of RT and targeted therapy for BM from driven mutation-positive NSCLC. Support: 81572279, 2016J004, LC2016PY016, 2018CR033.

Keywords: brain metastasis, cerebrospinal fluid, radiotherapy

POSTERS

P1.01-38 CLINICAL SIGNIFICANCE ACCORDING TO EGFR MUTATION SUBTYPES IN LUNG ADENOCARCINOMA: KOREAN MULTICENTER EXPERIENCE

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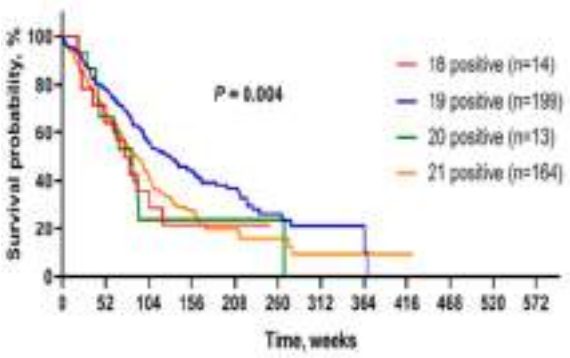
Background: Adenocarcinoma is the most common type of non-small cell lung cancer causing genetic mutations. The most common gene mutations associated with EGFR receptors are deletion at exon 19 and point mutation at exon 21, L858R. However, other uncommon mutations cover 10 to 18% of all EGFR mutations. Mutations in exon 18 and 20 are important in incidence among uncommon mutations. We aimed to analyze the clinical significance according to EGFR mutation subtypes in lung adenocarcinoma. **Method:** Data were collected from 5 university hospitals in Seoul and Gyeonggi province of Korea. During the period from 2010 to 2016, patients of lung adenocarcinoma of stage 3 to 4 who were not treated surgically and examined for EGFR mutation were enrolled. The total subjects were 1021 persons. Patients were retrospectively analyzed for clinical features by subtypes of EGFR mutation. **Result:** EGFR positivity was 38.1%: mutation positive group was significantly lower in males and smokers compared to mutation negative group, while in mutation positive group the proportion of patients receiving traditional chemotherapy or EGFR targeted therapy was significantly higher and also percentage of stage IV were significantly more than that of stage III. Among EGFR positivity, the incidence of mutations in exon 18, 19, 20, and 21 were 3.6%, 51.2%, 3.3%, and 41.9%, respectively. Among the four subtypes, the age was relatively low at exon 19 mutation (p=0.006), while the proportion of smokers was particularly high at exon 20 mutation (p=0.016). EGFR positive group survived significantly longer than the negative group (p<0.001), and there was a significant difference in survival among the four subtypes of EGFR positive group (p=0.004): mutation in exon 19 showed a better survival probability compared to the other subtypes (p<0.001), whereas mutation in exon 21 showed a poorer prognosis (p=0.006). Univariate and multivariate analysis showed that mutation in exon 19 was the only significant factor that lowered the mortality rate (HR:0.415, p=0.001) and mutations in exon 18, 20 and 21 were not significant. In EGFR positivity, TKI non-responder showed significantly higher proportion of exon 21 mutation, compared to TKI-responder (p<0.05).



Survival probability according to EGFR mutation subtype in EGFR positive adenocarcinoma

Conclusion: Presenting mutation of exon 19 in advanced lung adenocarcinoma prospects better survival than other EGFR mutations. Unlike the previous reports, mutation in exon 18 or 20 was not a worse factor than mutation in exon 21.

Keywords: adenocarcinoma, EGFR mutation, Survival

P1.01-39 IS THERE AN ASSOCIATION BETWEEN INTRACRANIAL PROGRESSION AND OVERALL SURVIVAL OR NEUROLOGIC DEATH IN PATIENTS WITH EGFR POSITIVE NSCLC?

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Background: Many studies have examined the incidence of Brain Metastases (BrM) in EGFRm+ NSCLC, and their impact on radiographic and survival outcomes. We have examined the incidence of ND and predictive factors in a retrospective cohort. The clinical significance of ICP remains controversial; patients who develop new lesions may be treated with further locoregional treatment such as stereotactic radiosurgery (SRS). This study examines the association between ICP and survival or ND, to help define appropriate endpoints for future trials. **Method:** All patients treated for BrM from EGFRm+ NSCLC between 2004 and 2016 were identified from an institutional registry. Clinical data regarding demographics, progression events, pattern of progression, and treatment were extracted from medical records and verified with imaging reports. A multivariable competing-risks model was constructed to test the association between ICP at 6, 12 and 18 months and the outcome of ND. A separate model tested the association between ICP and OS. **Result:** 198 patients were included in the study. Median age was 61 years, 67% of patients were female, 46% had BrM at NSCLC diagnosis. Median DS-GPA was 2.5. Median OS for the group was 20 months, and the 5-year cumulative incidence of neurologic death was 40%. 111 patients (56%) had ICP and median intracranial PFS was 16 months; 29% had ICP within 6 months and 33% between 6 and 12 months, 18% at 12-18 months and 21% at >18 months. ICP was due to new BrM in 51%, progression of existing BrM in 34% and leptomeningeal carcinomatosis in 15%. Among patients with ICP, earlier progression was associated with ND (HR 2.48, p=0.01, see table). In addition, pattern of ICP was significant; patients with leptomeningeal spread (HR 3.74, p<.001) had higher risk of ND than those with new BrM or progression of existing lesions. In a multivariable model, early ICP, pattern of ICP and more initial BrM were independently associated with higher risk of ND and also shorter OS.

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Regression models of ND and OS						
	Univariate Model of Neurologic Death		Multivariable Model of Neurologic Death		Multivariable Model of Overall Survival	
Covariate	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Intracranial Progression < 6 months 6-12 months 12-18 months >18 months	2.48 (1.21-5.08) 1.56 (0.75-3.23) 1.61 (0.72-3.57) ref	0.013 0.24 0.25	4.88 (2.13-11.19) 2.69 (1.06-6.80) 3.85 (1.44-10.29) ref	<.001 0.036 0.007	11.22 (5.11-24.64) 5.31 (2.47-11.42) 4.82 (2.16-10.77) ref	<.001 <.001 <.001
Pattern of Progression New lesion Progression of existing BrM Leptomeningeal Spread	ref 1.29 (0.70-2.35) 3.74 (1.96-7.15)	0.41 <.001	ref 1.12 (0.55-2.26) 4.70 (2.11-10.48)	0.76 <.001	ref 1.54 (0.93-2.57) 3.19 (1.64-6.20)	0.10 <.001
Number of Initial BrM 1-4 5-10 >10	ref 1.92 (0.95-3.86) 2.94 (1.60-5.39)	0.07 <.001	ref 2.43 (1.05-5.62) 2.57 (1.11-5.90)	0.038 0.027	ref 3.27 (1.61-6.62) 3.74 (1.96-7.15)	0.001 <.001
First Line CNS Treatment WBRT SRS Systemic alone	Ref 0.69 (0.38-1.24) 0.58 (0.27-1.23)	0.22 0.15	Ref 1.17 (0.49-2.75) 0.88 (0.42-1.87)	0.73 0.88	Ref 1.10 (0.57-2.11) 1.28 (0.70-2.34)	0.79 0.43
EGFR Exon 19 vs 21	0.73 (0.44-1.23)	0.24	0.71 (0.40-1.24)	0.23	0.72 (0.52-1.00)	0.05
BrM at Diagnosis	0.93 (0.54-1.60)	0.78	1.45 (0.77-2.73)	0.26	0.93 (0.65-1.32)	0.69

Conclusion: Among patients with brain metastases from EGFRm+ NSCLC, shorter time to intracranial progression was associated with higher rates of neurologic death, as was the pattern of progression. This supports the validity of studies using intracranial progression as an endpoint, particularly if pattern of disease is taken into account.

Keywords: Brain metastases, advanced NSCLC, EGFR

P1.01-40 EGFR CTDNA DETECTION: THE IMPACT OF SITE OF PROGRESSION AND BURDEN OF PROGRESSIVE DISEASE

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Background: *EGFR T790M* testing is standard of care for activating EGFR mutant (EGFRm) NSCLC progressing on 1st/2nd generation TKIs to select patients for osimertinib. Despite sensitive assays, detection of circulating tumour DNA (ctDNA) is variable and influenced by clinical factors. We reviewed the number and location of sites of progressive disease (SPD) at time of testing to explore the effect on ctDNA detection and T790M positivity. **Method:** Following extraction of cell-free DNA from plasma using the QIAamp Circulating Nucleic Acid Kit, custom ddPCR assays were used to test for *EGFR* ctDNA using the Bio-Rad QX200 system. The ddPCR assays have a limit of detection of <0.1% variant allele fraction. Baseline characteristics and imaging reports at time of blood draw were reviewed retrospectively for all patients undergoing ctDNA testing from February 2018-March 2019. **Result:** 175 patients with EGFRm adenocarcinoma had 211 *EGFR* ctDNA tests performed. At the time of testing: median age 66, 63% female, 61% never smokers, 53% Asian. Initial TKI: 63% gefitinib, 34% afatanib, 2% erlotinib. Tissue genotype: 54% exon 19 deletion, 35% exon 21 mutation, 10% >1/rare mutation, 1% de novo T790M mutation. *EGFR* ctDNA testing results: 57% indeterminant, 29% *EGFR*m + T790M, 12% *EGFR*m alone, 2% T790M alone.

Variable	OR for ctDNA positivity (95% CI)	p value	MVA for ctDNA positivity (95% CI)	p value
Progression (absent vs present)				
Intrathoracic	1.32 (0.69-2.48)	0.40		
Extrathoracic	2.11 (1.19-3.73)	0.01		
Site of progression disease (absent vs present)				
Adrenal	0.89 (0.24-3.26)	0.86		
Bone	2.92 (1.61-5.33)	<0.001	2.78 (1.44-5.38)	0.002
Brain/LM	0.68 (0.32-1.43)	0.31		
Liver	2.9 (1.23-6.85)	0.02	3.12 (1.22-7.18)	0.018
Lung	0.95 (0.53-1.7)	0.87		
Lymph nodes	1.83 (0.95-3.54)	0.07	1.73 (0.84-3.55)	0.14
Number of sites				
0-2 sites	1		1	
3-5 sites	2.71 (1.38-5.32)	0.004	2.03 (0.98-4.19)	0.057
6-10 sites	2.12 (1.01-4.43)	0.047	1.22 (0.53-2.77)	0.64
>10 sites	2.31 (0.78-6.81)	0.13	0.95 (0.28-3.29)	0.94

Of ctDNA positive specimens, T790M positivity was not influenced by location or number of SPD compared to EGFRm. **Conclusion:** EGFR ctDNA was most likely to be detected in patients with progressing liver or bone lesions, independent of the number of SPD. Clinicians may consider these predictive variables in selecting patients for ctDNA re-testing. If ctDNA was detected, T790M positivity was not dependent on location or number of SPD.

Keywords: EGFR, circulating tumour DNA

P1.01-41 INVOLVEMENT OF THE JNK PATHWAY IN BRUCEINE D-INDUCED APOPTOSIS IN HUMAN NON-SMALL CELL LUNG CANCER CELLS

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Background: Non-small cell lung cancer (NSCLC), which accounts for 80% of lung cancer, is the leading cause of cancer mortality. Bruceine D (BD), a quassinoid isolated from *Brucea javanica's* fruit (a traditional Chinese herbal medicine), exhibits anti-cancer activity. This study aimed to investigate the effect of BD for non-small cell lung cancer (NSCLC) cells *in vitro.* **Method:** CCK-8 was used to detect the proliferation inhibitory effects of different concentrations of BD on A549, H460 cells. Cell clone formation was observed by clone formation assay. Annexin V/PI assay was used to detect the apoptosis induced by different concentrations of BD, and Western blot was used to detect the expression of apoptosis-related proteins and p-JNK after BD treatment. **Result:** The proliferation of A549, H460 cells was significantly inhibited by the different concentrations of BD (0.75, 1.5, 3, 6, 12 μmol·L-1) for 48 h in a concentration-dependent manner ($P < 0.05$), with IC50 values of 0.6 and 0.5 μmol/L, respectively. Annexin V/PI assay of apoptosis showed that different concentrations of BD had significant apoptosis-inducing effect on the two NSCLC cells ($P < 0.05$). Western blot results showed that cleaved-caspase-3 and cleaved-PARP were activated 48 h after BD treatment in NSCLC cells. Mechanistically, p-JNK protein expression was significantly increased after BD treatment for 2 h. Furthermore, the anti-cancer effects of BD were alleviated effectively by a specific JNK inhibitor SP600125 in NSCLC cells. **Conclusion:** BD can inhibit the proliferation of NSCLC cells and induce its apoptosis in a concentration-dependent manner. Its mechanism may be through the activation of JNK-caspase-PARP signaling pathway. All results suggest BD exhibits potent usefulness for preventing and treatment of NSCLC.

Keywords: Brucein D, NSCLC, JNK

P1.01-42 WHOLE-EXOME SEQUENCING IDENTIFIES NOVEL SOMATIC MUTATIONS ASSOCIATED WITH PROGNOSIS IN LUNG CANCER METASTATIC TO THE BRAIN

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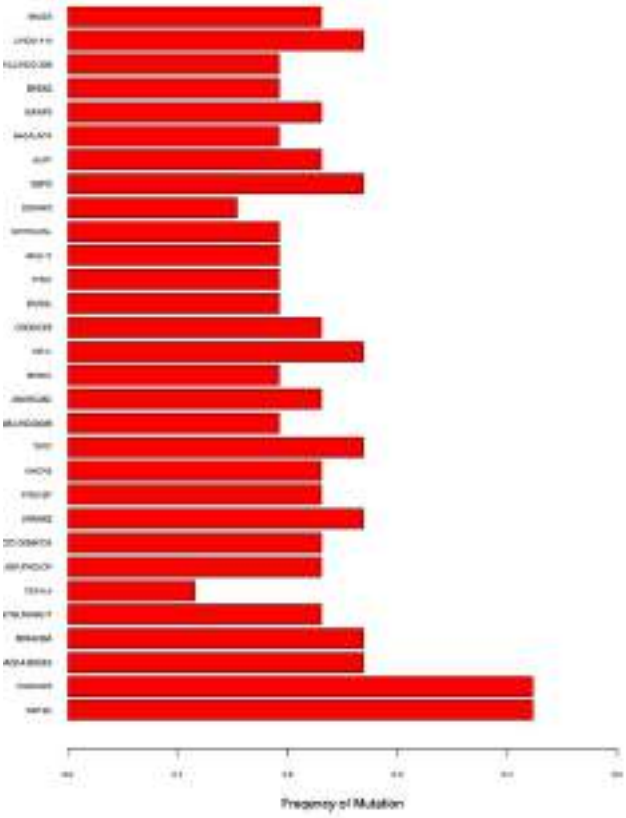
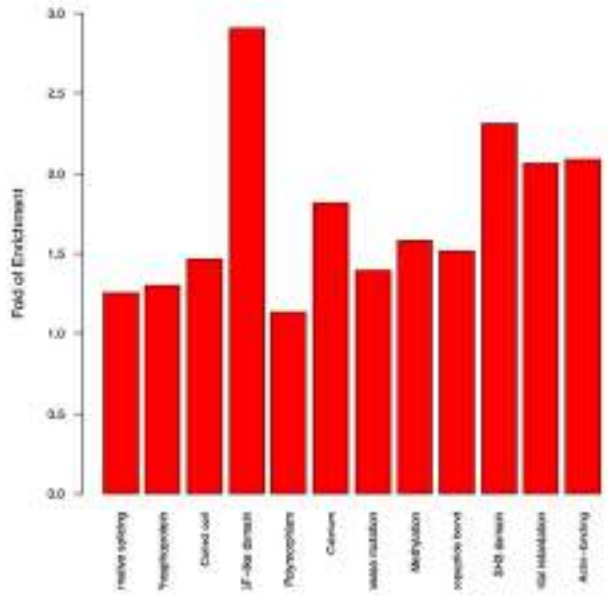
Background: Lung cancer is the leading cause of cancer-related mortality in China and worldwide. Patients with lung cancer are the major origin of metastastatic brain tumor. Understanding the difference between primary lung lesion and brain metastases may contribute to the treatment strategy. **Method:** To investigate the difference of somatic mutations in patients with non–small-cell lung cancer (NSCLC) and brain metastases. Whole-exome sequencing method were used in 13 paired lung cancer and brain metastasis samples from our institute. **Result:** 6,318 SNVs and 56,686 mutation events in 3864 genes were observed in 13 paired lung cancer and brain metastasis samples. We identified 46 driven gene mutations which are most frequently related to lung cancer. Several lung cancer metastases associated genes (KMT2C, BAGE2 and FER1L4) and epigenetic factors (CHEK2P2, miR-4436A, miR-6077) were found as well. A mean of 3.1 driver mutation events per tumor with the dN/dS of 2.06 (95%CI: 1.73-2.4) in these samples which indicating a significant enrichment of the cancer driven mutations. Mutation spectrum analysis found that these samples have more similar transition (Ti) and transversion (Tv) profile,in which C->T transitions is more frequently seen in brain metastasis samples, while lung primary tumor have a higher frequency of C->A transversion. Furthermore we found the most important tumor onset and metastasis pathways in these samples, such as focal adhesion,PI3K-Akt signaling pathway and MAPK signaling pathway. What's more, Glioma pathway were also identified which highly indicating the solid finding of the study.





Conclusion: In summary, we conducted an exome-wide sequencing through pairwised lung primary and brain metastasis samples and identified some novel cancer and metastasis related mutation which provided potential biomarkers for prognosis and novel therapeutics.

Keyword: lung cancer,brain metastases, prognosis

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P1.01-43 PROGRAMMED-DEATH LIGAND 1 SPECTRUM IN A LARGE COHORT OF GENETICALLY CHARACTERIZED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Programmed-death ligand 1 (PD-L1) expression, assessed by immunohistochemistry (IHC), is used to select patients (pts) for checkpoint inhibitors. However, the pattern of PD-L1 expression across rare oncogenic alterations remains poorly characterized. We aimed to evaluate PD-L1 expression in a large dataset of pts with activating molecular alterations to define the potential responsiveness to immunotherapy. **Method:** From 2016 to 2018, we prospectively characterized advanced NSCLC pts from a single institution. Tumor Proportion Score (TPS) for PD-L1 protein expression was evaluated by IHC (22C3 clone) using formalin-fixed paraffin-embedded tumor samples and scored into <1% (negative), 1-49% (weakly positive) and >=50% (high). DNA and RNA were extracted and analysed by Oncomine Solid Tumour panel (22 genes) and a customized nCounter-based panel (*ALK*, *ROS1*, *RET*, *NTRK1*, *METΔ14*). Associations between PD-L1 expression and the most prevalent driver alterations were assessed. Smoking habit and its possible relationship with PD-L1 expression was also appraised. Statistical analyses were performed using Kruskal-Wallis and Mann-Whitney tests. **Result:** TPS for PD-L1 expression was available for a total of 140 patients (pts) fully genotyped. The cohort included: 36% women; 89% adenocarcinoma; 87% smokers. TPS for PD-L1 expression was negative (<1%), weak (1-49%) and high (>=50%) in 40%, 35% and 25% of pts, respectively. Actionable drivers were found in 84 pts (60%) being *KRAS* (n=43.31%) the most commonly detected, followed by *EGFR* (n=22.16%), *BRAF* (n=7.5%), *METΔ14* (n=8.6%), *ALK* (n=3.2%) and *ERBB2* (n=1, 1%). Thirty (21.4%) [ME1] pts harboured *TP53* co-mutations. By comparing all genotyped cohorts, *METΔ14* alteration was associated with higher PD-L1 expression levels compared with other subgroups (median TPS 58.62 vs 25.26, p=0.017[ME2]). In addition, PD-L1 expression was also higher in pts harbouring any *TP53* co-mutation than those with any alteration but *TP53*-WT (median TPS 41.53 vs 21.45, p=0.035). When *KRAS-mut*, *BRAF-mut* and *EGFR-mut* were evaluated separately, PD-L1 expression was higher in *TP53 mutated* tumors compared to *TP53* WT only in *BRAF-mut* (p=0.028). Finally, no significant differences were found regarding patients' smoking status (p=0.527). **Conclusion:** Our results suggest differential expression of PD-L1 based on the presence of MET alterations and *TP53* mutations and highlight the need of further characterizing PD-L1 expression across oncogenic alterations.

Keywords: PD-L1, Non-Small Cell Lung Cancer, Oncogenes

P1.01-44 THE ROLE OF MICROBIOTA ON THE DEVELOPMENT OF NON-SMALL-CELL LUNG CANCER

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Background: The functional role of microbiota on the development of cancer has attracted an accumulating attention recently. However, the impact of fecal and sputum microbiome in the formation and development of Non-small-cell lung cancer (NSCLC) are mostly unknown. Our study aimed to characterize and compare fecal and sputum microbiome of NSCLC patients with healthy control subjects, and analysis the fecal microbiome of NSCLC patients with or without brain metastasis (BM). **Method:** We collected 102 fecal and 71 sputum samples from Wuhan Union Hospital. The Illumine Miseq sequencing platform was used to analyze 16S rRNA variable regions V3 and V4 in these samples. C57/BJ mice were treated with an antibiotic cocktail to postnatally deplete the microbiota. The effect of antibiotic was subsequently investigated both in xenograft model and brain metastases model. **Result:** Clinical characteristics of the participants including age, gender and body mass index were matched between the compared groups. (1) The sputum microbial diversity of healthy control group (n=18) was higher than NSCLC group (n=53, $P < 0.05$). Genus Actinomyces was significantly more abundant in sputum samples of NSCLC patients than the healthy controls ($P < 0.05$), while Neisseria was more abundant in the controls. The area under the curve of genus Actinomyces used to predict lung cancer was 0.71 (95% CI: 0.69 - 0.91). (2) However, no difference in alpha diversity was showed between the fecal microbial of healthy control group (n=22) and NSCLC group (n=80). Genus Haemophilus was significantly more abundant in fecal sample of NSCLC patients than the healthy controls ($P < 0.05$). The area under the curve of genus Actinomyces used to predict lung cancer was 0.75 (95% CI: 0.65 - 0.84). (3) The alpha diversity of fecal microbial was similar between patients with brain metastasis group (BM+, n=18) and patients without BM group (BM-, n=32). But there were some differences in the microflora structure between the 2 groups. (4) An impaired microbiota of mouse, antibiotic treatment, promoted tumorigenesis in subcutaneous xenograft, but inhibited tumorigenesis in brain metastasis. Impaired microbiota at least partially influenced the progression of Lewis cell line through acute and chronic inflammation of the intestine. **Conclusion:** The genus Actinomyces in sputum samples and Haemophilus in fecal samples were abundant in NCSLC group and exhibited moderate classification potential. The microflora structure of BM(-) and BM(+) group was significantly different. Antibiotic treatment at least partially influenced Lewis progression through acute and chronic inflammation of the intestine.

Keywords: brain metastasis, Microbiota, NSCLC

P1.01-45 A NGS-BASED CTDNA TEST TO MONITOR DISEASE PROGRESSION AND TREATMENT RESPONSE IN ADVANCED STAGE NON-SMALL CELL LUNG CANCER

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Background: The gold standard for clinical monitoring of lung cancer is CT imagining which is subjective and insensitive requiring a minimal of 2-3 months between repeat scans to be meaningful. As such, there is an urgent need to develop tests that can monitor anticancer treatment response and disease progression in real time. In this study, we evaluted the use of Next Generation Sequencing (NGS) for tumor associated genetic changes in circulating tumor DNA (ctDNA) to identify tumor mutations and the frequency of mutations detected in cfDNA to track tumor progression. We compared the results of a plasma based multigene mutation detection assay in advanced stage lung cancer patients to that of the routine CT scan and clinical observations. **Method:** EDTA whole blood were prospecitvely collected within 48 hours of the CT scan and during the course of patients' clinical treatment. Platelet poor plasma were collected within 6 hours of the blood draw and stored at -80°C until use. In total, we accrued 121 plasma samples from 46 consented patients with advanced stage lung cancer and undergoing therapy at Mayo Clinic in Rochester, Minnesota. All data are stored in a RAVE databased and RECIST criteria were reviewed individually by an attending oncologist. NGS analysis were performed using a modified Plasma*Select*-R™ (Personal Genome Diagnostics, Maryland) assay to assess mutation type and fraction of ctDNA in plasma sample from each patient. The results were compared with CT scans at the time of each blood draw for their ability to 1) detect the cancer based on tumor associated mutations and 2) correlate with the clinical status (RECIST) of the disease based on the fraction of ctDNA in plasma. **Result:** Among 121 plasma samples tested from 46 unique patients, 29 patients had three blood draws and 17 had a base line plus a follow up blood draw available for evaluation. More than 20 different tumor related mutations were observed. The number of mutations in each plasma sample ranged from 0 in eight patients to 5 in two individuals with allele frequencies ranging from 0.07% for *TP53* gene mutation to 29% in the *KRAS* gene. Tumor associated mutations were detected in approximately 70% of the plasma samples. In a pilot set of 10 cases with baseline and one follow up blood draw, those with progression of disease (PD, n=4) had tumor associated mutations detected in both baseline and follow up blood draws. In contrast, the remaining six patients with stable disease (SD) or partical response (PR) by RECIST had zero or fewer mutations at follow up. **Conclusion:** Our results suggeststst that a liquid biopsy approach is highly feasible and very promising in clinical settings. For patients whose tumors carry a mutation, the use of liquid biopsy to monitor treatment response and disease progression reduces patients' exposure to unnecessary radiation for surveillance of recurrent disease and enables a more sensitive and real-time monitoring of patients' clinical status to guide

further thearpeutic decisions. Complete mutational analysis with detailed clinical responses of each patients will be reported at the time of conference.

Keywords: liquid biopsy, Next generation sequencing, NSCLC

P1.01-46 RESPONSE ASSESSMENT USING PLASMA CELL-FREE DNA (CFDNA) – WHEN IS THE OPTIMAL TIME TO ASSESS RESPONSE?

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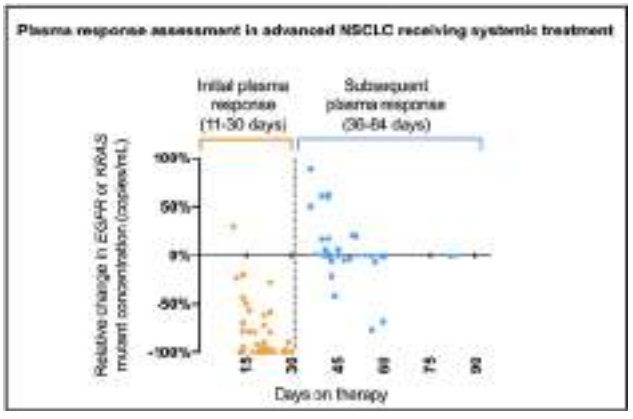
Background: Plasma cfDNA analysis is routine for non-invasive genotyping of advanced NSCLC, however response assessment using plasma cfDNA is not well characterized. We hypothesized that response in cfDNA would be an early process occurring well before routine imaging timepoints. **Method:** We retrospectively analyzed a total of 48 baseline and serial on-treatment plasma samples collected from 16 patients enrolled across three Experimental Therapeutics Clinical Trials Network (ETCTN) phase I trials of osimertinib combinations in advanced *EGFR*-mutant NSCLC. For validation, we also retrospectively analyzed a total of 201 baseline and serial on-treatment samples from an institutional cohort of 67 advanced NSCLC patients receiving systemic treatment. Using droplet digital PCR (ddPCR) of key *EGFR* or *KRAS* driver mutations, plasma response was defined as any decrease in mutation concentration to below baseline levels. We compared the magnitude of initial (baseline to day 11-30) and subsequent (day 11-30 to day 36-84) plasma response. Finally, we prospectively assessed response using serial amplicon-based plasma next-generation sequencing (NGS) in a pilot cohort of 8 NSCLC patients starting systemic therapy. **Result:** Of 15 ETCTN patients with any plasma response, best plasma response was seen at the initial response timepoint in 12 patients (80.0%) and ≥90% of the total plasma response was seen at the initial response timepoint in 14 patients (93.3%). In the validation cohort of 61 patients with any plasma response (Figure), best plasma response was seen at the initial response timepoint in 39 patients (63.9%) and ≥90% of the total plasma response was seen at the initial response timepoint in 52 patients (85.2%). Complete plasma responses (-100%) were seen as early as 11 days after initiating therapy. In the prospective clinical cohort, plasma NGS detected genomic alterations and enabled monitoring of changes in mutant allele fraction in all 8 patients. The median turnaround time of the assay was 8 days.



Conclusion: Plasma response is an early phenomenon, with the vast majority of plasma response seen within 30 days, and as early as 11 days. These findings suggest that early plasma cfDNA analysis may permit response assessment well before standard imaging timepoints, with potential as an early marker of drug effect. Additional investigation to understand the relationship between early plasma response, radiographic response, and durability of treatment effect is still needed.

Keywords: Plasma cfDNA, Plasma response, Early response assessment

P1.01-47 PROSPECTIVE STUDY FOR USEFULNESS OF PLASMA DNA ON PREDICTION OF THIRD GENERATION EGFR TYROSINE KINASE INHIBITORS (S-PLAT STUDY)

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Background: The AURA and FLAURA studies have shown that EGFR T790M mutation detected in cfDNA is correlated with efficacy of osimertinib as measured via overall response rate (ORR), and progression-free survival (PFS). However, the following clinical-related questions have been raised: Can other different assay systems confirm the results mentioned above? Does T790M level affect osimertinib treatment efficacy? Do mutations at loci other than EGFR influence treatment efficacy? **Method:** This is a prospective observational study, joining 27 Japanese hospitals. Plasma samples from patients with non-small cell lung cancer (NSCLC) who acquired resistance to EGFR-TKI (gefitinib, erlotinib, afatinib) were collected between Feb 2017 and Jan 2019. We tested T790M by MBP-QP method which has been newly developed using cfDNA and investigated the concordance with the result by cobas EGFR mutation Test v.2 (tissue and/or plasma) which is commercially available. We also checked the allele frequency (AF) of T790M in cfDNA by ddPCR and the mutational status of cancer related actionable genes by cfDNA specific NGS (Guardant360). The major objectives were ORR, disease control rate (DCR) to osimertinib and PFS in patients with T790M positive by MBP-QP method. **Result:** Among 145 NSCLC patients who acquired resistance to 1st or 2nd EGFR-TKI, T790M was detected in 57 patients by cobas (tissue and/or plasma), and these patients received osimertinib (80mg daily). T790M was detected by cobas in 16 patients from plasma, 44 patients from tissue, 3 patients from both samples. Among assessable patients, ORR, DCR and PFS in patients with T790M positive by cobas from plasma were 66.7%, 86.7%, 194 days, those of tissue were 53.5%, 97.7%, 186 days, respectively. In these 57 patients, MBP-QP also could detect T790M from 10 patients from plasma, and ORR, DCR and PFS in patients with T790M positive by MBP-QP from plasma were 75.0%, 87.5%, 184 days, respectively. These results suggest that T790M detection from cfDNA not only by cobas but also MBP-QP is correlated with RR of osimertinib. Now, using ddPCR and Guardant360, we have been investigating about the relationship between T790M AF and RR to osimertinib, and the influence of mutations at loci other on efficacy of osimertinib. **Conclusion:** cfDNA analysis can be predictive for osimertinib efficacy, just as re-biopsy. Whether comprehensive approach including AF and coexistence of other actionable genes is more precisely informative for drug efficacy has been continuously analyzed.

Keywords: Osimertinib, cfDNA, NSCLC

P1.01-48 EGFR TESTING IN ENGLAND – REAL WORLD EVIDENCE FROM THE NATIONAL LUNG CANCER AUDIT (NLCA) SPOTLIGHT ON MOLECULAR TESTING

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Background: In 2010, the use of tyrosine kinase inhibitors (TKIs) was approved for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation, and EGFR mutation analysis in these patients has become a standard of care. However, limited real world data exist in the UK on EGFR testing, and treatment and outcome. We therefore carried out a nationwide retrospective study to evaluate sample acquisition, testing, turnaround times and therapies related to EGFR testing in routine clinical practice. **Method:** In collaboration with Public Health England, a dedicated portal was designed allowing hospitals in England to log in and provide information on patients identified with stage 3B and 4 PS0-2 NSCLC diagnosed between June and December 2017. The portal for data collection was open for a period of 11 weeks, from 19 October 2018 to 4 January 2019. **Result:** Of the 142 hospitals in England, 60 took part in this spotlight audit of which 19 had on-site EGFR testing: 1,157 individual patient records were uploaded on to the portal; 512 (44%) patients were female, 353 (31%) were under the age of 65 and 758 patients (66%) had adenocarcinoma. Common methods of tissue acquisition were percutaneous lung or lymph node biopsy (31%), endobronchial ultrasound (EBUS) (24%) and from pleural fluid or pleural biopsy (11%). In a multivariate analysis, patients undergoing pleural procedures as an initial investigation were twice as likely to require a second procedure for molecular analysis as patients undergoing EBUS. Of the 758 patients with an adenocarcinoma subtype, 701 (92%) underwent EGFR testing. Testing failed in only 3% of patients and 71 (9.4%) had a sensitising EGFR mutation. The median time from biopsy to EGFR result was 18 days (interquartile range 14–23) with a median of 9 days from arrival in the molecular lab to EGFR result. In patients with a sensitising EGFR mutation, 53 (75%) received a first-line TKI, 3 (4%) received first-line chemotherapy, 1 (1%) patient received immunotherapy and treatment was unknown in 14 (20%). The median survival of patients with an EGFR mutation was 19 months **Conclusion:** In this study, samples acquired by pleural procedures were less suitable for EGFR testing. Comprehensive EGFR testing has been successfully implemented on a national scale using regional centres. Further quality improvement measures are required to reduce time to EGFR result.

Keywords: EGFR, adenocarcinoma, real world

P1.01-49 SERIAL CHANGES IN WHOLE-GENOME CELL-FREE DNA (CFDNA) TO IDENTIFY DISEASE PROGRESSION PRIOR TO IMAGING IN ADVANCED NSCLC

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Background: Response to treatment in advanced lung cancer is usually determined by clinical and imaging assessment. We analyzed longitudinal changes in blood whole-genome cfDNA to investigate whether a molecular response assessment could provide potentially actionable information prior to imaging. **Method:** We prospectively enrolled and serially collected blood from 35 patients with advanced non-small cell lung cancer (NSCLC). Baseline blood samples were drawn prior to initiation of a new treatment and at one or two additional time points, after the first cycle (median 21 days) and the second cycle (median 42 days). 4 mL of plasma was separated from peripheral blood collected in Streck tubes. Next, cfDNA was isolated from plasma and used to prepare libraries (15 with bisulfite conversion) for whole-genome sequencing at approximately 20X depth. Based on a patient-specific profile of whole-genome features, changes in the fraction of tumor-derived cfDNA were quantified over the initial course of treatment. Imaging was performed per standard practice with treatment response determined by an independent radiologist according to RECIST guidelines. **Result:** Median age of patients was 72 (range 48-87), and 49% were female. 69% of patients were on their first line of therapy (range 1-5). Patients were treated with an immune checkpoint inhibitor +/- chemotherapy (22), chemotherapy alone (11), or targeted therapy (2). Patients with predicted progression by cfDNA (n=4), indicated by an increase in tumor fraction at either post-treatment blood collection, had worse progression-free survival (PFS) compared to patients who did not show an increase (n=31) (hazard ratio 22.3, [95% CI 3.9-127.8], log-rank p=9 x 10-7). For the patients who were predicted to progress, the cfDNA assay preceded clinical evaluation by a median of 34 days. Median PFS was 56 days for patients with predicted progression versus 370 days for others. All patients with predicted progression were later confirmed to progress at the first follow-up evaluation (4/4, 100% positive predictive value). For the remaining patients, 27 of 31 did not progress (87% negative predictive value). Therefore, sensitivity for the assay was 50% and specificity was 100%. **Conclusion:** Analyzing tumor-derived cfDNA early in the course of a new therapy holds promise to identify patients with early disease progression across multiple types of treatment. This technology may enable early switching to other potentially effective therapies, increasing the value proposition of all delivered treatment.

Keywords: biomarkers, cell-free DNA, Non-Small Cell Lung Cancer

P1.01-50 IMPACT OF CONCOMITANT HER2 ALTERATIONS IN MEDIATING CLINICAL OUTCOMES OF EGFR-MUTANT PATIENTS TO DIFFERENT GENERATION OF EGFR-TKIS

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Background: The 2nd generation EGFR-TKI are selective and potent irreversible pan-HER inhibitors. Given their effect on HER2 besides EGFR, we investigated the role of *HER2* co-alterations in mediating the clinical outcomes of *EGFR*-mutant non-small cell lung cancers to 2nd generation or other generation EGFR-TKIs. **Method:** Plasma/tissue samples from advanced NSCLC before and after 1L EGFR-TKI treatment were sequenced using 168-/520-cancer-related gene panels, respectively. Clinical records of 94 *EGFR*-mutant pts (92 adenocarcinomas and 2 adenosquamous cell carcinomas) after 1st/3rd (n=73) or 2nd generation (afatinib, n=16; dacomitinib, n=5) EGFR-TKI treatment were collected for clinical outcomes evaluation. Event-time distributions were estimated using Kaplan-Meier and compared with long-rank test. **Result:** Among the 94 pts identified as *EGFR*-positive at baseline, 8 (8.5%) had concurrent *HER2* gain-of-function alterations (amplification or active mutation). Survival analysis showed that for those with concomitant *EGFR* and *HER2* alterations at baseline, pts achieved favorable PFS (23.2 vs 5.6 months, p=0.04) to 2nd generation (n=2) than to 1st/3rd generation EGFR-TKI (n=6) as 1L treatment. And for those receiving 1L 1st/3rd generation EGFR-TKI (n=73), the presence of baseline *HER2* alterations (n=6) was associated with shorter PFS (5.6 vs 9.8 months, p=0.16) and OS (15.7 vs 21.0 months, p=0.06) than absence of *HER2* (n=67), although the difference was not significant due to a small sample size. In addition, we found all the samples (n=21) obtained from pts after 2nd generation EGFR-TKI resistance were *HER2*-negative, but pts progressed on 1st or 3rd generation EGFR-TKI with *HER2* as the only resistance mechanism were observed in our study cohort. **Conclusion:** Our findings suggested that, for *EGFR*-mutant pts combined with *HER2* alterations at baseline or those resistant to 1L treatment of 1st/3rd EGFR-TKI due to *HER2* alterations only,2nd EGFR-TKI might be a better choice.Our findings suggested that, for *EGFR*-mutant pts combined with *HER2* alterations at baseline or those resistant to 1L treatment of 1st/3rd EGFR-TKI due to *HER2* alterations only,2nd EGFR-TKI might be a better choice.

Keyword: HER2 EGFR-TKI afatinib

P1.01-51 MICROPAPILLARY PREDOMINANT AND PATHOLOGIC STAGE WERE RISK FACTORS FOR POSTOPERATIVE BRAIN METASTASIS IN LUNG ADENOCARCINOMA

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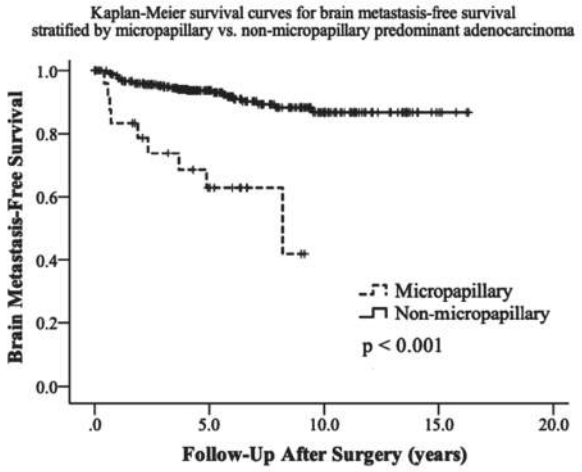
Background: Brain metastasis from non-small cell lung cancer following curative resection is a significant issue because it often causes critical symptoms and may require different therapeutic approaches from other recurrence. On this background, we aimed to investigate correlation between clinicopathological variables and brain metastasis in resected lung adenocarcinoma. **Method:** Clinicopathological data of 358 patients who had undergone complete resection for lung adenocarcinoma at Saiseikai Utsunomiya Hospital between 2002 and 2015 were retrospectively reviewed. Brain metastasis-free survival was calculated from the date of surgery to the date when brain metastasis was diagnosed or the date of last follow-up by using Kaplan-Meier method. We analyzed the risk factors of postoperative brain metastasis by log-rank analysis and Cox regression analysis. **Result:** The median follow-up period was 60.4 months (range, 1.0 - 195.6 months). Thirty-six patients developed brain metastasis after complete resection of lung adenocarcinoma during follow-up. Thirty-three patients were diagnosed as brain metastasis by contrast-enhanced brain MRI and the others were diagnosed by contrast-enhanced brain CT. Five-year brain metastasis-free survival rate was 91.4%. Log-rank analysis demonstrated that pathologic stage IB or higher ($p < 0.001$), lymphovascular invasion ($p < 0.001$), presence of spread through alveolar spaces ($p < 0.001$) and micropapillary predominant pattern ($p < 0.001$) were significantly associated with recurrence of brain metastasis. Cox regression analysis demonstrated that pathologic stage IB or higher ($p = 0.004$) and micropapillary predominant pattern ($p = 0.007$) were independent risk factors for brain metastasis.



Conclusion: Our findings suggest that careful follow-up may be required for patients with higher pathologic stage as well as micropapillary predominant lung adenocarcinoma after complete resection. It may also emphasize clinical significance of micropapillary subtype in resected lung adenocarcinoma.

Keywords: brain metastasis, lung adenocarcinoma, Micropapillary predominant

P1.01-52 CELL-FREE TUMOR DNA (CTDNA) UTILITY IN DETECTION OF ORIGINAL SENSITIZING AND RESISTANT EGFR MUTATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: With the use of personalized therapy the need for repeat biopsies in lung cancer patients (pts) has increased. For most lung cancer pts, a tissue biopsy can be quite challenging and potentially risky.The aim of this study was to evaluate the utility of ctDNA to detect the EGFR original mutation (OM) and to identify the T790M resistance mutation in advanced NSCLC pts who received EGFR-TKI. **Method:** This is a prospective cohort study utilizing theCobas EGFR ctDNA testing kit V2 in pts with confirmed EGFR-mutant advanced NSCLC by tissue biopsy. The blood was obtained from 66 pts at 4 time points: baseline, time of 1st CT, time of progression, and 1 month after starting new treatment. **Result:** From January 2017 to January 2019, 66 pts were enrolled in the study, of which 41(62%) had an exon 19 deletion and 25(38%) had an exon 21 mutation. 23/66 pts were TKI naive and 43/66 were already on TKI treatment. Adequate ctDNA was found in the plasma of 97% of cases. The OM was identified in 42 % of pts at first blood test with higher detection rates in TKI naïve pts 12/23(52%) compared to 16/43(37%) in TKI group. Best response to first line TKI was evaluated in 64 pts; in 56 (88%) pts, disease was controlled (CR+PR+SD) with TKI, in 8 (12%) pts the treatment had failed and was discontinued. A significant correlation between OM detection and response to first line TKI was found ($p = 0.05$) with higher detection rate in non-responders 6/8(75%) compared to responders 21/56 (38%). In TKI naïve pts OM was detected in 4/5(80%) of non-responders and in TKI group in 2/3 (67%) pts. The resistance mutation (T790M) was detected in 12/66 (18%) pts. All 12 (100%) pts initially responded to TKI and OM was no longer detected. Median duration of TKI until progression was 25.5 (SD 12.7) mo. The OM re-occurred in 11/12 (92%) at the time of progression. **Conclusion:** ctDNA can be noninvasively assessed in the circulation and be used to monitor responses to treatment and detect development of secondary resistance. The re-occurrence of OM on repeat liquid biopsy seems to be a sign of resistance to first line treatment. In the future, instead of extensive imaging and invasive tissue biopsies, ctDNA test by NGS panel could be used to find other mutations and to guide cancer treatment decisions.

Keywords: EGFR, ctDNA, NSCLC

P1.01-53 CLINICAL UTILITY OF TWO DIFFERENT PLASMA-BASED EGFR MUTATION TESTS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: When tumor biopsies from patients (pts) with advanced NSCLC yield infeasible or insufficient for successful molecular subtyping, plasma cfDNA genotyping has been widely adopted due to its convenience and high positive predictive value. However,a different assay sensitivity makes the optimal choice more difficult. In this study, we have analyzed the clinical utility of two different plasma-based EGFR-mutation (mEGFR) tests in pts with advanced NSCLC. **Method:** We prospectively enrolled consecutive pts with advanced NSCLC with adequate tissue before EGFR genotyping in single institution (June 2017-December 2018). EGFR tissue genotyping was performed using peptide nucleic acid (PNA) based PANAMutyper R EGFR assay (PANAGENE, Daejeon, Korea).EGFR plasma genotyping was performed using Cobas EGFR Mutation Test v2(Roche, Mannheim, Germany) and PANAMutyper R EGFR assay. All pts provided informed consent. **Result:** We included 72 patients. 44 (61%) were treatment naïve. Overall sensitivity for mEGFR positive was 52% (23/44) from tissue, but 34% (15/44) from Cobas and 30% (13/44) from PANAMutyper. Among 21 pts with tissue mEGFR-negative, plasma mEGFR test found additional 2 pts with mEGFR positive from Cobas and 1 pts from PANAMutyper. EGFR sensitivity with tissue increased to 57% and 55% when combining with plasma by Cobas and PANAMutyper, respectively. Concordance rate of tissue mEGFR was same as 73% with Cobas and

PANAMutyper (kappa 0.46). Among 28 pretreated mEGFR-positive advanced NSCLC, sensitivity for mEGFR positive was 71% (20/28, include 6 cases of T790M) from tissue re-biopsy, and 68% (19/28, include 8 cases of T790M) from Cobas and 57% (16/28, include 6 cases of T790M) from PANAMutyper. Cobas plasma mEGFR test found additional 2 pts with T790M. T790M sensitivity with tissue (30%) increased to 40% for both tissue and plasma by Cobas. In pretreated setting, concordance rate of tissue mEGFR was 96% with Cobas (kappa 0.92) and 86% with PANAMutyper (kappa 0.70). **Conclusion:** In pts with treatment naïve advanced NSCLC, sensitivity for tissue mEGFR was higher than plasma mEGFR genotyping. Though plasma mEGFR test found additional mEGFR positive patients, overall sensitivity was slightly increased when combining both methods. In pts with pretreated mEGFR-positive, overall sensitivity for tissue mEGFR was similar with Cobas plasma mEGFR genotyping with high concordance rate.

Keywords: Non-Small Cell Lung Cancer, plasma, EGFR mutation

P1.01-54 SOMATIC GENOME ALTERATIONS IN LUNG CANCER PATIENTS DIAGNOSED WITH LI FRAUMENI SYNDROME

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Background: Li-Fraumeni syndrome (LFS) is a rare hereditary condition that consists of *TP53* mutations inherited in autosomal dominant manner that confer high risk of developing cancer, including lung adenocarcinoma (LUAD). *EGFR*-mutated LUAD were reported in the context of LFS but there is no systematic description of somatic mutations and characteristics of lung cancer (LC) patients with LFS. **Method:** We present a retrospective analysis of clinical and molecular characteristics of patients with LFS diagnosed with LC at the Catalan Institute of Oncology from 1999 to 2019. We collected demographical and clinicopathological features, germline and somatic mutational alterations, treatment and progression-free survival (PFS) and overall survival (OS). **Result:** A total of 7 patients with LC and LFS were identified in the Genetic Counseling Unit database. They were carriers of germline mutations in *TP53*. Five of them were classified as pathogenic: c.638G>A; p.(Arg213Gln), c.725G>A; p.(Cys242Tyr), c.742C>T; p.(Arg248Trp), c.844C>T; p.(Arg282Trp) and c.1010G>A; p.(Arg337His) and two of them as likely pathogenic: c.374C>T; p.(Thr125Met) and c.473G>A; p.(Arg158His). Six out of 7 patients were female and 5 out of 7 never smoker. Median age at diagnosis was 38 year-old (range: 29-74). Five patients had stage IV at diagnosis and the most common histologic subtype was LUAD (5). Six patients had first grade family history of cancer with a median of 2 family members (range: 1-4) and 2 patients had prior history of cancer. Tumor somatic profile in LC was obtained in 6 patients, consisting on a *ROS-1* rearrangement in one patient and *EGFR* mutations in 5 patients (exon 19 deletion in 3 patients and missense mutations in 2 patients, p.(Gly719Ala) at exon 18 and p.(Leu858Arg) at exon 21) and in 1 patient was unknown. All patients with mutant EGFR received EGFR tyrosine kinase inhibitors (TKI) with a median PFS of 29 months (95% CI 0-67). Four had partial response and one a complete response to TKI treatment. At disease progression, one patient had small cell transformation and another acquired *EGFR T790M* mutation. Median lines of treatment were 4 (range 1-6). Two patients are alive at data cut off. Median OS is 47 months (95% CI 32-62). **Conclusion:** Patients diagnosed with LC and LFS are enriched with actionable genomic alterations and have an earlier onset of the disease. Clinical outcome of patients with *EGFR* mutations and LFS did not differ from *EGFR* mutated LC patients who do not carry *TP53* germline mutations.

Keywords: Lung cancer, Li Fraumeni Syndrome, EGFR mutant lung cancer

P1.01-55 UPDATED ANALYSIS OF OUTCOMES BY HISTOLOGY VS CYTOLOGY PD-L1 22C3 ANTIBODY TESTING IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (CPIs) have changed the treatment algorithm for advanced non-small cell lung cancer (NSCLC). PD-L1 expression using 22C3 immunohistochemistry (IHC) help determine the treatment options in which CPI are used. Previous studies demonstrated that PD-L1 expression is comparable on cytology versus solid biopsy/histology specimens and no difference in survival between the testing methods among PD-L1 high (≥50%) expression patients. We assess the clinical outcomes in an expanded population of patients tested for any PD-L1 status (<1%, 1 – 49%, ≥50%) using cytology versus histology specimens. **Method:** This retrospective cohort study reviewed both histology and cytology specimens processed for PD-L1 status between January 2015 and June 2017. All patients who had PD-L1 testing completed for advanced NSCLC and who had follow-up with a medical oncologist were included in the final analysis, regardless of PD-L1 status. Clinical characteristics were extracted from electronic medical records. Clinical outcomes were compared between cytology and histology specimens following a chart review, including overall survival (OS) (defined as time from diagnosis of advanced NSCLC to death). This was adjusted for age, ECOG, weight loss, Charlson Comorbidity Index, and receipt of palliative intent radiotherapy, targeted therapy, and CPI. **Result:** 512 patients with PD-L1 status testing were assessed. Amongst those, 152 fulfilled eligibility criteria with cytology (n=55) and histology (n=97) samples respectively. Baseline characteristics of the two groups are comparable in age, gender, ECOG, and histological subtype. Comparatively, the cytology group had more patients who were PD-L1 high (≥50%) (60% vs 39%) and had a significantly higher number of patients with baseline pleural effusion (29% vs 12%, p=0.011) and lymph node involvement (55% vs 37%, p=0.037). The histology group received more palliative intent radiation (67% vs 36%, p=0.001) while the cytology group was more likely to receive any systemic therapy (84% vs 64%, p=0.010) and any line of CPI (31% vs 28%, p=0.048). No difference was observed in OS between the cytology and histology groups. Median OS in the cytology group was 11.8 versus 9.8 months in the histology group (HR 0.94 (95% CI 0.676-1.321)). Amongst patients who received systemic therapy, survival was significantly longer if patients were exposed to CPI during their course of treatment regardless of cytology or histology groups. However, this finding is no longer significant among patients who receive second line treatment only (HR 0.92 (95% CI 0.54-1.58, p=0.78). On multivariate analysis, there is a significant improvement in survival with the receipt of any systemic therapy (HR 0.20 (95% CI 0.11-0.38, p=0.000), while a baseline ECOG status of 3 compared to an ECOG status of 0 was associated with worse survival (HR 4.37, (95% CI 1.17-16.27)). **Conclusion:** In advanced NSCLC, specimens analyzed by cytology versus histology were equivalent in survival, suggesting that the approach to biopsy should prioritize non-invasive procedures, patient preference and disease characteristics over the specimen type. Additionally, baseline performance status and receiving treatment are associated with improved outcomes, with a trend towards harm with higher ECOG scores, signifying the importance of careful patient selection in the era of CPI.

Keywords: PD-L1 testing, cytology, Histology

P1.01-56 INCREASED ROS1 AND RET TRANSCRIPTS IN FUSION-NEGATIVE NSCLC PATIENTS

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Background: Fusion involving anaplastic lymphoma kinase (*ALK*), RET proto-oncogene (*RET*) or v-ros UR2 sarcoma virus oncogene homolog 1 (*ROS1*) occur in non-small cell lung cancers (NSCLC) and are important biomarkers for targeted therapies. However, little is known about the RNA expression levels of these genes regardless of fusions. **Method:** We used a custom nCounter panel (NanoString Technologies) designed to detect several genetic alterations, including fusions and mRNA expression levels of *ALK*, *ROS1* and *RET* in formalin-fixed paraffin embedded (FFPE) samples. RNA was purified from NSCLC tumor samples and analyzed with the custom panel. The counts corresponding to the 3' probes were normalized using the geometrical mean of the housekeeping genes and then added to evaluate total mRNA expression levels. Cut-off values for overexpression were established as the average counts for each gene plus two times the standard deviation. **Result:** A total of 400 stage III-IV NSCLC patients (p) from two different institutions were retrospectively analyzed. Overexpression of ALK was found in 55 p (13.8%). Of them, 48 (87%) were also positive for EML4-ALK fusions. One ALK-translocated patient with low levels of ALK mRNA expression did not respond to therapy. Fifteen p (3.8%) showed ROS1 overexpression. In contrast with ALK, only three of them (15%) had a concomitant ROS1 fusion. Among the remaining 12 patients overexpressing ROS1, four were ALK positive, five harbored mutations in EGFR and three were non-smoker females with no known drivers. Regarding RET, high expression levels were found in 14 p (3.5%) and only one of them showed a RET fusion (7%). Among the remaining 13 p, three presented neuroendocrine features and seven were smoker or ex-smoker without other known drivers. **Conclusion:** Overexpression of ALK mRNA in NSCLC is associated with EML4-ALK translocations. In contrast, a significant number of fusion negative patients show high ROS1 or RET mRNA levels. Further research is warranted to determine the clinical relevance of this finding.

Keywords: ROS1, RET, nCounter

P1.01-57 ASSOCIATION OF INITIAL PD-L1 EXPRESSION WITH T790M-ACQUIRED RESISTANCE IN ADVANCED EGFR-MUTANT LUNG ADENOCARCINOMA PATIENTS

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Background: The primary objective was to investigate the association between initial programmed cell death-ligand 1 (PD-L1) expression levels and the frequency of T790M-acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase Inhibitor (TKI) in patients with advanced *EGFR*-mutant lung adenocarcinoma. **Method:** We examined patients with advanced *EGFR*-mutant lung adenocarcinoma whose initial PD-L1 expression levels and T790M-acquired mutation status after EGFR-TKI failure (gefitinib, erlotinib or afatinib) could be evaluated. We retrospectively investigated the patients' characteristics and survival, as well as the association between initial PD-L1 expression levels and frequency of T790M-acquired resistance **Result:** Overall, 100 patients were enrolled. Nine (9%) patients had an initial PD-L1 tumor proportion score (TPS) of ≥50%, 19(19%) had PD-L1 TPS of 1%-49%, and 72 (72%) had PD-L1 TPS of <1%. T790M-acquired mutation (T790M+) was identified in 57 (57%) patients. Initial PD-L1 expression levels were not associated with the frequency of T790M-acquired mutations in patients (p=0.822). Positive PD-L1 expression (PD-L1+) was associated with lower OS compared with negative PD-L1 expression (PD-L1-) (median overall survival [OS], 40.3 vs 74.3 months, p=0.0053). Furthermore, T790M+ was associated with longer OS compared with T790M- in total and PD-L1- population (total: median OS, 74.3 vs 41.3 months, p=0.0154, PD-L1-: median OS, 82.0 vs 41.2 months, p=0.00412), but not in PD-L1+ population (median OS, 36.2 vs 46.2 months, p=0.792). Among 57 patients with T790M-aquired mutation, 49 received osimertinib treatment. The estimated median progression-free survival rate of osimertinib was 13.2 months in PD-L1- patients (n=37) and 6.9 months in PD-L1+ patients (n=12) (p=0.224). **Conclusion:** There was no association between initial PD-L1 expression levels and the frequency of T790M-aquired mutations in patients. However, PD-L1+ expression levels in patients with treatment-naïve advanced *EGFR*-mutant lung adenocarcinoma predicted poorer outcomes. Intriguingly, T790M-aquired mutations were related to longer OS in PD-L1- patients, but not in PD-L1+. Thus, for patients with T790M-acquired mutant and initial PD-L1 positive lung adenocarcinoma in whom the use of osimertinib is indicated, other treatment options should be considered without hesitation if the treatment effects are not as expected.

Keywords: PD-L1, T790M-aquired mutation, EGFR mutation

P1.01-58 COMPREHENSIVE SERIAL BIOMATERIAL AQUISITION IN ADVANCED NSCLC: FEASIBILITY, CHALLENGES AND PERSPECTIVES

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Background: Availability of tumour material at baseline and disease progression is increasingly important for patient management in non-small-cell lung cancer (NSCLC), especially in tyrosine kinase and immune checkpoint inhibitor treatment. Here, we report the experience with prospective biobanking for advanced NSCLC from a pilot project in the academic setting. **Method:** Main objective was the longitudinal collection of snap-frozen in addition to formalin-fixed paraffin-embedded (FFPE) biopsies required for routine diagnostics, along with blood samples and detailed clinical annotation using standardized questionnaires. **Result:** Over five years, 205 patients were enrolled yielding 387 cryoconserved biopsies and 1098 serum, plasma and buffy-coat samples. The feasibility of obtaining cryoconserved in addition to FFPE biopsies was 89 % for newly diagnosed cases, but dropped down to 56 % and 47 % at first and second disease progression, respectively. Main obstacle was increased procedural risk due to patient deterioration, but no complications occurred. Biopsies had a tumour cellularity of 34 % and yielded 13.6 µg DNA and 12 µg RNA in median. **Conclusion:** Despite the poor condition and limited prognosis of most NSCLC patients, systematic, serial biomaterial acquisition including routine collection of cryoconserved biopsies is feasible in order to facilitate individualized management and support research that will advance therapeutic options.

Keywords: Biobanking, Tissue and Blood, NSCLC

P1.01-59 EXPANDING ACCESS TO LARGE-SCALE GENOMIC MUTATIONAL ANALYSES FOR PATIENTS WITH ADVANCED NSCLC IN ITALY

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Background: In NSCLC, large-scale mutational analysis facilitates access to targeted treatments but is still not routinely employed due to significant technological barriers. The Alleanza Contro il Cancro (ACC) network of Italian Cancer Centers developed an affordable targeted sequencing panel for the identification of multiple genetic alterations with potential clinical utility, and designed a prospective multicentric trial to recruit 1000 newly diagnosed advanced NSCLC patients, aiming to i) compare panel performance against a set of externally validated biomarkers, including alterations in standard-of-care (EGFR, ROS1 and ALK) and non-standard-of-care (KRAS, BRAF, MET) biomarkers; ii) identify alterations in a large dataset of driver and potentially actionable genes; iii) correlate genotypes to survival outcomes and toxicity; iv) carry out ancillary studies on additional biomarkers and/or on specific patient groups (e.g. mutational burden, cfDNA, extensive characterization of immunotherapy-treated patients); v) build a centralized data repository for mutation interpretation and clinical recommendation. **Method:** Through systematic literature mining and ad-hoc developed bioinformatic pipelines we identified: i) a set of 164 potentially actionable genes in solid tumors; ii) additional 18 genes with predicted driver function in NSCLC; iii) 70 actionable fusion transcripts; iii) 141 SNPs associated with pharmacogenomics markers. We designed a custom enrichment panel (~800 kb target) and compared PCR- and hybridization-based enrichment on semiconductor or by-synthesis sequencing to be subsequently deployed in a large observational trial. Sequencing is decentralized, to allow rapid turnaround time, but raw and processed data are collected in a single informatic infrastructure for centralized quality control and continuous bioinformatic pipeline improvement. **Result:** PCR/semiconductor sequencing was selected for deployment based on cost and feasibility (2-day, highly automated workflow). 182 patients have been enrolled to date (90% stage IV, 10% IIIB). Of 65 patients with treatment information available, 28 (43%) subsequently received immunotherapy and 13 (20%) targeted therapy. For 56 patients with complete sequencing data, EGFR and KRAS status was concordant in 9/10 and 38/41 cases; discordant cases are being validated with orthogonal methods. Clinically significant MET amplifications were called in 2/2 cases. Remaining target regions did not show pathogenic alterations. Multiple alterations in potentially actionable genes were identified. **Conclusion:** Large-scale sequencing is reliable, feasible and sustainable across multiple hospitals and provides clinically relevant results. The increased availability of genomic information may result in enhanced access to tailored therapies. Data and sample integration in centralized, shared repositories will allow multiple ancillary studies.

Keywords: NSCLC, Next-generation sequencing

P1.01-60 PROGNOSTIC IMPACT OF PD-L1 EXPRESSION ON EGFR TYROSINE KINASE INHIBITION IN LUNG ADENOCARCINOMA

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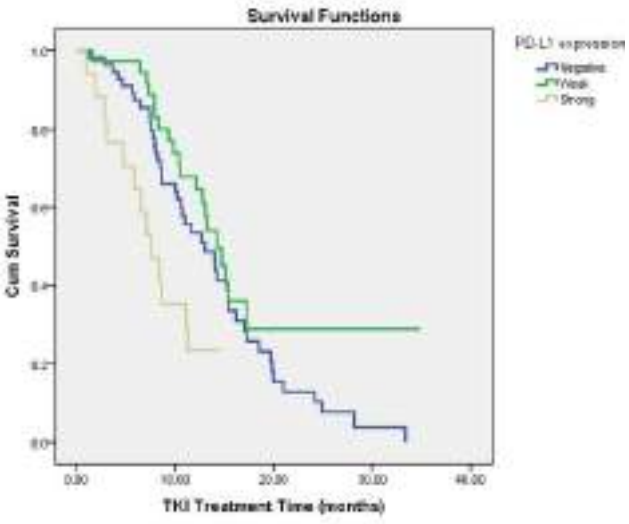
Background: EGFR tyrosine kinase inhibitors (TKIs) are recommended as first-line systemic therapy for advanced non-small cell lung cancer (NSCLC) with sensitizing EGFR mutations. The programmed death-ligand 1 (PD-L1) expression on tumor cells has emerged as a prognostic marker after surgical resection in various tumors including NSCLC. This study investigated the predictive value of PD-L1 expression on the duration of treatment and the emergence of T790M mutation in patients treated with EGFR-TKIs. **Method:** We retrospectively enrolled 109 patients with advanced NSCLC who had been treated with EGFR-TKIs as first-line systemic treatment at Seoul National University Bundang Hospital and Seoul National University Hospital between December 2012 and October 2018. Patients without sensitizing EGFR gene mutations (exon 19 deletion, exon 21 L858R, and L861Q) were excluded. The PD-L1 expression on tumor cells was scored using two immunohistochemistry assays (22C3 or SP263). The Kaplan-Meier survival estimation and log rank test were used for survival analyses. **Result:** Among the 109 patients (Median age 65; Male:Female = 37:72), 17 (15.6%), 37 (33.9%) and 55 (50.5%) patients had strong (≥50%), weak (1%-49%), and negative (<1%) PD-L1 expression, respectively. In univariate analysis, the median time-to-treatment failure (TTF) of EGFR-TKI treatment was 7.6 months in strong expression, 14.2 months in weak expression, and 13.0 months in negative expression (log-rank; Strong vs. Weak, P=0.008; Strong vs. Negative, P=0.031). There was no statistically significant difference of TTF between the patients with weak expression and negative expression (log-rank, p=0.191). After adjustment of age, sex, and smoking status, strong PD-L1 expression remained as a significant predictor of short TTF (hazard ratio [HR] for strong vs. weak, 2.68; 95% CI, 1.35-5.33; P=0.005). The detection rates of T790M mutation after EGFR-TKI failure were similar in three groups (23.53% in strong, 29.73% in weak, and 32.73% in negative PD-L1 expression; P=0.478). In patients treated with 3rd generation EGFR-TKIs (n=35), there was no statistically significant difference of TTF according to PD-L1 expression (p=0.889). Figure. Kaplan-Meier survival curve for TTF of 1st line EGFR-TKIs according to PD-L1 expression **Conclusion:** Strong PD-L1 expression of tumor might be a surrogate indicator of poor response to EGFR-TKIs in NSCLC patients with sensitizing EGFR mutations.

Keywords: NSCLC, PD-L1, EGFR



Means and Medians for Survival Time

PD-L1	Mean[a]				Meidan			
			95% Confidence Interval				95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Negative	13.863	1.104	11.700	16.026	13.000	1.840	9.394	16.606
Weak	18.302	2.230	13.930	22.673	14.230	1.112	12.050	16.410
Strong	8.110	1.105	5.943	10.277	7.570	1.258	5.105	10.035
Overall	13.997	.919	12.196	15.797	12.800	1.396	10.063	15.537

a.Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	10.256	2	.006

Test of equality of survival distributions for the different levels of PD-L1

P1.01-61 A PHASE II UMBRELLA STUDY OF CAMRELIZUMAB IN DIFFERENT PD-L1 EXPRESSION COHORTS IN PRE-TREATED ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER

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Background: The role of PD-L1 expression in 2nd line and beyond non-small cell lung cancer (NSCLC) remains controversial. Camrelizumab (SHR-1210) is a potent anti-PD-1 monoclonal antibody and has shown promising activity in NSCLC in Phase I studies. We report results from the SHR-1210-201 study (NCT03085069), a phase II umbrella study of camrelizumab monotherapy in different PD-L1 expression cohorts in Chinese patients with previously treated advanced or metastatic NSCLC. **Method:** Patients who progressed during or following platinum-based doublet chemotherapy were enrolled and assigned to one of 4 cohorts based on PD-L1 expression. Patients with EGFR or ALK genomic alterations were eligible provided they had disease progression with at least one approved tyrosine kinase inhibitor and with ≥50% PD-L1 expression in tumor. All enrolled patients received camrelizumab at 200 mg IV Q2W until loss of clinical benefit. The primary endpoint was objective response rate (ORR), other endpoints included progression-free survival (PFS) and overall survival (OS). **Result:** As of Aug 1st 2018, of all the 259 patients who underwent screen, 229 cases could be pathologically evaluated. PD-L1 expression were 47.6% (109/229) in PD-L1 < 1%, 27.1% (62/229) in PD-L1 ≥1-<25%, 8.7% (20/229) in ≥25-<50% and 16.6% (38/229) in ≥50%. A total of 63.8% (146/229) patients were enrolled. 89.0% of patients had stage IV NSCLC and 54.8% had non-squamous tumor histology. ORR was 18.5% (95%CI: 12.6%–25.8%) in ITT population. Subgroup analysis showed increased PD-L1 expression was associated with better response rate (Table 1). No response was observed in patients with EGFR mutation. The responders had durable response (median: 15.1 months; 95%CI: 5.5–not reached). Median PFS was 3.2 months (95%CI: 2.0–3.4) and median OS was 19.4 months (95%CI: 11.6–not reached) (Table 1). Treatment-related adverse events (AEs) occurred in 87.7% of patients (all Grade); 20.5% had ≥G3 related AE; and 15.8% had related SAE. 21.2% of AEs led to dose interruption and 7.5% led to treatment discontinuation.

Conclusion: In Chinese patients with previously treated advanced/metastatic NSCLC, camrelizumab demonstrated improved ORR, PFS, and OS compared with historical data of the 2nd line chemotherapy. The efficacy in patients with PD-L1 <1% is similar as the 2nd line mono-chemotherapy, while patients with higher PD-L1 expression derived greater benefit from camrelizumab, the ORR, PFS and OS in patients with PD-L1 ≥25% was comparable to the 1st line doublet chemotherapy in advanced NSCLC. Camrelizumab was well tolerated. This phase 2 data warrant further clinical studies of camrelizumab in NSCLC.

Keywords: camrelizumab, PD-L1 expression, advanced/metastatic non-small cell lung cancer

Table 1 - Efficacy data in subgroups

Population	No of pts	ORR, % (95%CI)	PFS (month), median (95%CI)	1YOS, % (95%CI)	OS (month), median (95%CI)
PD-L1<1%	74	12.2% (5.7%, 21.8%)	2.1 (1.9, 3.2)	47.1% (33.8%, 59.2%)	11.6 (7.8, NR)
PD-L1 ≥1% and < 25%	31	19.4% (7.5%, 37.5%)	3.1 (1.8, 4.9)	76.7% (57.2%, 88.2%)	NR (NR, NR)
PD-L1 ≥25% and < 50%	11	45.5% (16.7%, 76.6%)	6.0 (1.9, NR)	81.8% (44.7%, 95.1%)	NR (2.9, NR)
PD-L1 ≥50% (without EGFR mutation)	25	28.0% (12.1%, 49.4%)	7.6 (3.3, 11.4)	55.2% (32.3%, 73.2%)	NR (8.6, NR)
PD-L1 ≥50% (with EGFR mutation)	5	0	1.7 (1.2, NR)	40.0% (5.2%, 75.3%)	10.3 (1.2, NR)
ITT	146	18.5% (12.6%, 25.8%)	3.2 (2.0, 3.4)	56.6% (47.3%, 64.9%)	19.4 (11.6, NR)

Abbreviation: NR, Not Reached.

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P1.01-62 ASSOCIATION OF BASELINE PULMONARY FIBROSIS WITH THE OUTCOME OF PD-1 INHIBITOR IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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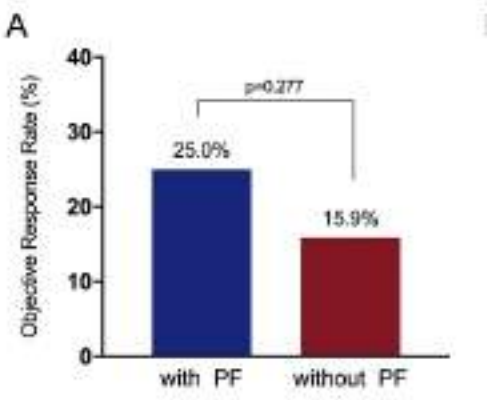
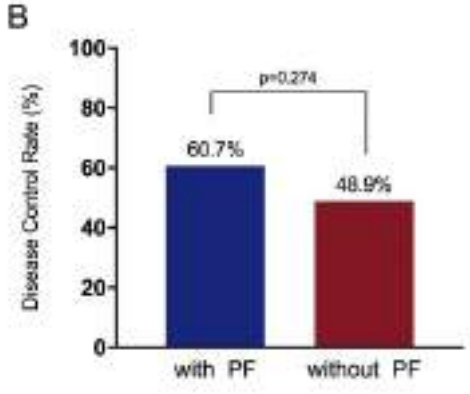
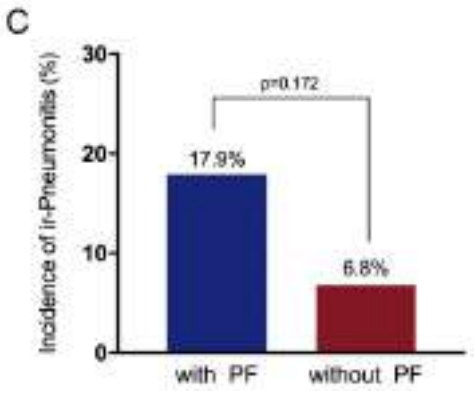
Background: PD-1/PD-L1 inhibitors have become standard care for previously treated advanced non-small cell lung cancer (NSCLC). However, not all patients are suitable for the immunotherapy. This study aimed to investigate the efficacy and safety of PD-1/PD-L1 inhibitors in patients with advanced NSCLC and pre-existing pulmonary fibrosis (PF). **Method:** Patients who had a NSCLC diagnosis, received anti-PD-1/PD-L1 monotherapy and had baseline chest HRCT screen at Shanghai Pulmonary Hospital, Tongji University were retrospectively collected from January 2016 to February 2019. The pre-existence of PF was identified by reviewing baseline chest imaging. Baseline clinicopathologic characteristics, treatment outcomes and immune-related pneumonitis were collected. **Result:** 116 patients were included with 61 age < 65. Among them, 97 (83.6%) were male, 76 (65.5%) were smoker, 51 (44%) were squamous, 61 (52.6%) received anti-PD-1 monotherapy (Pembolizumab n=62, Nivolumab n=28) as 2nd line setting, 28 (24.1%) had PF prior to PD-1 inhibitors. Baseline characteristics such as age, gender, ECOG PS, smoking history, pathology are similar between patients with or without PF. Patients with PF had a comparable response (ORR: 25% vs 15.9%, p=0.277, figure A), disease control (DCR: 60.7% vs 48.9%, p=0.274, figure B) and PFS (median 2.5 vs 2.8 months, p=0.950). The incidence of immune-related pneumonitis in the entire cohort was 9.2%, which was numerally higher in PF group (17.9% vs 6.8%, p=0.172, figure C). No death from immune-related pneumonitis occurred.







Conclusion: NSCLC patients with pre-existing PF showed comparable response to PD-1 inhibitors but a higher incidence to immune-related pneumonitis.

Keywords: NSCLC, pulmonary fibrosis, Immunotherapy

P1.01-63 IMPACT OF PRIOR RADIATION PNEUMONITIS ON INCIDENCE OF IMMUNOTHERAPY RELATED PNEUMONITIS

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Background: Patients with a history of radiation pneumonitis (RP) requiring steroids have generally been excluded from immuno-oncology (IO) trials of PD-1/PDL-1 monoclonal antibodies for safety concerns. The risk of IO-associated pneumonitis (IOP) in this group of patients (pts) is therefore unknown. We evaluated the frequency of IOP in pts who had prior RP. **Method:** We evaluated all pts with non-small cell lung carcinoma (NSCLC) treated at our institution between 2011 and 2018 who were diagnosed with RP and at a later point received IO. Demographics, tumor characteristics, steroid use and outcomes were extracted from the electronic medical record. Median overall survival (mOS), median progression free survival (mPFS), and median time to treatment failure (mTTF) from the start of IO were estimated from Kaplan-Meier curves. **Result:** We identified 29 pts: median age at diagnosis 63 yrs, 51.7% male, none had received prior targeted therapies. IO treatments were: atezolizumab (2), durvalumab (2), nivolumab (12), and pembrolizumab (13). Median time from RP diagnosis to start of IO was 14.2mo (2.2-75 mo). 23 pts (79%) had experienced prior grade ≥ 2 RP requiring steroids. Only 2 of the 29 pts (6.9%) developed IOP. Both pts had required steroids for prior RP and both received durvalumab; one pt was on prednisone ≥ 10mg at the start of IO. Both required steroid treatment of IOP, are still on IO and have not progressed (censored at 8.3mo and 9.9mo). OS and PFS after IO are similar (Table 1) whether or not pts required treatment for RP or were on prednisone ≥ 10 mg (or steroid equivalent) at the start of IO. Table 1: IO outcomes based on RP history and steroid use at start of IO

	RP Grade ≥ 2 n=23 (95% CI)	RP Grade < 2 n=6 (95% CI)	Prednisone ≥ 10mg n=7 (95% CI)	Prednisone < 10mg n=22 (95% CI)	All patients n = 29 (95% CI)
mPFS (mo)	5.44 (2.1-12.6)	12.95 (0.95-)	6.16 (2-)	5.44 (2.1-)	6.16 (2.4-)
mOS (mo)	6.6 (3.93-13.8)	NR	14.3 (5.3-)	8 (3.4-16.8)	8 (5.3-15)
mTTF[a] (mo)	2.3 (1.9-4.8)	2.3 (1.9-)	4.4 (2-)	2.3 (1.9-10.9)	2.75[a] (2-7)

[a]**n=28: 1 pt lost to follow up after start of IO**

Conclusion: In our cohort, the incidence of IOP after RP is low and similar to the rate of pneumonitis reported with pembrolizumab in pts with prior exposure to thoracic radiation.

Keywords: pneumonitis, Radiation pneumonitis, Immunotherapy

P1.01-64 PREDICTIVE VALUE OF K-RAS SUBSET MUTATIONS AND PD-L1 IN PULMONARY SARCOMATOID CARCINOMA (PSC)

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a rare malignant neoplasm that accounts for a 0.4% of non-small- cell lung carcinomas (NSCLC). It is associated with poor response to therapy. We studied clinical, genetic and molecular criteria of PSC by analyzing their KRAS, TMB, TP53 and PD-L1 status. **Method:** This is a retrospective study that included 8,469 NSCLC patients with equivalent number of samples collected prospectively. Next generation sequencing (NGS) was performed for molecular and genetic analysis of the samples.Categorical variables were reported as counts and percentages, and we used Fisher's exact test and Chi (X2) test for comparisons as appropriate. **Result:** Among the 8,469 patients there were 53 patients with pulmonary sarcomatoid carcinoma (PSC). PSC was more prevalent in males (64.2%) vs other NSCLC histopathological subtypes (49.8%) (P=0.039). PD-L1 analysis revealed 79.2% positive expression (>1%) in PCS vs 51.0% in other NSCLC histopathological subtypes (P<0.001). KRAS analysis showed that G12V was the most common mutatedKRAS codon in PSC (31.3%). Of the 53 patients with pulmonary sarcomatoid carcinoma, sixteen patients were k-ras mutant (31%). Of the 16 patients with mutant k-ras, fifteen had PD-L1 positive status (Table 1). PDL-1 was positive in 64.3% (n=27) of PSC cases with wild-type KRAS and 35.7% in mutant KRAS, P=0.087. (Table 2). KRAS MAF was higher in PSC (median 51.00 [34.50, 57.25]) vs 29.00 [19.00, 42.00] in other NSCLC histopathological subtypes (P=0.003). Using NGS, TP53 was found to be mutated in 58.8% of all NSCLC cases compared to 27.3% of the mutant k-ras where G12C was the most common subtype (39.1%). Our analysis revealed no difference in TP53 NGS, TP53 exon, TP53 MAF, KRAS NGS, KRAS codons or specimen site (P>0.05). We correlated the clinical and genetic profiles of 53 PSC patients and it was significant in the younger age population (r=-0.29, p=0.037). **Conclusion:** PSC was significant in males, younger age group with more common G12V k-ras sub-type (31.3%) compared to the G12c subtype (25%). PD-L1 expression was significantly higher in PSC (79.2%) compared to other NSCLC subtypes (51%). Table 1:showing the results for mutant KRAS subpopulation in relation to PDL122c3 expression. It also illustrates the percentage expression within each subtype of KRAS pathologic mutation:

KRAS mutation	PDL122c3 expression (n, %)		Total (n, %)
	Negative	Positive	
G12V	0 0.0	5 33.3	5 31.3
G12D	0 0.0	2 13.3	2 12.5
G12A	0 0.0	2 13.3	2 12.5
G12C	1 100.0	3 20.0	4 25.0
G12S	0 0.0	2 13.3	2 12.5
9.0	0 0.0	1 6.7	1 6.3
Total (n, %)	1 100.0	15 100.0	16 100.0

N= number

Keyword: Sarcomatoid, PD-L1, K-ras, NSCLC

P1.01-65 IMMUNE GENE EXPRESSION, BAYESIAN NETWORK AND GENETIC MUTATION ANALYSIS IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Immune checkpoint inhibitors (ICIs) have dramatically revoluzionized the therapeutic paradigm for NSCLC, but only a small subset of patients achieves durable benefit. The only adopted predictive biomarker, PD-L1 IHC testing, suffers from some limitations. A better understanding of biomarkers associated with response to ICIs is needed. Here, we studied immune gene-expression and genetic mutation profiles and association with clinical response to immunotherapy in advanced NSCLC patients treated with ICI. **Method:** A total of 37 Formalin-fixed, paraffin-embedded (FFPE) samples from advanced NSCLCs were analyzed by RNA-Seq using the Oncomine Immuno Response Assay (OIRRA) (ThermoFisher Scientific) on Ion Torrent PGM and Transcriptome Analysis Console (TAC) 4.0 Software. This panel measures the expression level of 395 genes associated with 36 functional groups including checkpoint pathways, lymphocyte regulation and cytokine interactions. Gene network analysis based on Bayesian algorithm was performed by GeneMANIA database querying with the genes selected through mRNA expression analysis. Cancer somatic mutation analysis were performed using Ion NGS Panel on PGM Instrument. **Result:** Among 37 FFPE samples only 18 showed more than 300 OIRRA detectable target genes. In this subgroup, gene expression analysis revealed 7 genes (CCR2, CRTAM, FASLG, SELL, TIGIT, TNFRSF4, and TP63) up-regulated and one gene (CXCL8) down-regulated (p-value < 0.05) in ICI-responders compare to ICI-no responders. Bayesian enrichment computational analysis of eight gene expression signature showed a more complex network which involves other 10 genes (SIRPG, GZMK, XCL2, CD8A, CD2, IFNG, SIT1, TAGAP, PTPRC and GZMH), correlated with different functional groups. Three main immune-pathways were identified (p < 0.01) (T cell activation, leucocyte activation and migration) involving TIGIT, TNFRSF4, CCR2 and CXCL8 genes among the gene expression signature identified. Gene mutational analysis was feasible for 28 samples. *KRAS* mutation was detected in 41% of ICI-responders respect to 12.5% of ICI-no responders. Conversely, no *STK11* mutation was found in ICI-responders, consistent with previous reports. **Conclusion:** Our results revealed an immune response gene expression signature of 8 genes differentially expressed between ICI and ICI-no responders. Cancer systems biology analysis approach strengthen our findings identifying an immune molecular network and confirm the correlation of the gene expression signature with relevant immune regulatory functions. If validated, our results may have an important role for the development of a robust test to select patients properly and predict immune response to enable precision immunotherapy. Furthermore, TMB assessment in such subset of patients is under investigation and more data will be available for the meeting.

Keywords: Immune gene expression profile, advanced NSCLC, Immunotherapy

P1.01-66 A CT-BASED RADIOMICS APPROACH TO PREDICT PD1 INHIBITOR RESPONSE IN NON-SMALL-CELL LUNG CANCER

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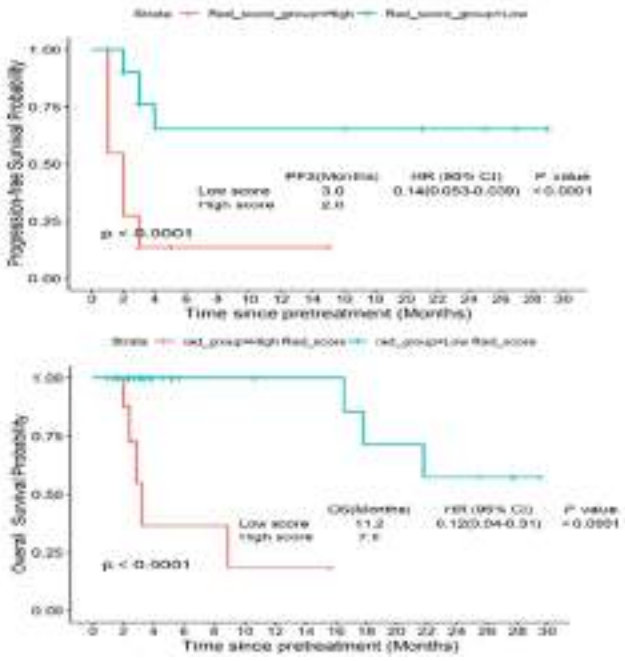
Background: The purpose of this study was to investigate the use of radiomics features as predictive parameters of clinical outcomes of non-small-cell lung cancer (NSCLC) patients treated with PD1 inhibitor. **Method:** Forty-three stage IIIB/IV NSCLC patients without EGFR mutation or ALK rearrangement who received nivolumab were enrolled between Apr 2016 and Jan 2019. High-dimensional quantitative feature analysis via Pyradiomics was applied to extract 852 radiomics features of pre-anti-PD1 treatment CT. A radiomic score model was constructed from these features with the use

of least absolute shrinkage and selection operator (LASSO) Cox regression. The radiomic score for each patient was computed using an equation in which the coefficients were derived from the LASSO Cox model to subgroup patients by progression-free survival (PFS). The median value of radiomic score was used as the cut-off value to cluster patients into high or low score groups. **Result:** We developed a radiomic signature for PFS that included seven variables. The median value of radiomic score was 0.23. The objective response rate (ORR) was 16.3% (7/43), the median PFS was 2 months and median overall survival (OS) was 3.2 months of all 43 patients. A low radiomic score was associated with a higher ORR (33.7% vs 0%, p= 0.0036), improved PFS (median: 3 months vs 2 months; HR 0.14, 95% CI 0.053-0.39, P<0.0001) and longer OS (median: 11.2 months vs 7.0 months; HR 0.12, 95%CI 0.04-0.31, p < 0.0001). Multivariate analysis also showed that a low radiomic score was related to better PFS (HR 0.12, 95% CI 0.041-0.32, P<0.0001) and OS (HR 0.11, 95%CI 0.03-0.28, p < 0.0001).



Conclusion: The radiomic signature as an imaging predictor provided a promising way to predict clinical outcomes for NSCLC patients treated with PD-1 inhibitor.

Keywords: Non small cell lung cancer, PD1 inhibitor, CT-based radiomics approach

P1.01-67 PH I/II CARBOPLATIN, NAB-PACLITAXEL AND PEMBROLIZUMAB FOR ADVANCED NSCLC (HCRN LUN13-175): OUTCOMES BY NAB-PACLITAXEL DOSE

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Background: Combination chemotherapy and immunotherapy have significantly improved survival for patients with treatment-naïve advanced non-small cell lung cancer (NSCLC). We sought to evaluate the safety and efficacy of adding pembrolizumab to a standard regimen at the time of study development, *nab*-paclitaxel and carboplatin. Safety data from phase I have been reported, and phase II commenced with the same chemotherapy doses and flat dosing of pembrolizumab at 200 mg. **Method:** Patients with treatment-naïve, stage IIIB/IV NSCLC AJCC 7 (all histology), any PDL1, no EGFR or ALK, ECOG 0-1, received carboplatin AUC 6 day 1, *nab*-paclitaxel 100 mg/m2 days 1, 8, 15, and pembrolizumab 200 mg day 1 q21 days for 4 cycles followed by maintenance pembrolizumab q3wks. Co-primary endpoints were progression-free survival (PFS) and response rate (RR). PDL1 was assessed prior to treatment and from biopsies obtained after cycle 4. **Result:** 46 patients enrolled, 14 on phase I and 32 in phase II, from June 2015–July 2018. Accrual stopped after data was presented from similar phase III trials. 43 were evaluable for the primary endpoints. Median age was 65 years, 48% female, 45% adenocarcinoma, 94% current/former smokers, 9% brain metastases. PDL1 expression (TPS) by <1%, 1-49%, and ≥ 50% cutoffs was 44%, 28%, and 28%, respectively. ORR was 28%. Median PFS was 5.6 months (CI, 4.2-10.5 mo). Median OS was 15.7 mo (CI 11.1-22.3 mo). There was no statistical differences in PFS or OS outcomes by PDL1 status. Paired PDL1 results from pre- and post-treatment biopsies were available in 8 patients. PDL1 status changed categories in 4/8 samples (n=3, 0% to positive; n=1, 99% to 0%). The most common grade 3-4 adverse events (AEs) were neutropenia (64%), anemia (31%), thrombocytopenia (24%), leukopenia (16%) and fatigue (11%). Other notable AEs included rash (58%), diarrhea (47%), neuropathy (22%), arthralgia (18%), transaminitis (13%), and myalgia (11%). 18% discontinued treatment due to AEs. In an exploratory analysis, there was no difference in median PFS for those receiving total *nab*-paclitaxel dose of 400–799 mg/m2 compared to ≥800 mg/m2 (6.2 mo vs. 8.2 mo, p=0.62). **Conclusion:** Although the study did not meet its pre-specified endpoints of PFS 9 months and RR of 50%, results were similar to previously reported phase III Keynote 407 (squamous histology). Despite hematologic toxicity, the combination could safely be administered, and outcomes were similar for those receiving moderate doses of *nab*-paclitaxel compared to those with an average of at least 200 mg/m2 per cycle.

Keywords: NSCLC, Pembrolizumab, nab-Paclitaxel

P1.01-68 MONITORING CLINICAL RESPONSES MEASURING PD-L1 IN CFRNA IN PLASMA OF NON-SMALL CELL LUNG CANCER PATIENTS UNDERGOING SYSTEMIC THERAPY

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Background: .Cell-free circulating tumor RNA (cfRNA) extracted from plasma of cancer patients (pts) can measure dynamic changes in gene expression that can help to evaluated disease status and predict outcome to anti-tumoral therapy in solid tumors [T. Ishiba et al. Biochem Biophys Res Commun. 2018 Jun 7; 500 (3):621-625]. We want to show that PD-L1 assessed by RNA RT-PCR is a potential biomarker that can be used to follow Immunotherapy responses in non-small cell lung cancer (NSCLC). **Method:** 54 pts with NSCLC undergoing systemic therapy (STX) were enrolled in a 1-year study. cfRNA was extracted from resulting plasma and generated random-primed cDNA. Total cfRNA was quantitated by qPCR of β-actin, and correlated with pt response (CR/PR/SD/PD) determined by CT scans. All gene expressions were measured relative to β-actin. Changes in PD-L1 expression were used to monitor response to immunotherapy in lung cancer pts. Ten milliliters of blood were collected in each of two tubes containing a proprietary nucleic acid preservation cocktail. Blood was drawn every 6-8 weeks with an average of 5 collections were done per pt. **Result:** Of the 54 enrolled pts, 30 completed 1-3 lines of STX with outcomes. The overall mutation frequency was 33% (10/30), with 27% in KRAS and 6% in EGFR. Increases or emergence of mutant allele fractions were predictive of PD status (later determined by imaging), while decreases or disappearance of mutations were predictive of SD and PR status after treatment. PD-L1 expression was detected in 87% (26/30) of pts in at least one blood draw. Immunotherapy: (Nivolumab, Pembrolizumab, Atezolizumab), 11/30 pts underwent immunotherapy (IO) txt at some point. Changes in PD-L1 during IO were associated with STX outcomes. Increases in PD-L1 were associated with PD, while decreases or no changes in PD-L1 were associated with SD and PR. Of the 23 blood draws from these 11 pts, the overall concordance between changes in PD-L1 and IO outcome was 91% (21/23). Chemotherapy: 19/30 pts were given carbo/pemetrexed at some point during their STX. Increases or decreases in PD-L1 across 28 blood draws during therapy were likewise associated with resistance or sensitivity to STX outcome (increases infer resistance; decreases infer sensitivity) in 24/28 (86%). **Conclusion:** A noteworthy concordance was observed

between clinical responses and changes in plasma PD-L1 done by RT-PCR cfRNA levels in NSCLC pts treated with IO or chemotherapy. Monitoring cfRNA expression levels of PD-L1 is a reliable method for predicting response and resistance to IO as well as chemotherapy irrespective of KRAS and EGFR

Keywords: RNA, Immunotherapy, liquid biopsies

P1.01-69 BLOOD SERUM AMYLOID A AS POTENTIAL PREDICTOR OF RESPONSE TO FIRST-LINE PEMBROLIZUMAB IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: The selection of patients (pts) deriving clinical benefit from immune checkpoint agents represents the modern challenge for clinicians. Tumor-derived Serum Amyloid A (SAA) inhibits the immune response through the expansion of IL-10-secreting neutrophils in pts with melanoma. We investigated the predictive value of blood SAA monitoring in a cohort of Advanced Non-Small-Cell Lung Cancer (ANSCLC) pts receiving up-front Pembrolizumab (P). **Method:** Pts with ANSCLC (PD-L1≥50%) receiving upfront P, were prospectively evaluated for blood SAA and radiological response at baseline and every 9 weeks during the treatment. The primary endpoint was response rate (RR) according Immune-related Response Evaluation Criteria in Solid Tumors (IrRECIST); the secondary endpoints were progression-free survival (PFS) and overall survival (OS). The most accurate SAA cut-off to predict response was established with a ROC-analysis. **Result:** Forty-two patients were enrolled. Pts characteristics: male/female (71/29%), number of sites 1/2/3/≥ 4 (5/38/40/17%), ECOG PS 0/≥ 1 (38/62%); never or former/current smokers (12/78%); median age 70.5 (range 35-86) years. The overall RR was 38% (95%CI 25-53%). After a median follow-up of 13.5 months (m), baseline SAA ≤ the ROC-derived cut-off (29.9 mg/L, AUC 0.74, 95% CI 0.59-0.87, *p=0.002*; 14 [33%] pts) was significantly associated with a higher RR *(*53.6vs 7.1%, OR 15, 95% CI 1.72-130.7*, p<0.01),* longer PFS (17.4 vs 2.1 m, HR 0.18, 95%CI 0.06-0.51*, p<0.0001)* and OS *(*not reached [NR]vs7.2 m, HR 0.08, 95%CI 0.02-0.39*, p<0.0001)* compared with SAA >29.9 mg/L. Multivariate analysis confirmed pre-treatment low SAA as independent predictor of longer PFS (*p=0.029*) and OS (*p=0.018*). Considering SAA at baseline and the dynamic monitoring (pts=40), the median PFS was 17.4 m (95% CI 10.7-14.7) when SAA remained low (n=14) compared with 2.1 m (95%CI 1.3-5.6) when SAA remained high (n=12) (*p<0.0001).*The SAA monitoring was also significantly associated with OS (*p=0.0002*), with a median OS of 7.2 m (95% CI 5.6-13.4) in pts maintaining high SAA versus NR median at 18-m for pts with SAA remained low or changed. No deaths occurred in the permanently low-SAA group at the current data-lock. **Conclusion:** Baseline low SAA predicts good outcomes of 1stline P and the SAA monitoring throught simple blood test could help to easily identify patients who derived the greatest benefit from immunotherapy. The strong relationship with RR and the known immunosuppressive activity support a potential predictive value of this serum marker. A multi-institutional validation set is currently ongoing to confirm the role of SAA in this setting.

Keywords: NSCLC, Pembrolizumab, predictive factor

P1.01-70 DOMINANT CIRCULATING MYELOID POPULATIONS ARE ASSOCIATED WITH POOR RESPONSE IN NSCLC TREATED WITH 1ST LINE PD-1 MONOTHERAPY

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Background: Immune subpopulations within the tumor microenvironment (TME) play a central role in determining response to checkpoint inhibitors. Myeloid derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells, have a predominantly immunosuppressive role by stimulating T regulatory cells. We hypothesize that elevated myeloid-to-lymphocyte measures in the peripheral blood predict for greater numbers of myeloid derived suppressor cells in the TME and worse outcomes. **Method:** We identified all advanced NSCLC patients treated with immunotherapy between 2010-2019 at the Princess Margaret Cancer Center. Patients who received first line monotherapy with a PD-1 inhibitor were reviewed for clinical information including age, sex, histology, stage, smoking status, ethnicity, PD-L1 expression and tumor genotype. Myeloid cells lines analyzed included neutrophils, monocytes and platelets, expressed as ratios to peripheral lymphocytes. Multivariate analyses were conducted using the cox and logistic regression models to adjust for confounders. **Result:** We identified 75 patients who were eligible for analysis. Disproportionate increases in the different myeloid cell types were highly correlated with each other (all Pearson's rho>0.8) and the neutrophil to lymphocyte ratio (NLR) was selected as representative. A high NLR (>5) was associated with shorter time-to-treatment-failure (median TTF 9.7 vs 29.4 months) that remained significant after adjusting for confounders including PD-L1 and presence of liver metastases (p=0.004). High NLR was also an independent predictor of poor OS (median 11.3 vs 56.8 months, HR 3.02, p=0.04). Although NLR was not predictive of radiographic response, there was a trend to association with a rapidly progressive phenotype defined by primary progressive disease and a duration of therapy ≤2 months (p=0.06). Other predictive factors included the presence of liver metastases, which was associated with a worse OS (HR3.37 p=0.05) but not TTF (p=0.14). An association was also seen between NLR and liver metastases (mean NLR 6.6 vs 25.2 in the absence and presence of liver metastases respectively, p<0.001). **Conclusion:** A disproportionate increase in peripheral immune myeloid populations may represent a systemic, myeloid-driven, immunosuppressive state that is significantly associated with primary refractory disease, rapid progression, and poor survival. A subset of about 50 patients with biobanked tissue are presently being analyzed using multiplex immunofluorescence to assess for MDSCs in the TME to correlate with peripheral blood findings.

Keywords: advanced NSCLC, myeloid immunosuppression, Checkpoint inhibitors

P1.01-71 BONE METASTASES AND SKELETAL-RELATED EVENTS IN PATIENTS WITH METASTATIC NSCLC TREATED WITH ICIS: A MULTI-INSTITUTIONAL STUDY

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Background: Skeletal-related events (SRE) occur frequently in patients (pts) with metastatic NSCLC (mNSCLC) and confer a poor prognosis. Data on SRE and the effects of bone modifying agents (BMA) in NSCLC pts treated with immune checkpoint inhibitors (ICI) are limited as is the effect of bone modifying agents (BMA) on development of SRE and overall survival (OS). Here we report the incidence, impact on survival, and risk factors for SRE in pts with mNSCLC treated with ICI in a multi-institutional cohort. **Method:** We conducted a retrospective study of pts with mNSCLC treated with ICI at our institutions from 2014 to 2017. Overall survival (OS) was calculated from the date of ICI initiation to death from any cause or last follow-up. Cox regression model was used to study the

association between OS and baseline bone metastases (BM). The associations between SRE and categorical outcomes were studied using chi-square/Fisher's exact test. The study was approved by each institution's ethics review board. **Result:**

Table 1. Multivariate survival analysis.

Parameter	Level	Hazard Ratio	95% HR Confidence Limits	P-value
BM at baseline	Absent	Ref		<0.0001
	Present	1.847	1.414-2.413	
ECOG	0	Ref		0.0006
	1	1.494	1.017-2.196	
	2	1.506	0.969-2.341	
	3	3.788	1.442-9.949	
Histology	Adenocarci-noma	Ref		0.969
	Squamous	1.057	0.786-1.420	
Lines of Therapy	1	Ref		0.0007
	2	1.580	1.123-2.223	
	>=3	2.064	1.417-3.005	

We identified a cohort of 330 pts: 259 (72%) treated in second line or beyond; 211 (64%) received nivolumab; median age 63.4; median OS 10.4 mo (95% CI: 8.6, 12.5). In our cohort, 124 (38%) pts had BM at time of ICI, and 43 (13%) developed SRE after ICI (median 2.8 months; 19 pathologic fractures, 1 cord compression, 26 palliative radiation, 8 surgery). Patients with BM at ICI had shorter OS after controlling for ECOG, histology, and line of therapy (Table 1; Hazard Ratio 1.847; 95% CI 1.414 - 2.413; p <0.0001) compared to pts without baseline BM. Development of SRE was associated with presence of BM at baseline but not age, histology, or mutation status (EGFR, KRAS, and TP53). The use of BMA was not associated with OS or decreased risk of SRE. The development of new or progression of existing BM (22% of pts) during ICI was associated with a worse prognosis (mOS 7.1 vs 11.6 mo, p=0.017). **Conclusion:** Bone metastases and SRE are a significant cause of morbidity in pts with mNSCLC treated with ICI. The presence of BM at baseline was associated with a worse prognosis after controlling for multiple clinical characteristics. In our cohort, the use of BMA was not associated with decreased risk of developing SRE, osseous progression, or survival.

Keywords: Skeletal related events, Immune Checkpoint Inhibitors, metastatic NSCLC

P1.01-72 A PHASE II STUDY OF SELECTIVE AXL INHIBITOR BEMCENTINIB AND PEMBROLIZUMAB IN PATIENTS WITH NSCLC REFRACTORY TO ANTI-PD(L)1

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Background: The RTK AXL is implicated in epithelial-to-mesenchymal transition, negative regulation of anti-tumour immunity and resistance to multiple therapies including immune checkpoint inhibitors. Bemcentinib (BGB324) is a first-in-class, oral, highly selective and potent AXL inhibitor which has been demonstrated to enhance anti-PD1 therapy. The combination of bemcentinib and pembrolizumab was well tolerated and showed promising efficacy in previously treated IO-naïve NSCLC patients (Cohort A, NCT03184571), particularly in those with AXL positive disease, including PD-L1 negative patients. The novel combination is now being assessed in patients refractory to anti-PD-(L)1 therapy, considering the emerging need in this population and AXL's role as a mediator of resistance. **Method:** This is an open-label, single-arm, 2-stage phase II study (Cohort B, NCT03184571) to evaluate the safety and efficacy of bemcentinib (200mg/d) in combination with pembrolizumab (200mg/q3wk) in patients post anti-PD-(L)1 therapy. The primary endpoint is overall response rate (ORR), and additional endpoints include efficacy by biomarker expression, duration of response (DoR), disease control rate (DCR), progression free survival (PFS), overall survival (OS), and safety. Clinical efficacy endpoints are based on tumour imaging evaluable by RECIST v1.1. Eligible patients received a maximum of 2 prior lines of therapy, with the most recent course having included a PD-(L)1 inhibitor. To be eligible, patients must have exhibited disease control (CR/PR/SD) for at least 6 months on prior PD-(L)1 inhibitor therapy with disease progression occurring within 12 weeks since last dose. Bemcentinib will be administered as a loading dose of 400mg on days 1, 2 and 3 followed by a dose of 200mg once daily. A fixed dose of 200 mg pembrolizumab will be given by intravenous infusion over 30 minutes every 3 weeks. Bemcentinib and pembrolizumab will be given until disease progression, unacceptable dose toxicity, or for a maximum of 35 cycles. Tumour specimens will be analysed for PD-L1 expression (22C3 pharmDx), AXL by IHC, and infiltrating immune cells. The pre-specified efficacy threshold for continuation into the second stage is 1 objective response among the first 13 patients, at which point up to a further 16 patients may be evaluated, for a total of 29 patients. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: bemcentinib, Pembrolizumab, AXL

P1.01-73 AN EXPLORATIVE ANALYSIS OF PEMETREXED +/- PEMBROLIZUMAB MAINTENANCE FROM KEYNOTE-189 VERSUS PARAMOUNT, PRONOUNCE, AND JVBL

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Background: Recently, the phase 3 KEYNOTE-189 study demonstrated improved progression-free survival (PFS) and overall survival (OS) when pemetrexed/platinum doublet was combined with pembrolizumab as first-line treatment in patients with non-squamous NSCLC. The specific benefits of maintaining pemetrexed in combination with pembrolizumab after the triplet with platinum has not been previously assessed. **Method:** Using patient level data, we selected patients who had ≥5 cycles of pemetrexed (including the induction phase with platinum) from 3 randomized non-pembrolizumab clinical trials (PARAMOUNT, PRONOUNCE, and JVBL; N=486). As such, patients in the KEYNOTE-189 trial who had ≥5 cycles of pemetrexed in both arms (placebo arm; N=135, versus pembrolizumab arm; N=310) were analyzed. PFS and OS were evaluated by Kaplan-Meier estimator and Cox proportional hazard model; treatment emergent adverse events (TEAEs) were compared by descriptive statistics. **Result:** Baseline characteristics of the selected population with ≥5 cycles of pemetrexed were comparable between the pooled trials and KEYNOTE-189. Median PFS for patients with ≥5 cycles of pemetrexed was 5.6 months (95% CI: 4.6-5.8) from the pooled non-pembrolizumab trials and 6.6 months (95% CI: 5.4-7.1) in the placebo plus pemetrexed/platinum arm in KEYNOTE-189 (un-stratified HR: 1.29; 95% CI: 1.02-1.62). Median PFS in the selected population with ≥5 cycles of pemetrexed in KEYNOTE-189 was 9.3 months (95% CI: 9.0-11.1) in the pembrolizumab plus pemetrexed/platinum arm, and when compared with the

placebo plus pemetrexed/platinum arm in KEYNOTE-189, resulted in an un-stratified HR of 0.53 (95% CI: 0.42-0.68). Incidence rates of TEAEs were similar in those 3 selected populations (Table 1).

Table 1. PFS and TEAE Grade 3-5 in patients with pemetrexed treatment ≥5 cycles: descriptive comparison between the pooled data (PARAMOUNT, PRONOUNCE, JVBL) and KEYNOTE-189 trial

	Pooled historical data Pemetrexed ≥5 cycles (N = 486)	KEYNOTE-189	
		Placebo Arm Pemetrexed ≥5 cycles (N = 135)	Pembrolizumab Arm Pemetrexed ≥5 cycles (N = 310)
Median PFS, months (95% CI)	5.6 (4.6-5.8)	6.6 (5.4-7.1)	9.3 (9.0-11.1)
TEAE Grade 3-5, n (%)	284 (58.4)	86 (63.7)	200 (64.5)

CI, confidence interval; PFS, progression-free survival; TEAE, treatment emergent adverse event

Conclusion: In a selected population with pemetrexed maintenance in KEYNOTE-189, the placebo arm showed numerically comparable efficacy with historical data on pemetrexed maintenance. Pemetrexed/platinum in combination with pembrolizumab proved consistent clinical benefit in the same population with ≥5 cycles of pemetrexed, compared to the placebo arm in KEYNOTE-189 and historical controls.

Keywords: NSCLC, Pembrolizumab, pemetrexed

P1.01-74 A RETROSPECTIVE STUDY EVALUATING CLINICAL PREDICTORS OF DURATION OF RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NSCLC

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Background: Immune Checkpoint Inhibitors (ICI) with/without chemotherapy have become the standard of care for the treatment of advanced/metastatic non-small cell lung cancer (NSCLC). Similar to the response rate, durability of response to ICI is quite variable. While PDL1 expression and Tumor Mutational Burden (TMB) have been described to predict response to ICI, little is known about the clinical predictors of duration of response (DoR). **Method:** A retrospective chart review of patients (pts) with advanced NSCLC treated with ICI based therapy at Karmanos Cancer Institute was conducted. Data were collected on demographics, clinical characteristics, and tumor characteristics. Univariable and multivariable cox regression analyses were performed for six pre-chosen covariates (histology, prior radiation therapy, brain metastasis, occurrence of immune-related adverse events (irAEs), statin use and smoking status) to see the associations with the DoR to ICI. **Result:** One hundred thirty-one pts were included in the analysis (68% adenocarcinoma, 60% received prior radiation, 20% had brain metastasis, 26% developed irAEs, 33% were on a statin, 69% former smokers, 12% current smokers and 19% never smokers). Overall median DoR was 149 days (range, 14-1934). On multivariable analysis, longer DoR to ICI was observed in pts with non-adenocarcinoma histology (HR: 0.65; p = 0.050; CI: 0.42-1.00, median DoR 242.5 days) and current smokers (HR: 0.53; p = 0.031; CI: 0.30-0.95, median DoR 206.5 days). Other variables, including the presence of brain metastasis, prior radiation therapy, occurrence of irAEs and statin use had no significant relationship with the DoR. **Conclusion:** Tumor histology and smoking status were statistically and clinically significant predictors of durability of response to ICI in advanced NSCLC, presumably secondary to higher TMB. Presence of brain metastasis did not adversely impact DoR to ICI.

Keywords: NSCLC, Clinical Predictors, Immune Checkpoint Inhibitors

P1.01-75 PROGNOSTIC IMPACT OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Recently, the neutrophil-lymphocyte ratio (NLR) has been attracting attention as a prognostic factor for advanced non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs). However, other chemotherapies have not been well reviewed about the usefulness of NLR. Therefore, we retrospectively examined whether NLR at the start of first-line chemotherapy, including cytotoxic anticancer drugs and molecular-targeted drugs, could be a useful biomarker for overall survival (OS). **Method:** We examined advanced NSCLC patients, including recurrent cases after surgery or radiotherapy, who received first-line chemotherapy at our institution between 2008-2018. Patients were divided into two groups according to gene expression (EGFR/ALK mutant type [mt] and wild type [wt]) to differentiate the therapeutic effects of first-line chemotherapies. Furthermore, only patients treated with molecular-targeted drugs as first-line therapy were included in the mt group, whereas only patients treated with cytotoxic anticancer drugs as first-line therapy were included in the wt group. Blood test to measure NLR was performed within 3 days prior to the initiation of first-line chemotherapy. According to the levels of NLR (NLR < 5 or NLR ≥ 5), OS curves between NLR-low and NLR-high subgroups were compared using log-rank test in the mt and wt groups, respectively. To evaluate the prognostic impact of NLR, background factors such as age, sex, performance status, smoking history, clinical stage, and LDH were adjusted using multivariate Cox proportional hazards model analysis. **Result:** 1113 cases were reviewed, 276 cases of which met the eligibility criteria, including 90 cases (32.6%) in the mt group and 186 cases (67.4%) in the wt group. In the mt group, median survival times (MSTs) of NLR-low and NLR-high subgroups were 37.2 months and 18.1 months, respectively (p < 0.001). Similarly, in the wt group, MSTs of NLR-low and NLR-high subgroups were 16.2 months and 6.3 months, respectively (p < 0.001). On the other hand, significantly independent factors for worse OS in the mt group were NLR-high (hazard ratio [HR]; 3.54, 95% confidence interval [CI]; 1.96 to 6.38, p < 0.001), LDH-high (HR; 2.31, 95% CI; 1.30 to 4.11, p = 0.004), and poor performance status (HR; 3.58, 95% CI; 1.98 to 6.48, p < 0.001). Similarly, significantly independent factors for worse OS in the wt group were NLR-high (HR; 2.10, 95% CI; 1.40 to 3.14, p < 0.001), LDH-high (HR; 1.57, 95% CI; 1.11 to 2.22, p = 0.009), and poor performance status (HR; 2.17, 95% CI; 1.48 to 3.20, p < 0.001). **Conclusion:** The low levels of NLR at the start of first-line chemotherapy might be associated with better OS regardless of the types of anticancer drugs.

Keywords: Neutrophil-to-Lymphocyte Ratio (NLR), Chemotherapy, Non Small Cell Lung Cancer (NSCLC)

P1.01-76 RANDOMIZED PHASE II STUDY OF IMMUNOTHERAPY WITH OR WITHOUT LOW DOSE CHEMOTHERAPY FOR PATIENTS WITH PERFORMANCE STATUS OF 2

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Background: Combination chemo-immunotherapy has become a standard of care for patients with non-small cell lung cancer (NSCLC) who have performance status (PS) of 0-1. Limited information is available regarding optimal immunotherapy treatment options for patients with PS 2. In the current study, we examined the clinical and immunologic effects of immunotherapy alone or in combination with low dose carboplatin and paclitaxel as a potential treatment option for the PS 2 population. **Method:** This randomized phase II study will enroll 40 patients total with 1:1 randomization to pembrolizumab 200 mg day 1 every 3 weeks or pembrolizumab 200 mg day 1 with carboplatin AUC 1 and paclitaxel 25 mg/m2 days 1, 8, and 15 every 3 weeks. At the time abstract preparation, 36 evaluable patients have been enrolled with 28 patients having completed response evaluation. Blood for circulating immune cell phenotyping, soluble program death ligand 1 (sPDL1), and immune-modulatory miRs was collected prior to treatment and at weeks 4 and 7. Investigator assessed irRECIST responses were examined at week 8 and every 12 weeks thereafter. **Result:** Responses have been observed in 6 out of 16 patients (38%) in the control arm and 7 out of 12 patients (58%) in the experimental arm. Treatment related adverse events have been similar between the two arms with increases in infusion reactions in patients receiving low-dose carboplatin and paclitaxel. Interim biomarker analyses indicate circulating myeloid derived suppressor cells numbers decreased in patients receiving pembrolizumab combined with carboplatin and paclitaxel but not in patients receiving pembrolizumab alone. Accrual is expected to complete soon with updated response rates and progression free survival are anticipated to be mature and will be presented at the time of the

meeting. **Conclusion:** The combination of pembrolizumab with low-dose weekly carboplatin and paclitaxel is well-tolerated and active in the PS 2 population. Comparison of this regimen to pembrolizumab alone will be performed once data have matured.

Keywords: performance status 2, Pembrolizumab

P1.01-77 IMPACT OF ORAL DRUGS ON THE PROGNOSIS OF NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH NIVOLUMAB

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Background: Nivolumab (Nivo) has shown promising effects in patients with non-small-cell lung cancer (NSCLC) as a second- or later-line treatment. However, some drugs are reported to influence the efficacy of immune checkpoint inhibitors (ICIs). For example, steroids are related with worth prognosis treated with ICIs. On the other hands, opioids have direct and indirect effects on anti-tumor immunity. The aim of this study is to disclose the impact of oral drugs in patients harboring NSCLC treated with Nivo. **Method:** In this study, data for 201 patients treated with Nivo during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We collected clinical data including age, sex, smoking history, performance status (PS) score, body mass index (BMI), histological types, tumor proportion score (TPS) of program death-ligand1 (PD-L1), epidermal growth factor receptor (EGFR) mutation status, number of previous treatments, steroid use, opioid use, statin use, biguanide use and fibrates use at the time of Nivo treatment commencement. We investigated relationship between progression free survival (PFS), overall survival (OS) and drug use at the time of Nivo treatment. Patients were followed-up for disease status until October 2017. **Result:** The median age at the time of administration Nivo was 68 years, 135 patients were male, 157 patients had smoking history, 152 patients had a PS score of 0–1, median BMI was 21.4kg/m^2, 42 patients had squamous cell carcinoma, 24 patients had PD-L1 TPS 50 or over, 37 patients had positive EGFR mutation, 78 patients received 3 or more treatments before Nivo treatment, 23 patients received steroids, 33 patients received opioids, 12 patients received statin, 6 patients received biguanide and 2 patients received fibrates. In the multivariate analysis including above factors, steroid use was significantly associated with poor PFS (hazard ratio [HR]: 2.17; 95% confidence interval (CI): 1.31–3.43; p = 0.003) and OS (HR: 2.10; 95% CI: 1.18–3.58; p = 0.014). Moreover, opioid use was significantly associated with poor OS (HR: 1.87; 95% CI: 1.11–3.08; p = 0.020). **Conclusion:** Steroid use at baseline was significantly associated with worse PFS and OS. Furthermore, opioid use at baseline was significantly associated with worse OS.

Keywords: immune checkpoint inhibitor, opioid, Steroid

P1.01-78 TREATMENT-RELATED ADVERSE EVENTS IN PATIENTS WITH ADVANCED NSCLC TREATED WITH FIRST-LINE ATEZOLIZUMAB CHEMOIMMUNOTHERAPY

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Background: Non-small cell lung cancer (NSCLC) accounts for majority of lung cancer, the leading cause of cancer-related mortality in both sexes. Atezolizumab, an anti- programmed death ligand 1 (PDL-1) antibody, has shown significant antitumor activity against NSCLC. Atezolizumab in combination with chemotherapy as a first-line treatment of advanced NSCLC have shown to improve survival in recent studies. Yet, there are notable adverse events. We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of treatment-related adverse events (TRAE) and treatment discontinuation due to TRAE. **Method:** We performed a comprehensive literature search using PUBMED, MEDLINE, EMBASE databases and various meeting abstracts from inception through March 2019. RCTs utilizing first-line atezolizumab combination regimen in patients with advanced NSCLC were incorporated in the analysis. The primary meta- analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q-statistic. **Result:** 4 RCTs (IMpower – 130, 131, 132 and 150) including 2725 patients with advanced NSCLC were included in the meta-analysis. The study arm used standard chemotherapy regimens in combination with atezolizumab while control arm utilized only standard chemotherapy regimens. The randomization ratio was 2:1 in IMpower130 study and 2:1 in other studies. The I^2 statistic for heterogeneity was 0, suggesting homogeneity among RCTs. All-grade TRAE incidence was 94.5% in study group vs 91.8% in control group (RR, 1.03; 95% CI: 0.99 – 1.06, P = 0. 01). High-grade TRAE was 12.94% higher in study arm compared to control arm (RR, 1.22; 95% CI: 1.14 – 1.30, P < 0.0001). Treatment-related deaths were reported in 34 (2.28%) in study arm vs 20 (1.62%) in control arm. The pooled RR was 1.45 (95% CI: 0.82 –2.54, P = 0.20) and RD was 0.01 (95% CI: - 0.00 – 0.02, P = 0.08). Treatment discontinuation due to TRAE was noted in 419 (28.10%) vs 255 (20.66%) in control group with RR of 1.36 (95% CI: 1.19 –1.56, P < 0.0001) and RD of 0.08 (95% CI: - 0.04 – 0.11, P < 0.0001). **Conclusion:** High-grade treatment-related adverse events were increased in front-line atezolizumab chemoimmunotherapy regimen and patients on the study arm experienced significant drop outs due to TRAE, despite showing survival benefits in studies. Good supportive care may enhance patients' quality of life and compliance.

Keyword: atezolizumab meta-analysis immunotherapy

P1.01-79 G8 SCREENING SCORES IN ELDERLY ADVANCED LUNG CANCER PATIENTS: A PROSPECTIVE SINGLE INSTITUTION STUDY

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Background: Standard evaluation of elderly patients based on ECOG performance status (PS) may lead to excessive toxicity or undertreatment and loss of efficacy. We used the G8 score classification to assess the correlations between G8 scores, treatment decisions and clinical outcomes. **Method:** Elderly patients (≥ 70 years old) with advanced lung cancer treated at the Royal Marsden hospital between July 2016 and July 2018 were prospectively assessed by standard clinical methods and the G8 questionnaire. The G8 score did not influence the physician decision. Total G8 scores were < 11 low score, 11-14 intermediate group, and > 14 as the high score group. We correlated treatment decisions, relative dose intensity (RDI) of first two cycle, proportion of dose attenuation, ≥G3 toxicity and hospitalisation in each G8 score group. **Result:** Patient characteristics and clinical outcomes in each G8 score group are listed as Table 1. The G8 score correlated inversely with PS. More patients in the low score group (56%) had PS ≥2 compared to other two groups. Physicians tended to offer BSC to low score patients; 49%, 12% and 5% patients in low, intermediate and high score group respectively did not receive any systemic treatment. More patients in high score group (53%) received full dose chemotherapy on first cycle. Patients in high score group also tended to tolerate full dose chemotherapy better with relatively high RDI for the first two cycles (0.9) and less frequent (0%) ≥G3 toxicity. Patients in intermediate score group had similar frequency of ≥G3 toxicity and hospitalisation to patients in low score group, who received chemotherapy.

	G8 < 11 points (high risk)	G8 11 - 14 (intermediate risk)	G8 > 14 (low risk)
No of patients: n (%)	45 (42)	42 (40)	19 (18)
Mean age: years (range)	81 (70-91)	78 (70-87)	75 (70-84)
Sex n (%)			
Male	30/45 (67)	24/42 (57)	8/19 (42)
Female	15/45 (33)	18/42 (43)	11/19 (58)
Histology n (%)			
Adenocarcinoma	22/45 (49)	17/42 (40)	11/19 (58)
SCC	7/45 (15)	8/42 (20)	3/19 (16)
Mesothelioma	8/45 (18)	11/42 (26)	4/19 (21)
SCLC	5/45 (11)	1/42 (2)	1/19 (5)
*Other	3/45 (7)	5/42 (12)	0
ECOG PS n (%)			
0-1	20/45 (44)	29/42 (69)	15/19 (79)
≥2	25/45 (56)	12/42 (29)	3/19 (16)
unknown	0	1/42 (2)	1/19 (5)
Smoking status n (%)			
Non-smoker	9/45 (20)	6/42 (14)	8/19 (42)
Ex-smoker	22/45 (49)	28/42 (67)	10/19 (53)
Current smoker	13/45 (29)	8/42 (19)	1/19 (5)
Unknown	1/45 (2)	0	0
Systemic treatment n (%)			
Chemotherapy	22/45 (49)	33/42(78)	15/19 (79)
BSC	22/45 (49)	5/42 (12)	1/19 (5)
Other (TKI, IO)	1/45 (2)	4/42 (10)	3/19 (16)
Chemotherapy treatment			
Median No of cycles	3.00	3.00	3.75
Median **RDI for first 2 cycles ChT	0.775	0.888	0.900
Full dose cycle 1 ChT n (%)	8/22 (36)	14/33 (42)	8/15 (53)
Patients receiving > 2 cycles of ChT n (%)	17/22 (77)	20/33 (61)	11/15 (73)
Patients with no change in ChT n (%)	4/22 (18)	8/33 (24)	5/15 (33)
Patients with toxicity and chemotherapy ChT n (%)	7/22 (32)	10/33 (30)	0
Patients with hospital admissions during ChT n (%)	5/22 (23)	6/33 (18)	3/15 (20)

*Other histology: mixed adeno-squamous, NOS; SCC – squamous cell carcinoma; SCLC – small cell carcinoma; TKI – tyrosine kinase inhibitor; ChT – chemotherapy; BSC – best supportive care; **RDI – relative dose intensity

Conclusion: The G8 screening score classification into low, intermediate and high supported clinical treatment decisions on dose and it appeared to correlate with risk of toxicity.

Keyword: G8 screening score, elderly, advanced lung cancer

P1.01-80 LUNG CANCER PROGNOSTIC INDEX PERFORMANCE IN US REAL-WORLD ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The Lung Cancer Prognostic Index (LCPI) is a previously validated index that uses routinely available risk factors to ascertain overall survival. The purpose of this analysis is to validate the performance of the LCPI in advanced non-small cell lung cancer (aNSCLC) patients using real-world data from the United States. **Method:** Using the US-based Flatiron Health electronic health record-derived database, adult aNSCLC patients diagnosed on or after January 1, 2011 were identified and followed through January 31, 2019. Patient-level LCPI scores were derived using stage, smoking status, age, sex, respiratory comorbidities and actionable mutation status (EGFR, ALK or ROS1 positivity), and 4 groups (1-4) were created; performance status and weight loss at diagnosis were omitted due to low data yield. Overall survival was estimated using the Kaplan-Meier method and Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of the LCPI with all-cause mortality. **Result:** Of 48,872 aNSCLC patients with a mean (SD) age of 68 (9.8) years, 53% were male, 88% had a history of smoking, 75% were stage IIIB or IV at diagnosis, 70% had a non-squamous histology and 20% were squamous, 25% had a respiratory comorbid condition and 67% did not have an actionable mutation. Median survival time for LCPI groups 1-4 was 652, 525, 371 and 258 days, respectively. In the adjusted model, compared to LCPI group 1, all-cause mortality (HR [95% CI]) for groups 2, 3 and 4 was 1.20 (1.15, 1.25), 1.55 (1.50, 1.61) and 2.09 (2.02, 2.17), respectively. **Conclusion:** For those in LCPI group 4, the risk for all-cause mortality was doubled and median survival time was less than half of that seen in LCPI group 1. The results from this analysis were consistent with the previously validated LCPI results, thus validating the performance of the LCPI in a large US cohort of aNSCLC patients. The predictive model includes clinical risk factors such as mutation status, and facilitates the use of precision medicine in routine practice to inform treatment decisions, clinical trial eligibility and standardized risk assessment for comparative research.

Keywords: prognostic index, real world, aNSCLC

P1.01-81 A NEW PROGNOSTIC INDEX COMBINES THE METABOLIC RESPONSE AND RECIST 1.1 TO EVALUATE THE THERAPEUTIC RESPONSE IN PATIENTS WITH LUNG CANCER

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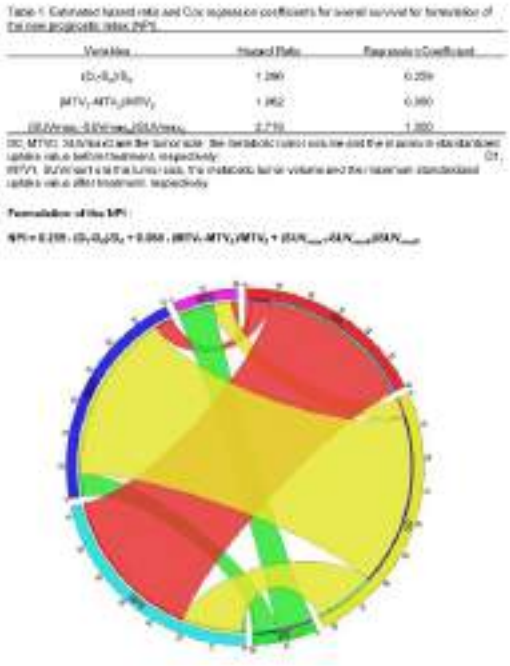
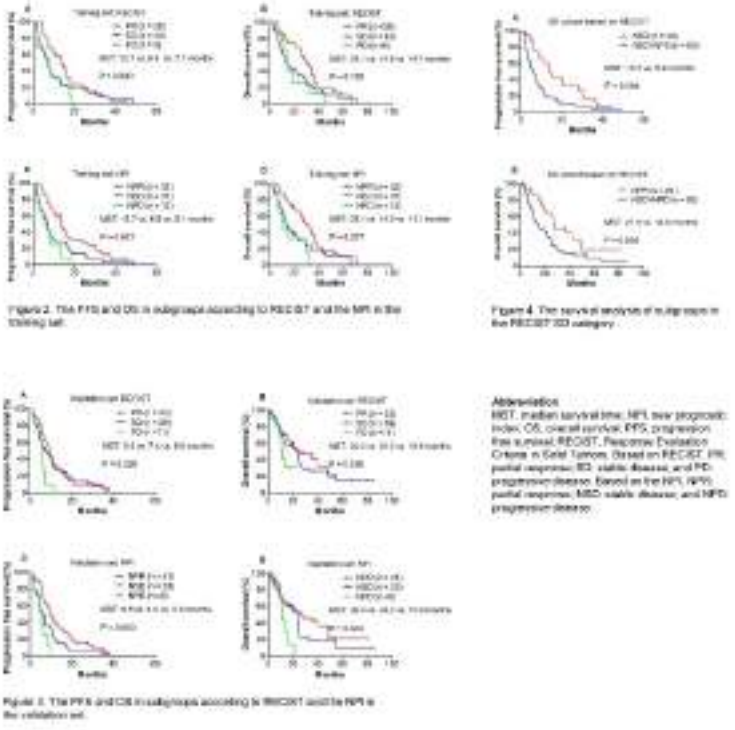
Background: Response Evaluation Criteria in Solid Tumors (RECIST) is occasionally insufficient for evaluation. We propose a new prognostic index (NPI) that combines the standardized uptake value (SUV), metabolic tumor volume (MTV) and RECIST. **Method:** In total, 163 patients with lung cancer who underwent positron emission tomography-computed tomography prior to and after treatment were included. We formulated the NPI by estimating the hazard ratios of overall survival for ΔMTV, ΔSUV_{max} and ΔD (tumor size based on RECIST). Then the regression coefficients were used, which gave rise to the HRs, as weights to formulate the new prognostic index (NPI). Progression-free survival (PFS) and overall survival (OS) were compared between RECIST and the NPI. **Result:** ROC curve analysis identified two cutoff values based on the NPI (≤-44.0% and >40.4%) to discriminate partial remission (NPR), stable disease (NSD) and progressive disease (NPD). The concordance rate between RECIST and NPI was 74.2% (κ = 0.572, P<0.001). Based on RECIST, survival analysis did not discriminate significantly on either PFS or OS between the PR, SD and PD groups. However, according to the NPI, PFS and OS differed significantly between the NPR, NSD, and NPD groups (training set: PFS, P = 0.007; OS, P = 0.027; validation set: PFS, P = 0.003; OS, P = 0.044). In total, 83 patients with SD were reclassified based on the NPI (20 with NPR, 57 with NSD, 6 with NPD), and the patients reclassified as NPR showed prolonged PFS (P = 0.004) and OS (P = 0.026) compared with those in the NSD+NPD group. **Conclusion:** The NPI shows superiority for evaluation of the therapeutic response and survival for patients with lung cancer, especially in the assessment of SD patients based on RECIST.

Keywords: metabolic response, RECIST, therapeutic response





P1.01-82 THE DIFFERENT FREQUENCIES AND GENETIC PROFILES OF HISTOLOGIC TRANSFORMATION AFTER DIFFERENT EGFR-TKIS IN EGFR-MUTANT ADENOCARCINOMAS

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Background: Histologic transformation is a mechanism of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor(TKIs) in *EGFR*-mutant non-small cell lung cancers(NSCLCs). Those adenocarcinomas with histologic transformation usually underwent poor prognosis. However, few studies have focused on the different occurrence rates and genetic profiles between *EGFR*-mutant adenocarcinomas treated with different generations of EGFR-TKIs. **Method:** Pathology was confirmed in 345 *EGFR*-mutant patients at baseline and recurrence. Among these patients,235 patients were treated with gefitinib or erlotinib,54 with afatinib and 56 with osimertinib. But only 11 patients with sufficient tumor specimens could be evaluated for the genetic profiles by next-generation sequencing (NGS). Demographics, disease features, and outcomes of these patients were analyzed. **Result:** The frequency of these *EGFR*-mutant adenocarcinomas with histologic transformation after the treatment of different generation TKIs were quite different. The frequency of gefitinib/erlotinib group was 7.2% (17/235),while the others were 5.6%(3/54, afatinib group)and 17.9%(10/56, osimertinib group). The median progression free survival (PFS)to EGFR-TKIs of those patients were 12.2 months(gefitinib/erlotinib group), 5.3 months (afatinib group)and 7.7 months(osimertinib group) respectively. Four adenocarcinomas treated with gefitinib/erlotinib all harbored *TP53* mutations at baseline. One adenocarcinoma treated with afatinib was founded to have acquired MET amplification and transformed to small-cell lung cancer meanwhile. Moreover, the PFS of one patient to afatinib was just 3 months and her genetic profile at baseline was characterized by *Rb1*, *TP53*, and *PIK3CA* mutations. There were 3 patients treated with osimertinib underwent histologic transformation from adenocarcinomas to squamous carcinoma. One patient after progressive disease of osimertinib did not have enough tissue to detect NGS,and her blood NGS result just showed *EGFR L858R* and *T790M* mutation. The tissue NGS result of the second patient showed *EGFR* p.Glu746-Ala750 deletion, *EGFR T790M* and *C797S* mutations, *CDK4/ CCND1/ EGFR/ KRAS* amplifications. The second patient received the chemotherapy of pemetrexed+ carboplatin + bevacizumab and the best response was partial response. The third patient take palbociclib and osimertinib meanwhile and his symptoms improved with the tissue NGS of EGFR T790M mutation and *CDK4/ MDM2/ EGFR* amplifications. They were characterized by *EGFR* amplification and *CDK4* amplification. The others transform from adenocarcinomas to small cell cancers or neuroendocrine tumors were seem to harbor with TP53, Rb1 and PIK3CA mutations. **Conclusion:** It seems more common in some subtypes that the *EGFR*-mutant adenocarcinomas treated with osimertinib undergo histologic transformation. The genetic profiles vary greatly between transformation to squamous carcinomas and transformation to small-cell cancers/neuroendocrine tumors in EGFR-mutant adenocarcinomas treated with osimertinib. Further verification is needed.

Keywords: histologic transformation, EGFR-mutant adenocarcinomas, The different frequencies and genetic profiles

P1.01-83 COMPARATIVE EFFICACY ANALYSIS BETWEEN ENTRECTINIB TRIAL AND CRIZOTINIB REAL-WORLD ROS1 FUSION-POSITIVE (ROS1+) NSCLC PATIENTS

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Background: Entrectinib is an oral tyrosine kinase inhibitor for *ROS1* fusion-positive (*ROS1+*) NSCLC. Three phase 1/2 single-arm studies showed entrectinib efficacy in this population (Doebele WCLC 2018). Due to the rarity of *ROS1+* patients generating direct comparative evidence in prospective randomized trials is difficult. We identified a retrospective real-world cohort of *ROS1+* NSCLC patients from electronic health records (EHR), to compare crizotinib, the current standard of care, to entrectinib as reported in clinical trials **Method:** Crizotinib-treated patients with advanced *ROS1+* NSCLC diagnosed 1 Jan 2011 to 30 Jun 2018, were identified with technology-enabled abstraction in the Flatiron Health EHR-derived database (>2.1 million cancer patients from US oncology practice). Entrectinib trial inclusion/exclusion criteria were applied to match the crizotinib cohort as closely as possible. Primary endpoint: time to treatment discontinuation (TTD), adapted from Gong (ASCO 2018); real-world progression-free survival (rwPFS; physician/scan report) and overall survival (OS) were secondary outcomes. Time-to-event analyses used Kaplan-Meier survival curves and Cox proportional hazard models on propensity score weighted populations; age, gender, race/ethnicity, smoking status, brain metastasis and previous lines of therapy were prognostic factors. **Result:** We analyzed 53 entrectinib and 69 crizotinib *ROS1+* NSCLC patients. Median weighted TTD: entrectinib, 14.6 months (95% CI: 8.3–23.8); crizotinib, 8.8 months (95% CI: 8.2–9.9). When rwPFS from crizotinib was compared to trial PFS, entrectinib had longer PFS vs crizotinib (weighted HR: 0.44; 95% CI: 0.27–0.74). Median OS with entrectinib was not reached (median follow-up: 15.5 months); weighted median OS with crizotinib was 18.5 months (95% CI: 15.1–19.9). Findings were consistent across multiple sensitivity analyses. **Conclusion:** Entrectinib was associated with longer TTD and PFS in *ROS1+* NSCLC patients vs a matched real-world crizotinib population. Control populations derived from real-world cohorts can supplement evidence from clinical trials in settings where new standards of care are needed, but where only limited data are available and randomization is not feasible. Funding: This study was funded by F. Hoffmann-La Roche

P1.01-84 INTERACTION OF LORLATINIB WITH CYP2B6, CYP2C9, UGT, AND P-GP PROBE DRUGS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Lorlatinib is a small-molecule anaplastic lymphoma kinase (ALK) inhibitor approved for treatment of patients with *ALK*-positive advanced non-small cell lung cancer (NSCLC). Because lorlatinib is an inducer and inhibitor of various cytochrome P450 (CYP) enzymes and transporters, an evaluation of its effect on these substrates at steady state is warranted. A drug-drug interaction (DDI) sub-study was conducted in patients with advanced NSCLC to evaluate the net effect of these interactions. **Method:** Probe drugs utilized included bupropion for CYP2B6, tolbutamide for CYP2C9, acetaminophen for uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT), and fexofenadine for P-glycoprotein-1 (P-gp). Thirty-two patients (to have at least 6 evaluable patients per probe drug) were administered a single dose of a probe drug alone on Day −2 to determine plasma exposure of the probe drug alone. Starting on Cycle 1 Day 1, patients began lorlatinib tablets 100 mg daily. On Cycle 1 Day 15, another single dose of the same probe drug was administered concurrently with lorlatinib. **Result:** Co-administration of lorlatinib 100 mg with bupropion, a sensitive CYP2B6 probe drug, decreased bupropion geometric mean plasma AUC_{inf} and C_{max} by 25% and 27%, respectively. For tolbutamide, a sensitive CYP2C9 probe drug, lorlatinib decreased tolbutamide AUC_{inf} and C_{max} by 43% and 15%, respectively. Likewise, for acetaminophen, a sensitive UGT substrate, lorlatinib decreased acetaminophen AUC_{inf} and C_{max} by 45% and 28%, respectively. Finally, for fexofenadine, a sensitive P-gp substrate, lorlatinib decreased fexofenadine AUC_{inf} and C_{max} by 67% and 63%, respectively.

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Conclusion: Critical steady-state–based DDI evaluations can be conducted in patients with cancer in carefully designed studies. Per FDA guidance, strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates by ≥80%, ≥50% to <80%, and ≥20% to <50%, respectively. Based on these criteria, lorlatinib behaved as a net weak inducer of CYP2B6, CYP2C9, and UGT; and a net moderate inducer of P-gp. The results of this sub-study can help guide recommendations for dose modifications when lorlatinib is given concomitantly with drugs that are metabolized by these enzymes or transporters. Based on the current results, only drugs that are P-gp substrates of narrow therapeutic index may require dose adjustments when used concomitantly with lorlatinib.

Keywords: DDI, lorlatinib, NSCLC

P1.01-85 TREATMENT FOR ADVANCED NSCLC WITH EGFR MUTATIONS AND DE NOVO MET AMPLIFICATION/ OVEREXPRESSION

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Background: Combination of epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) tyrosine kinase inhibitors (TKIs) are effective in advanced non-small-cell lung cancer (NSCLC) patients harboring *EGFR* mutation and acquired *MET*-amplification. However, there are few reports about treatments of patients with *EGFR* mutation and *de novo MET* amplification/ overexpression. **Method:** We retrospectively screened 88 consecutive advanced NSCLC patients harboring *EGFR* mutation and *de novo MET* amplification/overexpression at Guangdong Provincial People's Hospital of China from January, 2014 to December, 2018. Among them, a total of 41 patients receiving first-line targeted therapy were included and stratified into *EGFR*-driven, *MET*-driven and *EGFR/MET* co-driven groups illustrated respectively in Table 1.

Table 1. Classification of advanced NSCLC with EGFR mutation and MET overexpression/amplification.

Group	*EGFR* mutation	*MET* overexpression/ amplification	Response to first-line TKI
EGFR-driven	Exon 19 deletion or exon 21 L858R mutation (tested by next generation sequencing (NGS) or amplification refractory mutation system (ARMS) or polymerase chain reaction (PCR)).	Overexpression: strong intensity staining was in more than 50% of tumor cells (tested by immunohistochemistry (IHC)). Amplification: CNG≥5, or *MET*/ centromeric portion of chormosome 7 ratio≥2.2, with an additional criterion of focal amplification was in more than 10% of tumor cells (tested by fluorescence in situ hybridization (FISH)).	PFS>3 months, best response is complete response (CR)/partial response (PR)/stable disease (SD); not receiving MET-TKIs in later-line treatment, or had MET-TKIs but PFS≤3 months.
MET-driven			PFS≤3 months, receive MET-TKIs monotherapy or MET-TKIs plus EGFR-TKIs in later-line treatment and PFS>3months, or PFS≤3 months,but with acquired mechanism to *MET*.
EGFR/ MET co-driven			Response to EGFR-TKIs at least one time, receiving EGFR-TKIs plus MET-TKIs in later-line treatment and PFS>3 months, or PFS≤3 months, but with acquired mechanism to *MET*.

Result: Among enrolled patients, 40 of them received first-line first-generation EGFR-TKIs while 1 treated with MET-TKI. Twenty-eight received targeted therapy in the later-line treatments after resistance. Thirty-one (75.6%), 5 (12.2%) and 5 (12.2%) patients were classified into *EGFR*-driven, *MET*-driven and *EGFR/MET* co-driven groups. Median progression-free survival (PFS) was 12.1, 1.0 and 5.3 months respectively in the first-line setting. Objective response rates were 58.1%, 0.0% and 20.0% (P=0.028) respectively. Among 28 patients receiving subsequent targeted therapies, 58.1% (18/31), 100.0% (5/5) and 100.0% (5/5) were *EGFR*-driven, *MET*-driven and *EGFR/MET* co-driven respectively. Median PFS was 7.0, 6.5 and 10.3 months for the *EGFR*-driven group receiving subsequent EGFR-TKIs, the *MET*-driven group receiving MET-TKIs with or without EGFR-TKIs, and the *EGFR/MET* co-driven group treating with EGFR-TKIs plus MET-TKIs respectively (P=0.399). Also, no significant difference was observed in overall survival for these 28 patients (33.8 vs. 11.8 vs. 27.9 months, P=0.098). **Conclusion:** Subsequent individualized targeted therapy or co-targeted therapies might favor clinical outcomes for both *MET*-driven and *EGFR/MET* co-driven patients with advanced NSCLC after resistance to first-line EGFR-TKIs.

Keywords: advanced NSCLC, EGFR mutations, de novo MET amplification/overexpression

P1.01-86 OCCURRENCE OF DE NOVO DUAL HER2/HER3 OR HER2/EGFR TMD MUTATIONS: EXTENDING THE SPECTRUM OF TARGETABLE MONO-HER2 TMD IN NSCLC?

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Background: HER2 (ERBB2) TMD mutations have recently been described as novel solo actionable drivers in NSCLC responsive to afatinib in small series. However, dual occurrence of de novo EGFR or HER3 (ERBB3) TMD mutations together with HER2 TMD mutations, which may have implications for dimerization patterns and treatment, has not been described. **Method:** Hybrid-capture based comprehensive genomic profiling was performed on blood-based circulating tumor DNA (n=5,200) or FFPE tissue (n= 45,780) samples collected during clinical care from 50,980 unique NSCLC patients. **Result:** HER2 TMD mutations were identified in 0.12% (60/50,980) of cases and included V659E (n=33), V659D (n=8), G660D (n=15), V659E+G660R, V659_I661>VVEGI, G660E>R, and S653C (1 each). Within this subset, the median age of patients was 61 years (range 33-91) and 62% were female. No co-occurring known NSCLC driver alterations were detected, except one case with *EGFR* exon 19 deletion and one case with EGFR L858R and lung co-primary tumors noted. However, co-occurring HER3 (I649R) or EGFR (G652R) TMD mutations were found in 18% (11/60) and 5.0% (3/60) of cases, respectively. Notably, these ERBB3 or EGFR TMD mutations only co-occurred with HER2 TMD V>D (8/9 cases) or G>D (7/15 cases), but not with V>E changes (0/34 cases; p=0.0002). *HER2* amplification co-occurred with V659E in 15% (5/34) of cases, and G660D mutation was seen with the oncogenic extracellular domain S310F mutation in one case. Importantly, neither EGFR G652R nor ERBB3 I649R was found in the absence of a HER2 TMD mutation. Preliminary modelling studies suggest formation of a salt-bridge which would increase propensity for HER2/HER3 and HER2/EGFR heterodimerization favoring receptor activation. Two patients in this series with V659E were previously reported to have responded to afatinib and 1 patient with G660D+I649R did not respond to afatinib. Updated clinical data for these patients and others treated with HER2-tageted therapies will be presented. **Conclusion:** HER2 TMD mutations (V659D/E or G660D/R) are uncommon but targetable driver alterations in NSCLC. In cases with HER2 TMD V>D or G>D, a de novo co-existing EGFR or HER3 TMD mutation was frequently observed (88% and 47%, respectively), which may explain differential dimerization preference and in turn response to ERBB inhibitors. We hypothesize that dual HER2/HER3 or HER2/EGFR TMD mutants may be more aggressive than single HER2 TMD mutants due to the arginine-aspartic acid interaction, and these dual mutants may require combined kinase inhibitor + antibody therapy to block dimerization. Studies utilizing models to further characterization these co-alterations are in progress.

Keywords: HER2, transmembrane domain, Receptor tyrosine kinase

P1.01-87 OSIMERTINIB ACQUIRED RESISTANCE MECHANISMS AND POST-PROGRESSION OUTCOMES IN STAGE IV EGFR POSITIVE NON-SMALL LUNG CANCER

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Background: Osimertinib is a 3rd generation TKI approved for stage IV EGFR+ NSCLC in the first line or post-progression with *T790M*. The spectrum of osimertinib resistance mutations and clinical outcomes post-osimertinib progression are not well described. **Method:** Single-center retrospective review of patients with stage IV EGFR+ NSCLC treated with osimertinib was conducted. Resistance mutations were determined via tissue biopsy or circulating tumor DNA (Guardant) prior to and at time of progression on osimertinib. PFS was calculated using Kaplan-Meier method. PFS1 is start of osimertinib to radiographic progression. PFS2 is start of next therapy after osimertinib to next radiographic progression. **Result:** We identified 95 patients with stage IV EGFR+ lung adenocarcinoma treated with osimertinib detected via NGS (56/95), real-time PCR (29/95), Sanger sequencing (8/95), and other techniques (2/95). Most patients were female (63/95) and never smokers (72/95). Osimertinib resistance and post-progression patterns are shown in Table 1. Potentially targetable mutations were found in 55% (26/47) samples and 14% (6/47) samples had oncogenes targetable with available TKIs. *TP53* mutations prior to osimertinib did not significantly influence PFS (36 weeks vs 39 weeks; p = 0.13). *MET* amplification was only seen in the setting of undetectable *T790M* or in patients who received first line osimertinib. Median PFS1 for 1st line EGFR TKI (n=17), 2nd line EGFR TKI (n=41), 3rd or greater line EGFR TKI (n=29) was 36, 45 and 39 weeks respectively (p=0.268) with median follow up of 59, 81, and 64 weeks. 10 patients received locally ablative radiotherapy for oligoprogressive disease (defined as ≤ 3 progressive sites) and continued osimertinib post-progression with median PFS2 of 49 weeks.

	Osimertinib in first line	Osimertinib after prior EGFR inhibitor
EGFR mutations at stage IV disease	**N = 18**	**N = 77**
Exon 19 deletion	12/18 (67%)	42/77 (55%)
L858R	4/18 (22%)	28/77 (36%)
G719X	1/18 (5%)	3/77 (4%)
L861Q	1/18 (5%)	1/77 (1%)
Exon 20 insertion	0/18 (0%)	3/77 (4%)
Systemic therapy prior to osimertinib	**N = 18**	**N = 77**
No chemotherapy or immunotherapy	17/18 (94%)	51/77 (66%)
Chemotherapy	1/18 (6%)	22/77 (28%)
Immunotherapy	0/18 (0%)	2/77 (3%)
Radiographic progression on osimertinib	**N = 17**	**N = 70**
Yes	10/17 (59%)	57/77 (74%)
No	7/17 (41%)	13/77 (26%)
Osimertinib resistance testing available	**N = 7**	**N = 40**
Liquid biopsy	5/7 (72%)	20/40 (50%)
Tissue biopsy	1/7 (14%)	12/40 (30%)
Both	1/7 (14%)	8/40 (20%)
Resistance EGFR alterations	**N = 7**	**N = 40**
T790M not detected	0/7 (0%)	19/40 (48%)
C797S	0/7 (0%)	9/40 (23%)
792 H/V	0/7 (0%)	2/40 (5%)
A289T	0/7 (0%)	2/40 (5%)
L718Q	0/7 (0%)	1/40 (3%)
Targetable oncogenes with approved agents	**N = 7**	**N = 40**
MET amplification (MET/CEP7 ≥ 3)	2/22 (10%; tissue only)	2/22 (10%; tissue only)
EML4-ALK fusion	0/7 (0%)	1/40 (3%)
BRAF V600E	0/7 (0%)	1/40 (3%)
Potentially targetable mutations	**N = 7**	**N = 40**
Non-BRAF V600E	0/7 (0%)	4/40 (10%)
FGFR 1 / 2	0/7 (0%)	4/40 (10%)
PDGFRA	0/7 (0%)	2/40 (5%)
KRAS	0/7 (0%)	2/40 (5%)
GNAS	0/7 (0%)	3/40 (8%)
PIK3CA	0/7 (0%)	2/40 (5%)
BRCA 1 / 2	0/7 (0%)	3/40 (8%)
Post-progression therapies	**N = 10**	**N = 54**
Chemotherapy with osimertinib	2/10 (20%)	9/54 (16%)
Chemotherapy without osimertinib	0/10 (0%)	8/54 (15%)
Immunotherapy alone	0/10 (0%)	2/54 (4%)
Chemoimmunotherapy with osimertinib	2/10 (20%)	1/54 (2%)
Chemoimmunotherapy without osimertinib	0/10 (0%)	6/54 (11%)
Radiotherapy	3/10 (30%)	9/54 (17%)
Addition of new targeted TKI therapy	0/10 (0%)	5/54 (9%)
Clinical Trial	2/10 (20%)	3/54 (5%)
Other / Hospice	1/10 (10%)	9/54 (16%)

Conclusion: There is utility to repeat biopsy after progression on osimertinib as targetable oncogenes can be found. Presence of *TP53* prior to starting osimertinib did not influence PFS1. Continuing osimertinib and adding radiotherapy for oligoprogressive disease does increase post-progression PFS.

Keyword: osimertinib, resistance, EGFR

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P1.01-88 PS 2 PATIENTS WITH ADVANCED EGFR MUTANT NSCLC: SUBSET ANALYSIS OF A PHASE III RANDOMIZED TRIAL COMPARING GEFITINIB TO GEFITINIB WITH CHEMOTHERAPY

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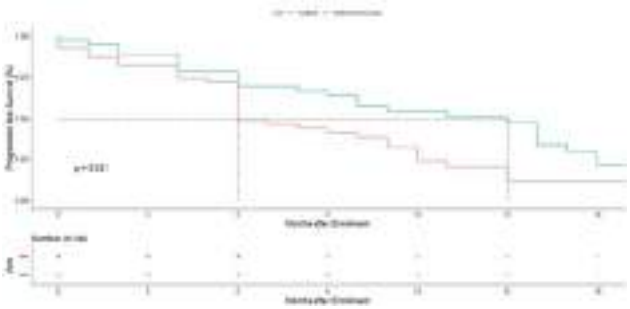
Background: Performance status is an important prognostic indicator in lung cancer. Most landmark trials excluded PS 2 patients; however, many patients we see in the clinic are PS 2, hence management of these patients is an extrapolation of the data from trials done in fitter patients. **Method:** We had conducted a Phase III randomized trial in patients with advanced NSCLC harboring *EGFR* sensitizing mutation, ECOG PS 0 to 2 planned for first-line palliative therapy. Performance status was a stratification factor, thus there was an equal proportion of PS 2 patients in the two arms. Randomization was 1:1 to gefitinib 250 mg orally daily (gef) or pemetrexed 500 mg/m^2 and carboplatin AUC 5 IV 3-weekly for 4 cycles, followed by maintenance pemetrexed with gefitinib from day 1 (gef+C). Primary end-point was progression-free survival (PFS); secondary end-points included overall survival (OS), response rate and toxicity. We present the subset analysis of the PS 2 patients in the trial. **Result:** Between 2016 and 2018, 75 PS 2 patients were randomly assigned to gef (n=39) and gef+C (n=36). The median age was 56 years, 63% were females, 23% had brain metastases and 50% had comorbidities. Median follow-up was 20 months (range, 7 to 28). Radiologic response rates were 83% and 67% in gef+C and gef arms respectively, P=0.117. Estimated median PFS was significantly longer with gef+C than gef [15 months, (95% CI, 10.6 to 19.4) versus 6 months (95% CI, 4.3 to 7.7); hazard ratio for disease progression or death, 0.57; 95% CI, 0.33 to 0.98; P=0.031] (Fig 2). Data for OS are immature. Clinically relevant ≥ grade 3 toxicities occurred in 58% and 28% of patients in gef+C and gef arms respectively, P=0.008.



Conclusion: In *EGFR* mutant PS 2 patients, combining pemetrexed and carboplatin chemotherapy with gefitinib led to a significant PFS prolongation, with an increase in clinically relevant severe toxicities. PS 2 patients with driver mutations appear to benefit from treatment intensification.

Keywords: Poor PS, PS 2, EGFR mutant

P1.01-89 A MULTICENTER PHASE 1/2A TRIAL OF CLN-081 IN NSCLC WITH EGFR EXON 20 INSERTION MUTATIONS

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Background: First and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are largely ineffective against EGFR exon 20 insertion mutations (ins20) and, while several novel agents targeting EGFR ins20 are in development (poziotinib, TAK-788), preliminary reports suggest that EGFR-related adverse events are common and may limit long-term efficacy (Heymach, WCLC 2018, Neal WCLC 2018). Targeted therapies which are safe and effective in patients with EGFR ins20 are needed. CLN-081 (also known as TAS-6417) is a novel, orally available EGFR TKI that selectively inhibits ins20 mutant EGFRs (Mol Cancer Ther 2018; 17:1648). In a cell-based assay using genetically engineered cell lines, CLN-081 potently inhibited intracellular phosphorylation of a wide spectrum of ins20 mutant EGFRs. The selectivity for mutant over wild type EGFR (WT/mut ratio) ranged from 4 to 134-fold depending on the specific mutation, representing an unprecedented level of mutant specificity. **Method:** This is an adaptive phase 1/2a trial evaluating CLN-081 as monotherapy in advanced non-small cell lung cancer (NSCLC) harboring EGFR ins20. Dose escalation will proceed initially according to an accelerated titration (AT) design, converting to a rolling six (R6) design based upon pre-specified safety criteria. Cohort expansion in Phase 1 can occur at one or more doses where responses are observed in R6 cohorts. Transition from Phase 1 into Phase 2a is based upon a Simon-Two Stage design. The starting dose will be 60mg. Once daily and twice daily dosing will be explored. Approximately 90 patients will be enrolled. Eligible patients will have advanced, exon 20 insertion mutation positive NSCLC, and at least one prior platinum containing treatment regimen. EGFR ins20 will be identified based on local testing (tissue or plasma). Patients who have discontinued a previous EGFR TKI due to progressive disease will be allowed in AT dose escalation cohorts but will be excluded from R6, and the Phase 1 and 2a expansion cohorts. The primary objectives in Phase 1 are to demonstrate safety and determine the maximum tolerated dose. Secondary Phase 1 objectives include evaluation of PK and preliminary efficacy. The primary objectives in Phase 2a are to define the recommended phase 2 dose and evaluate the overall response rate. The secondary Phase 2a objectives include additional measures of response and confirmation of CLN-081's safety profile. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: NSCLC, EGFR, Exon20

P1.01-90 UPDATE PHASE II RESULTS OF EARLY PRIMARY TUMOR STEREOTACTIC BODY RADIOTHERAPY COMBINED WITH FIRST-LINE EGFR-TKI IN ADVANCED EGFR MUTATED NSCLC

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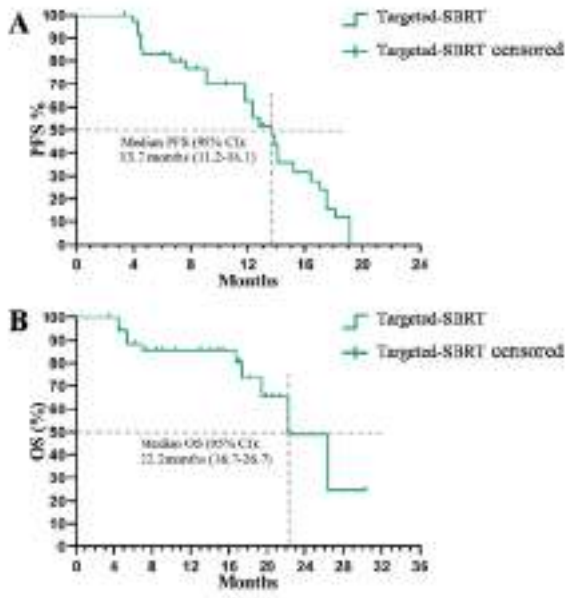
Background: Our previous work (ChiCTR-OIN-17013920) has reported the efficacy and safety of early primary tumor stereotactic body radiotherapy (SBRT) combined with Icotinb in advanced EGFR mutated (EGFRm) NSCLC patients (2018 IASLC WCLC Abstract #11985). Hani Ai-halabi et al. reported that about 80% of EGFR TKI drug resistance was at the primary site. Here we report the updated results. **Method:** Patients with pathologically confirmed advanced NSCLC with 19/21 EGFRm were enrolled between September 2016 and March 2019. SBRT was performed during the first month of oral first-line EGFR-TKI (Icotinib 125mg three times daily or Gefitinib 250mg once daily) in patients who were assessed as partial response or stable disease according to RECISE v1.1 assessment. The primary tumor was given SBRT at dose of 50Gy/5F or 60Gy/8F for peripheral and central primary, respectively. The primary endpoints were progression free survival] (PFS) and pattern of failure, while the second endpoints were overall survival time (OS) and adverse events (AEs). **Result:** 36 patients were recruited in this study. The follow-up time was 14.5 months (range 3.4-30.4). Median age was 66 years (range 49-83). There were 20 males and 16 females. Eighteen patients with 19-del mutation and 18 had L858R mutation. Overall, median PFS and median OS was 14.1 months and 26.3 months (Figure 1), respectively. Three patients had progression at the primary site, 5 patients had mixed progression and 19 patients with distant progression only. In subgroup analysis, the median PFS was 14.1 months vs. 12.8 months in 19-del vs. L858R mutation patients. The median OS was 19.4 months in L858R mutation group while that in 19-del mutation was immature. Additionally, there was no ≥grade 3 AEs in patients treated with this regimen.



Conclusion: This study suggested that early primary tumor SBRT may play a role to delay resistance of first-line EGFR-TKI in advanced EGFRm NSCLC patients. Patients with 19-del mutation may gain a better survival time compared with L858R mutation. The promising results are to be validated in a multi-center, comparable randomized phase III clinical trial (Target-SBRT, NCT03727867).

Keywords: Drug resistance, Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), Stereotactic body radiotherapy (SBRT)

P1.01-91 CLINICAL OUTCOMES OF VARIOUS RESISTANCE MECHANISMS OF OSIMERTINIB IN CHINESE ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Increasing efforts have been invested in elucidating the resistance mechanisms to osimertinib. Major resistance mechanisms include but not limited to acquired *EGFR* mutations, predominantly C797, mutations in bypass pathways and small cell lung cancer (SCLC) transformation. However, no study has comprehensively investigated clinical outcomes of various mechanisms of resistance. **Method:** 103 T790M positive advanced Chinese non-small cell lung cancer (NSCLC) patients who progressed on 1st generation EGFR-TKI were enrolled. Targeted sequencing, using a panel consisting of 168 lung cancer related genes, was performed on paired plasma samples collected prior to osimertinib and after the development of disease progression (PD) to profile mutation spectrum. 7 patients with no mutation detected at PD were excluded from analyses. **Result:** Major acquired mutations included 25% *EGFR* mutations, predominantly C797 and L792, 16% *MET* amplification, 8% *TP53* mutations, 4% *KRAS* mutations, 4% *RET* fusions, 4% *ERBB2* amplification and 6.25% RB1 mutations. Acquired *RB1* mutation may indicate the possibility of SCLC transformation. Approximately, 30% of patients with no known resistance mechanisms at PD. In this cohort, we had 61 patients with 19 deletion and 35 patients with EGFR L858R prior to the initiation of osimertinib. We revealed patients with 19del acquired more mutations (p=0.014) and were more likely to acquire mutations in MAP/PI3Kpathway (p=0.04) and *TP53* at PD (p=0.021). On the other hand, acquired *ERBB2* amplifications were only detected in L858R-mutant patients (p=0.047). Furthermore, 36 patients preserved T790M and 60 patients lost T790M at PD. Our data revealed patients retaining T790M, often associated with activation of bypass signaling pathways or continued *EGFR* activation through tertiary mutations, had a longer progression-free survival (PFS) (p=0.047) and overall survival (OS) (p=0.04) comparing to patients with T790M loss, often with diverse and *EGFR*-independent mechanisms. We also show that patients with acquired C797S had significantly longer PFS (p=0.031), while patients with acquired *MET* amplifications had significantly shorter PFS (p=0.033). **Conclusion:** Collectively, we revealed differential clinical outcomes associated with various resistance mechanisms, representing an important step in advancing the understanding of resistance mechanisms of osimertinib.

Keywords: osimertinib resistance mechanism, resistance mechanism

P1.01-92 UNDERLYING MECHANISMS THAT POTENTIALLY AFFECT PROGNOSIS TO EGFR-TKI IN EGFR-POSITIVE PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Conventional detection methods cannot fully reflect the overall landscape of tumor, which misguide the use of targeted drugs and lead to poor prognosis. Here, based on the results of genomic profiling obtained by NGS, we interrogate the underlying mechanism of differential response to EGFR-TKI in *EGFR*-positive patients with lung cancer. **Method:** 207 patients with advanced non-small cell lung cancer (NSCLC) carrying *EGFR*_L858 or 19del (identified by conventional methods) from 7 clinical trials (such as FLAURA, CTONG1405 and CTONG1509) were enrolled. 457 plasma (n=335) or tissue (n=122) samples from baseline and follow-up points of the cohort were profiled using 168-/520-cancer-related gene panels. Molecular characteristics in patients with rapid progression (PFS<3 months, n=10) and durable response (PFS>24 months, n=6) to EGFR-TKI treatment were analyzed. **Result:** The accuracy of NGS and conventional methods for identifying *EGFR* driver mutations in tissue samples was 97.1%, and that of driver mutation detection in plasma and tissue samples was 81.9%. Using NGS, several alterations at baseline that may potentially affect prognosis were identified, in addition to *EGFR* oncogenic mutations revealed by traditional methods. Ten patients progressed rapidly on EGFR-TKI therapy (no response, n=4; stable disease, SD, n=2; partial response, PR, n=4). Of the 4 patients who did not respond to EGFR-TKI, *ALK* fusion, *NTRK* fusion, *MET* amplification (*METamp*) and *EGFR*_E709A were identified at baseline using NGS. Of the 2 patients received SD, NGS revealed that one case carried mutations in *TP53*, *PMS2*, *PALB2* and *ARID1A*, while another case carried *TP53*_R213* and *ERBB2amp*. As to the 4 patients achieved PR, NGS results showed that one patient carried *TP53*_R342* and *EGFR*_L62R; one patient with *CDK4amp* and *RET* pathogenic mutation; one patient had *TP53*_V216L, *CDK4amp*, *ERBB2amp* and *EGFRamp*; and another patient harbored *CDK4amp*. In contrast, of the 6 patients achieved durable response to EGFR-TKI, NGS revealed that 4 patients did not carry any alteration or well-established factor associated with poor prognosis other than *EGFR* driver mutations. The other 2 patients with *TP53* mutation and *EGFRamp* received combination treatment of EGFR TKI and chemotherapy. **Conclusion:** NGS had good consistency with conventional methods in identifying *EGFR*-driver mutation. Compared with traditional methods, NGS can represent more comprehensive landscape of tumor and provide more reliable guidance for treatment. For patients with *EGFR*-driver mutations along with tumor suppressor or oncogene mutations, combination therapy of TKI and chemotherapy might be a better option than TKI alone. In addition, we revealed that *EGFR*_E709A and *EGFR*_L62R may be potential resistance mechanisms of EGFR TKI.

Keyword: NGS NSCLC EGFR

P1.01-93 METASTASES SITES AS A PROGNOSTIC FACTOR IN A REAL-WORLD MULTICENTER COHORT STUDY OF SPANISH ALK-POSITIVE NSCLC PATIENTS (P)

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Background: ALK gene rearrangements are detected in 3-7% of Non-Small-Cell-Lung-Cancer (NSCLC) p. EML4-ALK translocation was first identified as an oncogene in NSCLC p in 2007. To date, published real-world data on the prognostic factors of patients with ALK-positive advanced NSCLC in Spain are limited. We aim to evaluate the effect of number of metastases (M1) organs on overall survival (OS) in a multicenter cohort of Spanish ALK-positive NSCLC p diagnosed between 2008 and 2017. **Method:** We included p with stage IV at diagnosis since 2011 to April 2018. OS (months [m]) was estimated with the Kaplan-Meier method. Survival curves were compared between groups of p using the log-rank test. Hazard risk (HR) to death was estimated with multivariable Cox model, adjusted by site of metastases, gender, age and first line type of treatment. **Result:** Out of the 163 p in the cohort a total of 98 p were included, with a median follow-up of 28.6 m and 45 deaths reported. Characteristics at diagnosis were median age 58 years, female 46.9%, never-smokers 59.2%, 50% with comorbidities, PS by ECOG 0-1 93%, 58.2% lung M1, 45.9% central nervous system M1, 42.9% bone M1, 22.4% liver M1 and 29.6% pleural M1. 54.3% p and 89.4% p were treated with ALK inhibitors as first line and second line respectively. The median OS was 34.4 months, being 46.9 months in p treated with ALK inhibitors and 38.8 months in p treated with chemotherapy as first line (p= 0.9). There were 72 p who presented M1 in more than one organ and 26 p in a single organ. The risk of death increased with greater number of organs involved at diagnosis (HR= 3.0, p=.016), and presenting liver M1 at diagnosis (HR=2.2, p=.046, with OS of 19.1 m), compared to p single site involvement (OS: 45.4 m). **Conclusion:** OS was worse with increased metastatic sites involved at diagnosis in p with ALK positive NSCLC, being liver M1 associated with the highest risk of mortality. Brain metastases at diagnosis were not a prognostic factor for OS in our series.

Keywords: Metastases sites, ALK-positive NSCLC, Prognostic factor

P1.01-94 JNJ-61186372, AN EGFR-CMET BISPECIFIC ANTIBODY, IN EGFR EXON 20 INSERTION-DRIVEN ADVANCED NSCLC

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Background: JNJ-61186372 (JNJ-372), a bispecific antibody that targets the EGFR and cMet receptors, is currently being explored in a first-in-human study in patients with non-small cell lung cancer (NSCLC). Preliminary JNJ-372 clinical data have suggested activity in patients with diverse EGFR mutations, including Exon 20 insertions (Exon20ins), which carry primary resistance to tyrosine kinase inhibitors (TKIs; Cho BC et al. *Ann Oncol* 2018;29(suppl_8):mdy292.118). To better understand the mechanism of JNJ-372 activity in this patient population, we conducted preclinical studies exploring the activity of JNJ-372 in different EGFR Exon20ins models. **Method:** BaF3 cells were transduced with retrovirus expressing various EGFR Exon20ins, as described. Cell titer glo assays were used to measure cell proliferation; western blot analysis was used to study EGFR and cMet signaling cascade events. For mouse tumor models, JNJ-372 was administered i.p. daily at 10mg/kg or 30mg/kg. Referenced patients with Exon20ins disease were administered 1050mg JNJ-372 i.v. weekly for the first 4-week cycle, then biweekly for each subsequent cycle (Park et al. *J Thorac Oncol* 2018;13:S344-5). **Result:** In a dose-dependent manner, JNJ-372 inhibited the growth of BaF3 cells harboring diverse Exon20ins mutations. Mechanistic assays revealed down-modulation of EGFR and cMet receptor levels and decreases in phospho-EGFR and cMet, as well as inhibition of downstream signaling events including p-ERK, p-Akt and p-S6. Cleaved caspase-3 and BIM_{EL} were upregulated at antiproliferative doses, suggesting caspase-mediated cell death as part of the mechanism of action. JNJ-372 demonstrated corresponding antitumor activity in PDC and PDX models harboring different Exon20ins mutations with concomitant inhibition of EGFR signaling and induction of apoptosis. In the ongoing first-in-human trial, two patients with Exon20ins disease (P772_H773insPNP and H773delinsNPY) continue to demonstrate durable clinical benefit (13 and 22 cycles), with maximum tumor reductions of –23% and –63%, respectively, as demonstrated by baseline and postbaseline CT scans. **Conclusion:** In EGFR Exon20ins disease, JNJ-372 demonstrates preclinical antitumor activity and initial clinical responses. Preclinically, JNJ-372 induces antitumor activity in models of EGFR Exon20ins disease by decreasing EGFR and cMet receptor levels, inhibiting downstream signaling cascades, and activating apoptotic signaling. These results provide an understanding of the activity of JNJ-372 being observed in the ongoing clinical study and support the continued examination of JNJ-372 in NSCLC patients with Exon20ins and other EGFR mutations.

Keywords: Exon 20 insertion, EGFR, cMet

P1.01-95 EFFICACY AND SAFETY OF ANLOTINIB IN COMBINATION WITH CHEMOTHERAPY AS FIRST-LINE THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Anlotinib (AL3818) is a novel multi-target angioenesis TKI targeting the VEGFR, FGFR, PDGFR and c-Kit. In the ALTER0303 trial, Anlotinib as third-line treatment significantly improved progress-free survival (PFS) and overall survival (OS) in advanced NSCLC patients. This is the first trial evaluating the combination of chemotherapy and anlotinib in treatment-naive advanced NSCLC and is one arm of Phase II anlotinib-based trial (NCT03628521). **Method:** Patients with previously untreated EGFR/ALK/ROS1 negative advanced NSCLC were enrolled. Eligible patients received anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) combined with carboplatin (AUC 5) and pemetrexed (adenocarcinoma, 500mg/m^2)/gemcitabine (squamous, 1.0g/m^2,day1&8) for four to six cycles (21-day cycle). Maintenance treatment was followed by using pemetrexed and anlotinib (anlotinib alone for squamous) until disease progression or treatment intolerance. The primary outcome was objective response (ORR) and secondary outcomes were PFS, disease control rate (DCR) and OS. **Result:** Until the 21st March 2019, the curative effect was assessed in 30 enrolled patients according to the RECIST 1.1. Among these patients, eighteen of them achieved PR (all confirmed), eleven of them achieved SD and only one patient developed to disease progression. The objective response rate was 60.0 % while the disease control rate was 96.7 %. The most common Grade 3 adverse events were decreased platelet count (20 %), hypertriglyceridemia (10 %) and oral mucositis (6.67 %). 3 patients showed Grade 4 decrease of platelet count (10 %), and both of them belong to the gemcitabine group. **Conclusion:** The combination of anlotinib and chemotherapy showed the potential effect and a manageable safety profile in patients with previously untreated EGFR/ALK/ROS1 negative advanced NSCLC. Table 1: Response rates

Response	Assessed
CR	0
PR	18/30(60.0%)
SD	11/30(36.7%)
PD	1/30 (3.3%)
ORR, n/N(%)	18/30 (60.0%)
DCR, n/N(%)	29/30 (96.7%)

Keywords: combination of chemotherapy and anlotinib, NSCLC, first-line therapy

POSTERS

P1.01-96 US REAL-WORLD MANAGEMENT OF EGFR-MUTATED ADVANCED NSCLC: SURVIVAL AFTER FIRST-LINE EGFR-TYROSINE KINASE INHIBITOR TREATMENT

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Background: Outside of the clinical trial setting there are limited data defining clinical outcomes in patients with EGFR mutation-positive (EGFRm) advanced NSCLC treated with first-line EGFR-tyrosine kinase inhibitors (TKIs). To understand the impact of clinical features on outcomes to first-line EGFR-TKI treatment, we investigated overall survival (OS) across a range of variables obtained from real-world clinical practice in the US using the CancerLinQ database. **Method:** We utilised the American Society of Clinical Oncology CancerLinQ Discovery® database to characterise a cohort of patients with EGFRm advanced NSCLC receiving first-line EGFR-TKIs. CancerLinQ Discovery includes de-identified, demographically, and geographically diverse, longitudinal data. Data were obtained from a network of US cancer centres and community oncology practices participating in CancerLinQ. Patient-level data were derived from electronic health records or underlying data warehouses as structured data, and augmented through technology-assisted human curation of unstructured notes and scanned documents, and include diagnosis, anatomic pathology, imaging, surgery, medications, radiotherapy, molecular pathology, etc. OS was assessed as the duration between the start date of first-line treatment and last follow-up. **Result:** We identified 426 patients with EGFRm advanced NSCLC who had received first-line EGFR-TKI treatment between 2011–2017. Median (interquartile range [IQR]) age at diagnosis was 65.0 years (55.0–75.0); 240 (56%) patients were female; 378 (89%) adenocarcinoma histology; 165 (39%) former/current smoking status. Median (IQR) time between diagnosis of advanced staging and first-line EGFR-TKI treatment was 31.0 days (18.0–57.8). First-line treatments received were erlotinib (n=376, 88%), afatinib (n=48, 11%), and gefitinib (n=2, 0.5%). Median (IQR) duration on first-line treatment was 7.8 months (2.7–14.3). Overall OS was 25 months (95% confidence interval: 21–29). Further OS data are summarised in the table. **Conclusion:** OS for patients with EGFRm advanced NSCLC receiving first-line EGFR-TKIs in US clinical practice is in line with expectations based on clinical trials of first- and second-generation EGFR-TKIs

	n	Events	Median overall survival (95% CI), months
All patients with EGFRm advanced NSCLC	426	228	25 (21, 29)
EGFR mutation type			
Exon 19 deletion/L858R	200	106	28 (25, 33)
Other mutations/mutation not reported	226	122	20 (17, 27)
Brain metastases present before or after first-line treatment	304	137	30 (17, 26)
No brain metastases reported	122	91	30 (16, 41)
ECOG performance status*			
0/1	186	99	24 (20, 30)
≥2	53	25	17 (13, NA/A)
Unknown or missing	187	104	27 (22, 31)
Age group at diagnosis of advanced NSCLC			
18–64 years	211	117	25 (21, 36)
65–74 years	99	48	31 (21, 58)
75+ years	116	63	24 (16, 30)

*ECOG performance measure at initial diagnosis of advanced NSCLC or as the first measurement after diagnosis.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFRm, epidermal growth factor receptor mutation-positive; N/A, not applicable.

Keywords: EGFRm, NSCLC, real-world

P1.01-97 MODIFIED RANO-LM CRITERIA TO EVALUATE THE RADIOLOGICAL RESPONSE OF OSIMERTINIB IN EGFR T790M POSITIVE NSCLC WITH LEPTOMENINGEAL METASTASES

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Background: There is no standardized method in tracking the clinical response of leptomeningeal (LM) disease. Based on the recently proposed RANO criteria for LM, we made a further modification which could apply to the clinical trials and real clinical setting. In this study, the feasibility of modified RANO-LM criteria is tested in the exploratory dataset from our prospective clinical trials conducted in EGFR T790M positive non-small cell lung cancer patients with LM (NCT0325712). **Method:** Based on the previous RANO-LM criteria, up to five leptomeningeal nodules, leptomeningeal enhancement and cranial nerve (CN) enhancement from the baseline was recorded and then changes were scored between -3 to 3 at each post-baseline time point of brain MRI imaging using modified RANO-LM criteria. According to the pre-defined scoring system (figure), all LM lesions were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Presence of hydrocephalus or parenchymal lesion is seperately assessed as non-LM lesion

Modified RANO criteria scoring system

	Baseline	1st MRI		2nd MRI	3rd MRI
Leptomeningeal (LM) lesion	Presence or absent (1 or 0)	Presence or absent (1 or 0)	Changes compared to baseline (-3 to 3)		
Nodules (subarachnoid or ventricular, up to five lesions)					
Leptomeningeal enhancement					
Cranial nerve enhancement					
Sum of score					
LM response* (CR/PR/SD/PD)					
Non-leptomeningeal lesion	Presence or absent (1 or 0)	Presence or absent (1 or 0)	Changes comment		
Hydrocephalus					
Parenchymal (brain metastases)					
Non-LM response¶ (CR/PR/SD/PD)					
Overall response					

*LM response based on sum of score:
if only 1 LM lesion is observed (ex. Cranial nerve enhancement only), +3 (CR), +2 (PR), +1 (SD)
if 2 LM lesions are observed (ex. Leptomeningeal enhancement, cranial nerve enhancement), +6 (CR), +4 to +5 (PR), +1 to +3 (SD)
if 3 LM lesions are observed, +9(CR), +8 to +5 (PR), +4 to -2 (SD)
PD is assessed if -2 or -3 score change is observed in any lesion or sum of score is below -3.

¶ Non-LM response based on the following:

PD if any new lesion (hydrocephalus or parenchymal metastasis) develops. CR if all lesions disappear.
Parenchymal metastasis is assessed as nodule (up to five lesions) – PD: increase by >25% in the summed product of orthogonal diameters.
PR: decreases by >50% in the summed product of orthogonal diameters.
If hydrocephalus persists, SD regardless of the volume.

Result: Response of osimertinib in LM was evaluated in 34 patients. Baseline MRI identified LM enhancement in 67.6% (n=23), CN enhancement in 55.9% (n=19), hydrocephalus in 35.3% (n=12) and parenchymal metastases in 79.4% (n=27) but no nodular lesion (n=0). LM specific overall response rate was 63.9% by showing CR (n=10, 29.4%), PR (n=13, 38.3%), SD (n=8, 23.5%), PD (n=1, 2.9%) in evaluable patients. Eight patients showed treatment resistance by showing disease aggravation in LM lesion (n=2), non-LM lesion (n=5) and both (n=1). **Conclusion:** Modified RANO-LM criteria seems to be effective in evaluating treatment response and disease progression in patients with LM. Despite the complexity of the scoring system, modified RANO-LM criteria is a feasible method to evaluate LM status which could be applicable both to the clinical trials and to daily clinical practice. Further validation in independent patient cohort will be performed.

Keywords: leptomeningeal metastases, RANO-LM

P1.01-98 OUTCOMES IN ADVANCED NSCLC PATIENTS TREATED WITH 1ST LINE EGFR-TKI BASED ON MUTATION DETECTION FROM TISSUE OR CFDNA-BASED GENOMIC SEQUENCING

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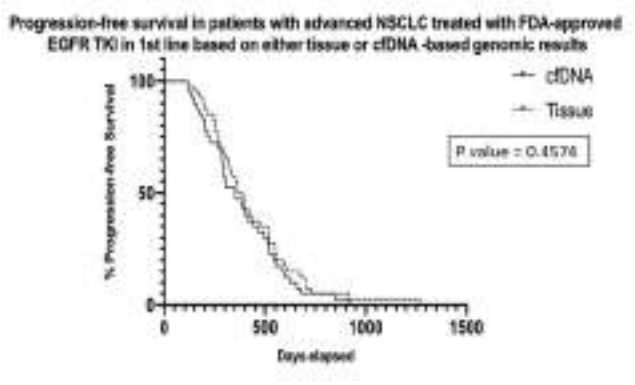
Background: Tumor genomic information from tissue has been the standard of practice for identifying actionable molecular alterations. The same genomic profiling is also widely available by a non-invasive blood test (cfDNA). We hypothesized that treatment naïve patients with advanced non-small cell lung cancer (NSCLC) and actionable oncogenic driver mutations identified by tumor and cfDNA would have similar clinical outcomes after treatment with targeted therapies. **Method:** Patients with any EGFR-TKI sensitive mutation and received FDA-approved EGFR-TKI as first line therapy for their advanced NSCLC were included in this retrospective analysis. Consecutive patients were identified from our GEMINI database with therapy initiated that was based solely from either the tissue or cfDNA report were divided into each cohort, respectively. Assessment of PFS was from date of therapy initiation until disease progression. Tissue genomic profiling was performed on our institution's CLIA-certified hotspot NGS assay covering 40-50 genes. For blood based genomic profiling, blood was sent for NGS of cfDNA with a panel of up to 70 cancer-related genes at a CLIA-certified lab (Guardant360, Guardant Health, Redwood City, CA). Kaplan–Meier methodology was used to calculate median PFS with Log-rank (Mantel-Cox) test assessment at significance level 5%. **Result:** Forty patients for each group were identified between 2014-2016. The results as summarized in table and PFS graph below:

	Tissue (n=40)	cfDNA (n=40)
Gender (Female/Male)	22/18	23/17
Age (median, range)	63(42-81)	57(30-83)
EGFR mutations:		
Exon 19 del	21	20
L858R	18	16
others	1(G719A)	4(L718Q, L861Q x 2, S768I)
PFS (median, range)	379 days (118-1266)	352 days (115-919)
Log-rank (Mantel-Cox) test	P value	0.4196



Conclusion: There was no progression-free survival difference in patients treated with FDA-approved front-line EGFR-TKI directed by genomic profiling from tissue vs blood -based testing. These results indicate that similar treatment outcomes with targeted therapy based on tissue or blood-based NGS profiling are both viable options for patient with newly diagnosed, advanced NSCLC.

Keywords: cfDNA, EGFR, advanced NSCLC

P1.01-99 EGFR-WILD TYPE PATIENTS RESPONDING TO TKI: REVISITING PATHOLOGY WITH NEWER TECHNOLOGY

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Background: Molecular testing of lung adenocarcinoma is now considered standard of care and an integral component of the diagnostic algorithm. Technology platforms are rapidly evolving and becoming more sensitive, specific, comprehensively cover clinically relevant actionable mutations and adapted for low input of limiting samples. Targeting EGFR receptors is an important treatment modality in EGFR-mutant patients. However, despite demonstrated benefit in overall survival (OS) and progress free survival (PFS) wild-type patients are deemed to be not suitable for TKIs therapy. Data on long-term responders to TKI among EGFR-wild type patients is limited and requires investigation. Herein, we re-tested samples, which tested negative for EGFR by in-house real-time PCR testing, of patients who responded to TKIs in order to explore the possible indicators of response using FoundationOne NGS assay. **Method:** This is a prospective cohort study of EGFR-wild-type patients by in-house testing (period 2004-2016, real-time PCR) who were light or non-smokers and were treated with TKI (Erlotinib) at the single Academic Centre of the Jewish General Hospital. Erlotinib was given to patients in first- or second-line after failure of systemic chemotherapy. The Formalin Fixed Paraffin Embedded tissue (FFPE) of samples were sent to be analyzed by FoundationOne assay. **Result:** Nineteen samples of patients who were treated with Erlotinib were sent to be tested. 16/19 were treated with TKI for ≥6 mo, 11/16 responded to TKI (defined as staying on treatment over 100 days with median response of over 600 days). Only 2/11 responders received erlotinib in first line, the 9/11 received it after progressing on first-line platinum-based doublets. Sensitizing EGFR mutations were found in 4/11 responders, which can be explained by increased coverage and sensitivity of the NGS platform. Among the remaining 7 patients that were confirmed to be negative by FoundationOne test, one patient had a rearrangement of EGFR (truncation), and two had RBM10 mutations, one an ERBB2 amplification, and 3 had MAP3K1 mutations as well as multiple novel alterations of unknown significance. These alterations may shed light to patient responses and require further exploration. **Conclusion:** The algorithms for molecular testing is based on the specimen pathology and local clinical and laboratory circumstances. There are a multitude of platforms available for somatic mutational and fusion testing and these are rapidly evolving with availability and accessibility of NGS. Comprehensive NGS panels and multidimensional data sets will widen our understanding of genetic dependencies associated with responses and pave the road to new therapeutic avenues.

Keywords: NSCLC, EGFR-wild type, FoundationOne

P1.01-100 EFFECT OF OSIMERTINIB IN NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES AFTER PROGRESSION FOLLOWING FRONT-LINE EGFR-TKI THERAPY

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Background: Osimertinib has been adopted as the standard of care for T790M-mediated acquired epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance. In this study, we aim to investigate the effect of osimertinib in advanced NSCLC with brain metastases after the failure of first-line therapy. **Method:** We retrospectively studied 43 NSCLC patients with BM received osimertinib after progression following front-line EGFR-TKI therapy from January 2013 to December 2016 at our institution. Overall survival (OS) was measured from the date of brain metastases. **Result:** Among the 43 patients, 25(58.1%) received EGFR-TKIs as first-line therapy, 15(34.9%) were treated with EGFR-TKIs therapy after the progression of chemotherapy, and there're also 3(7.0%) received the combination of EGFR-TKIs and chemotherapy as first-line therapy. 16(37.2%) were EGFR T790M positive, 4(9.3%) were EGFR T790M negative and 23(53.5%) were unknown T790M status. 34(79.1%) patients had received local radiation therapies (RT). The median overall survival (OS), and the median intracranial progression free survival (iPFS) was 32.0 months, 14 months, respectively. Patients with EGFR T790M mutation had the median OS of 24.7 months, these without T790M mutation had the median OS of 17.0 months, and the patients with unknown status of T790M showed the longest OS of 34.4months, although it did not reach statistical significance (*P* =0.727). There was also no difference in iPFS among the T790M-positive group, T790M-negetive group and the unknown status group (5.0 vs. 7.0 vs. 18.0 months, P=0.195). Similar results in OS were found among the first line TKIs group, chemotherapy followed by EGFR-TKI therapy group and the combination of TKIs and chemotherapy group (*P*=0.491). Three patients had leptomeningeal metastasis (LM), showed to have a worse iPFS of 12 months compared to 14 months of these without LM (*P*=0.991). **Conclusion:** Osimertinib had a good efficacy in patients with brain metastasis of advanced non–small-cell lung cancer in whom disease had progressed following front-line EGFR-TKIs.

Keywords: Osimertinib, Brain metastases, epidermal growth factor receptor tyrosine kinase inhibitor

P1.01-101 EFFICACY OF IMMUNE CHECKPOINT INHIBITION IN RET FUSION POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Activating RET fusions are oncogenic drivers in 1-2% of non-small cell lung cancer (NSCLC). Ongoing clinical trials indicate that the investigational selective small molecule inhibitor LOXO-292 is efficacious in RET fusion-positive NSCLC patients, with fewer side effects than available anti-RET multikinase inhibitors. While immune checkpoint inhibitors (CPIs) are standard treatment for advanced NSCLC in multiple treatment settings, a growing body of evidence suggests that CPIs are less active in oncogene-driven NSCLC than in driver-negative cancers. We undertook to examine the efficacy of CPIs in a large cohort of RET fusion-positive NSCLC patients **Method:** A retrospective search for NSCLC patients with RET fusions was performed using multiple electronic health record (EHR) databases. Patients with NSCLC harboring a RET fusion

and a history of treatment with a CPI (either as monotherapy or in combination with chemotherapy) were selected. Data extracted from these sources includes: descriptive demographic information such as age and sex, line of therapy in which CPI was administered and time on CPI. **Result:** 106 RET fusions were identified out of over 13,500 total NSCLC patients queried. Of these, over 30 have a history of treatment with a CPI. In this cohort of CPI-treated patients, we will report the time on therapy as the main outcome, which will serve as a surrogate marker for efficacy of CPI in RET fusion NSCLCs. **Conclusion:** While CPIs are generally accepted to be less effective in EGFR-mutant and ALK fusionpositive NSCLC, their efficacy (or lack thereof) is not understood in other oncogenic driver-positive NSCLCs. The aim of this study is to examine the real-world efficacy of CPIs in RET fusion-positive NSCLC patients identified from multiple EHR databases. These results are expected to guide the selection of CPI and TKI therapy for patients with RET fusion-positive NSCLC.

Keywords: RET-altered NSCLC, efficacy of checkpoint inhibitors, driver-positive NSCLC

P1.01-102 ACTIONABLE GENE ABERRATION AND THE RESPONSE OF MATCHED THERAPY AMONG PATIENTS WITH NON-SMALL-CELL LUNG CARCINOMA

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Background: Tumor genotyping using multiplex gene panel is now standard for precision medicine in non-small-cell lung carcinoma (NSCLC). We sought to assess the prevalence of actionable genomic alterations among NSCLC patients using our next-generation sequencing panel (NCC Oncopanel) and the response of matched therapy. **Method:** This is a post-hoc analysis of prospective study in which patients with advanced solid cancer were prospectively enrolled to undergo the comprehensive genomic profiling panel (NCC Oncopanel) conducted between July 2013 and March 2018 in National Cancer Center Hospital. The NCC Oncopanel assay, a multiplexed next-generation sequencing (NGS) assay of 114 cancer-associated genes, was performed in a CLIA-compliant laboratory in National Cancer Center. Subjects were primarily patients without any known actionable alteration such as *EGFR* or *ALK*. Patients with NSCLC were extracted into this analysis. Clinical data and treatment outcomes were retrospectively collected. **Result:** In total, 100 patients were extracted. Sufficient tumor tissue for NGS analysis were available in 91 patients; median age was 57 (range 30-77); 74 (81.3%) adenocarcinoma; 44 (48.4%) female; 42 (46.2%) never smoker. According to the OncoKB and CIViC database, and the Clinical Practice Guidelines for NGS in Cancer Diagnosis and Treatment issued by three major Japanese cancer-related societies, 85 patients (93.4%) had at least one potential pathogenic alteration. Actionable gene aberrations were identified in 49 (53.9%). Evidence levels were ranked as follows: 24 (26%) harbored level 1 aberrations (*ALK, EGFR, ROS1, BRAF*); 15 (16%) harbored level 2 (*RET, DDR2, MET, ATM, BRCA2, CDK4, CTNNB1, EZH2, JAK2, NRAS, TSC1*); 10 (11%) harbored level 3A (*CDKN2A, ERBB2, HRAS, PTEN, SMARCA4, STK11*). Matched therapy was administered into 29 (31.9%) leading to the objective response rate of 58.6% and the disease control rate of 79.3% with the median progression-free survival of 10.5 months (95%CI; 5.1-15.8). **Conclusion:** Multiplex gene panel is feasible and useful in screening candidates for matched therapy among NSCLC patients. NSCLC patients without any known actionable mutations should be considered to undergo comprehensive genomic profiling.

Keywords: Non-small-cell lung carcinoma (NSCLC), Actionable gene aberrations, Multiplex gene panel

P1.01-103 PRELIMINARY RESULTS OF BRIGATINIB IN JAPANESE PATIENTS (PTS) WHO PREVIOUSLY RECEIVED ALECTINIB: BRIGATINIB-2001 STUDY

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Background: Brigatinib is a next-generation ALK inhibitor with broad preclinical activity against ALK resistance mutations. To evaluate efficacy and safety of brigatinib in Japanese pts, a single-arm, multicenter, phase 2 study of brigatinib in pts with ALK-positive NSCLC (NCT03410108) in Japan is ongoing, with the primary endpoint of objective response rate (ORR) by independent review. This study has a safety evaluation lead-in phase to confirm the tolerability and pharmacokinetics of brigatinib with a small number of Japanese pts prior to the expansion phase. Here we report the preliminary results from pts in the safety lead-in phase who had been heavily pre-treated with ALK tyrosine kinase inhibitors (TKIs), including alectinib and ceritinib. **Method:** Stage IIIB, IIIC, or IV NSCLC with documented ALK rearrangements were enrolled. Up to 4 ALK TKIs (alectinib, ceritinib, crizotinib and lorlatinib) and 3 lines of prior other systemic anti-cancer treatment were allowed only for the safety evaluation lead-in phase. Brigatinib of 180 mg QD with 90 mg QD lead-in for the first 7 days (90→180mg QD) was administered and efficacy was evaluated every 8 weeks. **Result:** All 9 pts previously received prior alectinib, of whom 6 received 2 or more prior ALK TKIs. The standard dose of 90→180mg QD was well tolerated among Japanese pts. Only 1 dose-limiting toxicity (DLT) was observed: grade 3 lipase increase without clinical evidence of pancreatitis. The most common AEs were increased blood creatine phosphokinase (n=7), increased aspartate aminotransferase (n=6), and hypertension (n=5). By investigator assessment, 5 of 9 pts (56%) had confirmed partial response by the end of cycle 6. Tumor samples from 5 pts were collected prior to the start of brigatinib treatment, and 2 cases had secondary mutation, including one pt with a G1202R mutation who had a confirmed partial response to brigatinib by investigator assessment. Intensive PK sampling data in Japanese pts are comparable with those in non-Japanese pts. **Conclusion:** Standard dose of brigatinib 90→180mg is tolerable in Japanese pts and show promising preliminary anti-tumor activity in the post-alectinib setting.

Keywords: brigatinib, advanced NSCLC, ALK

P1.01-104 SURVIVALS IN ROS1-REARRANGED ADVANCED NON-SMALL-CELL LUNG CANCER TREATED WITH FIRST-LINE CRIZOTINIB

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Background: The c-ros oncogene 1 (*ROS1*)-rearranged non-small-cell lung cancer (NSCLC) can be treated effectively with crizotinib, a tyrosine kinase inhibitor (TKI) of anaplastic lymphoma kinase (ALK), ROS1, and mesenchymal-epithelial transition (MET). However, few studies have investigated on survivals in *ROS1*-rearranged advanced NSCLC patients treated with first-line crizotinib. **Method:** We retrospectively analyzed clinicopathological and survival data of *ROS1*-rearranged patients with advanced NSCLC treated with crizotinib between August 2013 and January 2019 at the Guangdong Provincial People's Hospital. *ROS1* rearrangements were detected by Reverse Transcription-Ploymerase Chain Reaction(RT/PCR),Fluorescence in situhybridization (FISH), or Next-generation Sequencing (NGS) . Overall survival (OS) and progression-free survival (PFS) were compared between first-line crizotinib, chemotherapy followed by crizotinib and first-line chemotherapy without any subsequent targeted therapy. **Result:** Among totally 40 patients with *ROS1*-rearranged advanced NSCLC, 29 were treated with crizotinib (16 with first-line; 13 with second- or further-line), and 11 were not treated with crizotinib at data cutoff (April 4, 2019).

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Median OS was significantly prolonged in patients with first-line crizotinib (N=16) than those with first-line chemotherapy followed by subsequent crizotinib (N=9), not reached vs. 27.1 months, *P*=0.042. However, there was no significant difference in median PFS between the two groups, 16.3 vs. 5.7 months, *P*=0.054. Meanwhile, first-line crizotinib (N=16) was significantly superior to first-line chemotherapy without any subsequent targeted therapy (N=8) in both median OS (not reached vs. 9.1 months, *P*=0.024) and PFS (16.3 vs. 4.8 months, *P*=0.017). **Conclusion:** First-line crizotinib prolongs survivals than chemotherapy for patients with *ROS1*-rearranged advanced NSCLC.

Keywords: ROS1-rearrangement, crizotinib, Chemotherapy

P1.01-105 US REAL-WORLD MANAGEMENT OF EGFR-MUTATED ADVANCED NSCLC: PRESCRIBING AND ATTRITION DATA FROM FIRST-TO-SECOND-LINE TREATMENT

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Background: Following first-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy for EGFR mutation-positive (EGFRm) advanced NSCLC, not all patients are able to receive second-line treatment. A significant proportion of patients die before second-line treatment, or are only eligible to receive palliative care. To better understand patient attrition, we investigated temporal trends in treatment patterns among first-line EGFR-TKI treated patients in real-world practice in the US. **Method:** We utilised the American Society of Clinical Oncology CancerLinQ Discovery® database to characterise a cohort of patients with EGFRm advanced NSCLC receiving first-line EGFR-TKIs between 2011–2017. CancerLinQ Discovery includes de-identified, demographically, and geographically diverse, longitudinal data. Data were obtained from a network of US cancer centres and community oncology practices participating in CancerLinQ. Patient-level data were derived from electronic health records or underlying data warehouses as structured data, and augmented through technology-assisted human curation of unstructured notes and scanned documents, including diagnosis, anatomic pathology, imaging, surgery, medications, radiotherapy, molecular pathology, etc. Patient data were divided into two cohorts: those who were diagnosed and received first-line treatment pre-2015 versus 2015 onwards. **Result:** We identified 426 patients with advanced EGFRm NSCLC who received first-line EGFR-TKI treatment between 2011–2017. Median (interquartile range [IQR]) age at diagnosis was 65.0 years (55.0–75.0); 240 (56%) patients were female; 378 (89%) adenocarcinoma histology; and 165 (39%) former/current smokers. Median (IQR) time between diagnosis of advanced staging and first-line treatment was 31.0 days (18.0–57.8); median (IQR) first-line treatment duration was 7.8 months (2.7–14.3). The table shows first- and second-line treatments received, and patient attrition data. Osimertinib was the most common second-line treatment in the 2015 onwards cohort. **Conclusion:** These real-world data confirm that approximately 44% of patients with EGFRm advanced NSCLC receive second-line treatment, and nearly one-third of patients die without receiving second-line treatment.

Patients, n (%)	EGFRm cohort (n=426)		
	Pre-2015 (2011–2014) cohort (n=237)	2015 onwards (2015–2017) cohort (n=189)	Total (n=426)
First-line treatment received			
Crizotinib	227 (96)	149 (79)	376 (88)
Afatinib	10 (4)	38 (20)	48 (11)
Gefitinib	0 (0)	2 (1)	2 (<1)
Received second-line treatment	114 (48)	75 (40)	189 (44)
Second-line treatment received*			
Third-generation EGFR-TKI	18 (16)	31 (41)	49 (26)
Single agent chemotherapies	22 (19)	13 (17)	35 (19)
First/second-generation EGFR-TKI	36 (32)	12 (16)	48 (25)
PD-1/PD-L1-based therapies	6 (5)	12 (16)	18 (10)
Anti-VEGF-based therapies	17 (15)	5 (7)	22 (12)
Platinum-based chemotherapy combinations	10 (9)	1 (1)	11 (6)
Other therapies	4 (4)	1 (1)	5 (3)
ALK inhibitors	1 (1)	0 (0)	1 (<1)
No second-line treatment received	123 (52)	114 (60)	237 (56)
Excluding patients with ≤3 months follow-up†	104 (44)	77 (41)	181 (43)
Attrition of patients with no second-line treatment during follow-up†			
Total number of deaths	153 (65)	75 (40)	228 (54)
Deaths following first-line treatment	83 (35)	50 (26)	133 (31)
Died within 3 months	45 (19)	36 (19)	81 (19)
Died after 3 months	38 (16)	14 (7)	52 (12)
Follow up <3 months	19 (8)	37 (20)	56 (13)
Follow up 3–6 months	7 (3)	7 (4)	14 (3)
Follow up >6 months	14 (6)	30 (11)	34 (8)

*Percentages calculated from total number of patients that received a second-line treatment.
†Death or follow-up are from the end date of first-line treatment.
ALK, anaplastic lymphoma kinase; EGFRm, EGFR mutation-positive; EGFR-TKI, EGFR tyrosine kinase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.

Keywords: EGFRm, NSCLC, attrition

P1.01-106 OSIMERTINIB PLUS PLATINUM/PEMETREXED IN NEWLY-DIAGNOSED ADVANCED EGFRM-POSITIVE NSCLC; THE PHASE 3 FLAURA2 STUDY

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Background: Osimertinib is a third-generation, CNS-active EGFR-TKI that potently and selectively inhibits both sensitizing EGFR and T790M mutations. Osimertinib is considered the standard of care for patients with newly-diagnosed advanced/metastatic NSCLC harbouring EGFR-activating mutations, based on results of the phase 3 FLAURA trial, which demonstrated a statistically and clinically significant progression-free survival (PFS) benefit for osimertinib over erlotinib or gefitinib. Evidence indicates that adding chemotherapy to gefitinib improves efficacy outcomes versus EGFR TKI monotherapy in newly-diagnosed patients with EGFRm NSCLC (Nakamura et al JCO 2018;36:9005). Adding platinum/pemetrexed to osimertinib could further improve outcomes for newly-diagnosed patients with EGFRm-positive NSCLC. **Method:** The phase 3, open-label, FLAURA2 study aims to assess the efficacy and safety of osimertinib plus cisplatin/carboplatin plus pemetrexed in adults with locally-advanced/metastatic *EGFR*m-positive (Ex19del and/or L858R) NSCLC who have not received prior therapy for advanced disease. Patients are required to have a WHO performance status (PS) 0-1, life expectancy >12 weeks and not be amenable to curative surgery or radiotherapy. An initial non-randomised run-in phase (n=30) will assess the safety and tolerability of osimertinib 80 mg once daily (QD) with either cisplatin or carboplatin, and pemetrexed, both administered every 3 weeks (Q3W) for 4 cycles, followed by osimertinib 80 mg QD plus pemetrexed maintenance Q3W until progression or discontinuation. Based on evaluation of safety data from the run-in after ≥12 patients from each group have received ≥3 cycles of study treatment or discontinued therapy, the second phase will randomise approximately 556 patients 1:1 to receive osimertinib 80 mg QD with pemetrexed and cisplatin/carboplatin for 4 cycles followed by osimertinib plus pemetrexed maintenance Q3W or osimertinib alone (80 mg QD), to be continued until progression or discontinuation. Randomisation will be stratified by race (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and tissue EGFR mutation test at enrolment (cobas® EGFR Mutation Test vs local assessment). A futility analysis of the randomized phase is planned for when approximately 83 PFS events have occurred. The primary endpoint is PFS based on investigator assessment of

response using RECIST 1.1 criteria (blinded central assessment is included as a sensitivity analysis). Secondary endpoints include overall survival, objective response rate, duration of response, PFS2, health-related quality of life and safety. Effects on CNS metastases in patients with lesions at baseline will be included as an exploratory endpoint. Enrolment is planned for Q3 2019 for the safety run-in and Q1 2020 for the randomized phase. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Osimertinib, Non-Small Cell Lung Cancer, newly-diagnosed

P1.01-107 KEYNOTE-495/KEYIMPACT: PHASE 2 BIOMARKER-DIRECTED STUDY OF PEMBROLIZUMAB-BASED THERAPY FOR NON–SMALL CELL LUNG CANCER

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Background: Immune checkpoint–based therapy has revolutionized the care of patients with non–small cell lung cancer (NSCLC). Pembrolizumab-based combination therapy aims to improve clinical outcomes over pembrolizumab monotherapy. Identification of biomarkers associated with improved response to different combination therapies may improve overall outcomes and yield a more precise approach to the use of immunotherapies in NSCLC. To test the clinical usefulness of a biomarker-informed, pembrolizumab-based combination therapy, this phase 2 KEYNOTE-495 trial (NCT03516981) will be carried out in patients with treatment-naive, advanced NSCLC. **Method:** KEYNOTE-495 is a randomized, multicenter, open-label, phase 2 trial. Tumor tissue from patients with treatment-naive, advanced NSCLC will be initially screened for 2 validated, independent, next-generation biomarkers: T cell–inflamed gene expression profile (GEP) and tumor mutational burden (TMB). Based on the results of this biomarker screening, patients will be assigned to 1 of 4 groups: $TMB^{low}GEP^{low}$, $TMB^{high}GEP^{low}$, $TMB^{low}GEP^{high}$, and $TMB^{high}GEP^{high}$. Within each group, patients will be randomly assigned to receive pembrolizumab combined with MK-4280 (anti–LAG-3), lenvatinib, or MK-1308 (anti–CTLA-4). This is a group-sequential, adaptive randomization trial. Patients will be randomly assigned to MK-4280 or lenvatinib first, after which MK-1308 will be introduced; randomization has been modified to accommodate the delayed introduction of MK-1308. Response will be assessed by tumor imaging every 9 weeks for the first year, then every 12 weeks thereafter using RECIST v1.1. Treatment will continue for 35 cycles (~2 years). Patients in the pembrolizumab + lenvatinib arm who complete 35 treatments may continue with lenvatinib monotherapy until disease progression or toxicity. After a patient experiences disease progression or starts new anticancer therapy, the patient will be followed up and contacted every 12 weeks until death, withdrawal of consent, or study end, whichever occurs first. Safety will be monitored throughout the study and for 30 days after treatment or before initiation of a new anticancer treatment, whichever occurs first. Treatment arms may be terminated during the interim analysis because of safety, prespecified futility criteria, or both. The primary end point is investigator-assessed objective response rate (RECIST v1.1). Secondary end points are progression-free survival, overall survival, and safety. Recruitment and screening are ongoing in more than 14 countries and will continue until ~288 patients are randomly assigned across the biomarker-defined groups to determine the optimal treatment for each subgroup. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Pembrolizumab, tumor mutational burden, gene expression profile

P1.01-108 PACIFIC-6: A PHASE II STUDY OF DURVALUMAB FOLLOWING SEQUENTIAL CHEMORADIOTHERAPY IN PATIENTS WITH STAGE III, UNRESECTABLE NSCLC

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Background: Non-small cell lung cancer (NSCLC) represents 85% of all lung cancers, with ~30% of patients (pts) presenting with Stage III disease. Platinum-based chemoradiotherapy (CRT) has historically been the standard of care (SoC) in this setting, but with poor long-term outcomes. Durvalumab is a selective high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. The phase III PACIFIC trial assessed durvalumab vs placebo in pts with locally advanced, unresectable, Stage III NSCLC, who did not progress following ≥2 overlapping cycles of platinum-based concurrent CRT (cCRT) (Antonia et al, NEJM 2017; 2018). Significant improvements in progression-free survival (PFS) and overall survival (OS) were observed with durvalumab (HR for PFS, 0.52; 95% CI 0.42–0.65; P<0.001; HR for OS, 0.68; 99.73% CI 0.47–0.997; P=0.0025). This data, along with comparable safety profiles between durvalumab and placebo in PACIFIC, supports the PACIFIC regimen (durvalumab following cCRT) as the new SoC in this setting. However, a proportion of pts are ineligible for cCRT for various reasons, and receive sequential CRT (sCRT) instead. PACIFIC-6 (NCT03693300) will assess the safety, efficacy, and quality of life of durvalumab in NSCLC pts who have not progressed following platinum-based sCRT. **Method:** PACIFIC-6 is a phase II, open-label, multi-centre study to be conducted in 6 countries across Europe and North America. Pts ≥18 years old, with histologically or cytologically documented Stage III, unresectable NSCLC who have not progressed following platinum-based sCRT, and are ECOG PS ≤2 are eligible for inclusion; enrolment is not restricted to a biomarker-defined population. Approximately 150 pts will receive durvalumab (1500 mg intravenously) every 4 weeks for 24 months or until disease progression. Pts will be divided into 2 cohorts according to PS status. Pts will be assessed every 12 weeks, until death, withdrawal of consent, or the end of the study. The primary objective is to assess the safety and tolerability of durvalumab, as defined by grade 3 and 4 treatment-related adverse events (TRAEs) occurring within 6 months from initiation of durvalumab. Secondary objectives include investigator-assessed efficacy measurements such as PFS, overall response rate, duration of response (according to RECIST v1.1), as well as OS, lung-cancer mortality, and further safety assessments of all AEs and serious AEs. Exploratory objectives include assessment of pt-reported symptoms and quality of life, as well as evaluation of the association of tumour-based biomarkers (including PD-L1 expression and tumour mutational burden) with efficacy. Recruitment is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: durvalumab, NSCLC, sequential chemoradiotherapy

P1.01-109 PHASE II TRIAL OF PEMETREXED/ CARBOPLATIN/BEVACIZUMAB +/- ATEZOLIZUMAB IN NSCLC PATIENTS THAT ARE EGFR MUTATED OR NEVER SMOKED

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Background: Patients with advanced NSCLC who harbor an EGFR mutation or are never smokers do not benefit from single-agent immunotherapy. Retrospective subgroup analyses from recent phase III trials suggest that immunotherapy-chemotherapy +/- VEGF inhibition may overcome the resistance to immunotherapy seen in these patients, though further prospective research is needed and no checkpoint inhibitor to date is approved in the first-line for EGFR patients after TKI failure. This trial will exclusively examine a population of patients with stage IV non-squamous disease who either have an EGFR exon 19 or 21 mutation or are never smoker wild-types to determine whether the PD-L1 inhibitor atezolizumab in combination with pemetrexed/carboplatin and bevacizumab can improve outcomes. **Method:** This is a phase II double-arm, multi-

center, open-label trial to assess pemetrexed/carboplatin and bevacizumab +/- atezolizumab in 117 subjects with stage IV non-squamous NSCLC. Randomization will be 2:1 with twice the number in the + atezolizumab arm, and randomization will be stratified by EGFR mutation status (i.e. EGFR exon 19 or 21 vs. never smoker wild-type) to ensure equal distribution in each arm. Never smoker wild-type is defined as smoking < 100 cigarettes in a lifetime and without any EGFR mutation or ALK or ROS1 rearrangement. Patients with EGFR exon 19 or 21 mutations must have progression or intolerance of treatment with prior TKI therapy. All patients must be chemotherapy, immunotherapy, and VEGF inhibitor therapy naïve. Primary endpoint will be progression-free survival (PFS). Secondary endpoints will include overall survival (OS), overall response rate, duration to response, and time to response. Primary objective is to compare PFS between arms. Secondary objectives include a safety analysis in all treated subjects, and comparisons of PFS and OS between arms for the subset of patients with tumors with EGFR exon 19 or 21 mutations. Correlative studies will include evaluation of biomarkers of the signaling network and tumor microenvironment, and characterizing the potential contribution of estrogen metabolites. Enrollment for this trial will open in August of this year and accrual will continue for 31 months. **Result:** Section not applicable - Trial in progress **Conclusion:** Section not applicable - Trial in progress

Keywords: EGFR mutation, Trial in progress, never smoker

P1.01-110 NOVEL REGIMENS VERSUS STANDARD-OF-CARE IN NSCLC: A PHASE II, RANDOMIZED, OPEN-LABEL, PLATFORM TRIAL USING A MASTER PROTOCOL

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Background: Although non-small cell lung carcinoma (NSCLC) is intrinsically resistant to immunotherapy agents, a subset of tumors are susceptible to T cell-mediated antitumor effects. Treatment regimens combining agents that target different processes within the cancer immunity cycle have the potential to enhance response in relapsed or refractory NSCLC. GSK3359609 is a humanized IgG4 antibody with potent agonist activity against Inducible T cell Costimulator (ICOS) and no or low depleting effect on antibody-dependent cell-mediated cytotoxicity. **Method:** This is a randomized, phase II, open-label, platform trial utilizing a master protocol in patients with advanced NSCLC who have progressed on initial PD1/PDL1-based immunotherapy and platinum-based chemotherapy. The trial will consist of several sub-studies, with each sub-study comparing novel combinations vs. current standard-of-care (SOC). No treatment crossover is allowed. Additional sub-studies may be added over time following protocol amendments. In the first sub-study, patients are centrally randomized by internet to SOC (docetaxel) or novel ICOS drug combination (NIDC) (GSK3359609 + docetaxel) in a 1:2 ratio, stratified by squamous versus non-squamous NSCLC and line of PD1/PDL1; randomization to SOC is minimized thereafter. Primary endpoint is overall survival (OS). Secondary endpoints are survival rate at 12 and 18 months; tumor response according to RECIST 1.1 and iRECIST criteria; pharmacokinetic parameters of the novel immunotherapy; and safety. Exploratory endpoints include tumor and blood-based biomarker evaluations such as tumor mutational burden and gene expression. Interim analysis of OS will be done after approximately 45 deaths in both study groups, with ≥18 deaths in the combination immunotherapy group; final analysis will be done after 85 deaths (35 in combination immunotherapy group). The study will employ a Bayesian decision-making framework based on predictive probability of observing a significant improvement in OS in a future phase III trial. A sample size of ≤70 participants in each combination immunotherapy group and ≥35 participants in the SOC group will provide ≥81% power with a type 1 error of ≤2.3% for each pairwise comparison. Sub-study 1 will compare the efficacy of GSK3359609 plus docetaxel versus docetaxel alone. At least 105 patients are expected to enroll. GSK3359609/docetaxel will be administered for ≤2 years or 35 visits, or until disease progression, death or unacceptable toxicity. Both drugs are given as an IV infusion (docetaxel 75mg/m^2; GSK3359609 80 mg). **Result:** Study enrollment has begun and the primary endpoint results of sub-study 1 are expected mid-2020. **Conclusion:** The study will provide information on the efficacy of novel immunotherapies used in combination. GlaxoSmithKline (NCT03739710).

Keywords: ICOS-agonist, GSK3359609, advanced NSCLC

P1.01-111 ATEZO-BRAIN, A SINGLE-ARM PHASE II STUDY OF ATEZOLIZUMAB COMBINED WITH CHEMOTHERAPY IN STAGE IV NSCLC PATIENTS WITH UNTREATED BRAIN METASTASES

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Background: Brain metastases (BM) are a frequent complication in non-small cell lung cancer (NSCLC), have significant impact on quality of life and are associated with poor prognosis. Systemic therapies might be an alternative approach to whole brain radiotherapy (WBRT) to avoid cognitive-related adverse events. Immune checkpoint inhibitors (ICI) showed intracranial activity in advanced NSCLC patients with BM. However clinical data about efficacy and safety of immune checkpoint inhibitors in combination with chemotherapy in patients with untreated BM are limited and further research in this setting is needed. We hypothesize that addition of ICI to conventional platinum-based chemotherapy may increase intracranial tumor response and provide clinically relevant benefit in terms of PFS, OS and quality of life to the patients with asymptomatic and non-previously treated BM. **Method:** This is an ongoing multicenter, open-label, single-arm phase 2 study (EUDRACT: 2017-005154-11) to evaluate the efficacy and safety of atezolizumab 1200 mg combined with 4-6 cycles of carboplatin AUC 5 and pemetrexed 500mg/m2 every 3 weeks followed by maintenance with atezolizumab 1200 mg plus pemetrexed 500mg/m2 every 3 weeks in stage IV non-squamous NSCLC patients with untreated synchronous BM. Patients should have multiple and measurable BM, adequate performance status and organic function, do not harbor EGFR or ALK genomic alterations, be treatment naïve and do not have any contraindication to receive immunotherapy. Exclusion criteria consist of active neurological symptoms, dexamethasone dose ≥ 4 mg QD, prior treatment with brain radiotherapy, presence of leptomeningeal carcinomatosis, spinal or hemorrhagic metastases in the central nervous system. Primary endpoints are progression-free survival (PFS) at 12 weeks according to RANO-BM and RECIST v1.1 criteria and safety based on CTCAE v4. Both primary endpoints will be assessed in 40 patients in 15 sites using a Bayesian approach. Patients will undergo tumor assessments by body CT scan and brain MRI at baseline every 6 weeks for the first 12 weeks and thereafter tumor assessments will be performed every 9 weeks until disease progression or loss of clinical benefit. Secondary endpoints: intracranial and systemic objective response rate and duration of response. Exploratory endpoints: to assess neurocognitive function and quality of life; to determine time to neurological deterioration and time to need of salvage brain radiotherapy. Enrollment started on August 2018 and currently 12 patients have been included in the study. **Result:** Clinical trial in progress **Conclusion:** Clinical trial in progress

Keywords: Brain metastases, non-squamous NSCLC, Atezolizumab

P1.01-112 PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL OF FIRST-LINE PEMBROLIZUMAB WITH OR WITHOUT LENVATINIB IN METASTATIC NSCLC: LEAP-007

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Background: The anti–PD-1 antibody pembrolizumab, as monotherapy or in combination with chemotherapy, is the standard of care for most patients with untreated metastatic non–small-cell lung cancer (NSCLC) with no *EGFR/ALK* aberrations. Lenvatinib is an anti-angiogenic multireceptor tyrosine kinase inhibitor that enhanced the antitumor activity of PD-1 inhibitors *in vitro* and showed clinical activity in combination with pembrolizumab in patients with metastatic NSCLC in a recent open-label, phase 1b/2 study (NCT02501096). LEAP-007 (NCT03829332) further evaluates the safety and efficacy of pembrolizumab plus lenvatinib in patients with metastatic NSCLC. **Method:** This randomized, double-blind, phase 3 trial enrolls previously untreated adult patients with stage IV NSCLC and PD-L1 TPS ≥1% without sensitizing genetic aberrations. Patients are randomized 1:1 to pembrolizumab 200 mg Q3W plus lenvatinib 20 mg daily or pembrolizumab plus matching placebo, stratified by geographic region (East Asia vs other), ECOG PS (0 vs 1), and TPS (1%–49% vs ≥50%). Treatment continues until verified disease progression (PD), unacceptable AE, illness, withdrawal of consent, noncompliance, or administrative reason. Radiographic imaging occurs Q9W from randomization through 54 weeks, then every 12 weeks until confirmed PD or start of a new anticancer regimen, and is assessed by blinded independent central review (BICR) using RECIST v1.1. Primary outcomes are PFS (RECIST v1.1 by BICR) and OS. Secondary outcomes include ORR (RECIST v1.1 by BICR), safety (AEs graded according to NCI CTCAE v4.0), and health-related quality of life. PFS and OS will be analyzed using the Kaplan-Meier method and stratified log-rank test; hazard ratios will be estimated using a stratified Cox regression model. ORR will be analyzed using the stratified Miettinen and Nurminen method, and differences will be estimated using the stratified Miettinen and Nurminen method with strata weighting by sample size. Target enrollment is 620 patients from 165 sites. As of April 5, 2019, 13 patients have been screened. **Result:** Not applicable **Conclusion:** Not applicable

Keywords: first-line, Pembrolizumab, lenvatinib

P1.01-113 PHASE 1B TRIAL OF CABOZANTINIB OR CABOZANTINIB PLUS ATEZOLIZUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Cabozantinib is an inhibitor of tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, RET, ROS1, and TAM family kinases (Tyro3, AXL, MER). Preclinical and clinical studies suggest that cabozantinib promotes an immune-permissive tumor environment, which may enhance response to immune checkpoint inhibitors (ICIs) such as the anti–PD-L1 mAb atezolizumab. Cabozantinib has demonstrated clinical activity in phase 1/2 studies of advanced NSCLC. Atezolizumab is approved for select patients with advanced NSCLC as monotherapy or as part of a combination regimen. Clinical studies in solid tumors, including NSCLC, indicate that the combination of a VEGF-targeting agent with an ICI may reverse ICI resistance.Here we present the study design of an ongoing phase 1b trial of cabozantinib alone or in combination with atezolizumab that includes cohorts with advanced non-squamous (nsq) NSCLC. **Method:** This global, phase 1b, open-label trial (COSMIC-021) is evaluating the safety, tolerability, preliminary efficacy, and pharmacokinetics of cabozantinib alone or in combination with atezolizumab (NCT03170960). The study consists of a dose-escalation stage (completed) and an expansion stage. In the expansion stage, 18 cohorts are being enrolled at the recommended expansion dose of cabozantinib (40 mg po qd) + a standard dose of atezolizumab (1200 mg q3w IV), including 3 advanced NSCLC cohorts: (1) nsqNSCLC with prior ICI therapy, (2) nsqNSCLC without prior systemic anticancer therapy for metastatic disease, and (3) EGFR-mutant nsqNSCLC with prior EGFR-targeting therapy. Thirty patients are being enrolled per cohort, with potential for extended enrollment pending Study Oversight Committee review. Two exploratory single-agent cohorts (N=30) are being enrolled to receive a 60-mg dose of cabozantinib, including a cohort of patients with nsqNSCLC who received prior ICI therapy. Patients will continue treatment as long as they experience clinical benefit per investigator or until unacceptable toxicity. The primary endpoint of the expansion stage is the objective response rate for each cohort. Exploratory objectives include correlation of tumor and plasma biomarkers and immune cell profiles with clinical outcome. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: cabozantinib, NSCLC, Atezolizumab

P1.01-114 A PHASE 2 STUDY OF MLN4924 (PEVONEDISTAT) IN COMBINATION WITH CARBOPLATIN AND PACLITAXEL IN ADVANCED NSCLC PREVIOUSLY TREATED WITH IMMUNOTHERAPY

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Background: Development of combination strategies after development of resistance to front-line immunotherapy is an area of unmet need in advanced NSCLC. One developing novel therapeutic strategy in NSCLC considers the molecular pathway of the ubiquitin (Ub)/proteasome system (UPS) and is a promising therapeutic target being investigated in hematologic and solid malignancies. Up-regulation of the neddylation pathway has been shown in NSCLC. In a study evaluating expression of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) (E1) and NEDD8-conjugating enzyme (E2) expression and global-protein neddylation, both squamous cell and adenocarcinoma NSCLC tumors consistently demonstrated overactivation of the entire neddylation pathway and higher expression of neddylation pathway was associated with poor overall survival (OS). MLN4924 (pevonedistat) is a first-in-class, small molecule NAE inhibitor. The combination of carboplatin/paclitaxel and MLN4924 (pevonedistat) has been investigated in the phase I setting in multiple solid tumors. Consistent with preclinical studies reporting synergy between MLN4924 (pevonedistat) and platinum-chemotherapy, the objective responses in patients resistant to prior platinum/taxane therapy suggest the potential reversal of resistance by the addition of MLN4924 (pevonedistat). **Method:** This is a phase 2, single arm study of MLN4924 (pevonedistat) 20 mg/m2 (Days 1, 3, 5) + carboplatin AUC 5 (Day 1) and paclitaxel 175 mg/m2 (Day 1) every 21 days for at least 4 cycles in patients with advanced NSCLC. At any time after 4 cycles of the combination, pts may continue with a) carboplatin, paclitaxel, and MLN4924 (pevonedistat), or b) continue carboplatin and MLN4924 (pevonedistat) without paclitaxel, or c) observation. Target accrual: 25 patients. Eligible patients have ECOG PS 0-1, measurable disease per RECIST 1.1, progression on prior checkpoint inhibitor and platinum-doublet chemotherapy, and adequate organ function. The primary endpoint is overall response rate (ORR). Secondary endpoints include progression-free survival, OS and safety. Correlative studies include: to evaluate the NQO1 and SLC7A11 gene expression, changes in the total number of circulating tumor cells (CTCs) and evaluate markers of DNA damage on CTCs, and tumor NAE1 and UBC12 protein expression. **Result:** Clinical Trials in Progress: Section not applicable. **Conclusion:** This study has been approved by the Cancer Therapy Evaluation Program (CTEP)/NCI and will open through the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) in August 2019.

Keyword: NSCLC, MLN4924(Pevonedistat), Carboplatin/paclitaxel

P1.01-115 LONG-TERM EFFECTS OF CONCURRENT CHEMORADIOTHERAPY ON QUALITY OF LIFE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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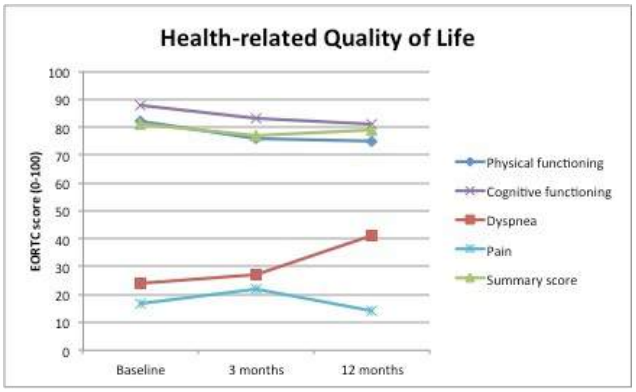
Background: Concurrent chemoradiotherapy imposes beneficial effects on overall survival (OS) in patients with locally advanced non-small cell lung cancer (NSCLC). Currently, it is unknown what the effects on long-term health-related quality of life (HRQOL) are. Therefore, we investigated long-term HRQOL in locally advanced NSCLC patients treated with concurrent chemoradiotherapy, using an accelerated fractionation scheme of 24 x 2.75 Gy +/- Cetuximab. **Method:** A 2-armed phase II, multi-center study (NTR2230) was performed with the initial aim to assess the effect of additional Cetuximab to concurrent chemoradiotherapy in locally advanced NSCLC patients. Arm A received high dose accelerated radiotherapy (24 x 2.75 Gy) and concurrent daily low-dose cisplatin (6 mg/m^2). Arm B additionally received weekly Cetuximab (400 mg/m^2 one-week pre-treatment followed by weekly 250 mg/m^2). HRQOL was assessed using the EORTC QLQ-C30 at baseline, 3 months post treatment and after 1 year. The primary endpoints included dyspnea, pain, physical functioning, cognitive functioning and the QLQ-C30 summary score. Following the EORTC guidelines, the scores of the endpoints were linearly transformed to 0–100 scales. Higher scores correspond to improved functioning for the functioning scales and for the summary score while for symptom scales (pain and dyspnea), higher scores indicate more symptoms. Linear mixed-modeling was used to assess differences over time. Standardized effect sizes based on the t-test statistic were calculated: (2*t)/(√degrees of freedom). Effect sizes of 0.2 were considered small, 0.5 moderate and clinically relevant, and 0.8 large. **Result:** Between February 2009 and May 2011, 102 patients were randomly allocated in two arms; 51 patients (50%) in arm A and 51 patients (50%) in arm B. Of those, 79 (77%) patients had at least one evaluable questionnaire. Figure 1 shows the development of the HRQOL endpoints over time. Over time, physical functioning (ES 0.48, P-value 0.003), cognitive functioning (ES 0.37, P-value 0.020), dyspnea complaints (ES 0.67, P-value <0.001) and the summary score (ES 0.44, P-value 0.006) significantly worsened. Only pain showed a reversing pattern in which pain was less present at 1 year (ES 0.37, P-value 0.021). No differences between the two arms were found.



Conclusion: In this randomized study of locally advanced NSCLC patients treated with concurrent chemoradiotherapy with or without Cetuximab, a clinically meaningful and long-term decline for all HRQOL endpoints except pain was observed. This analysis suggests that although concurrent chemoradiotherapy improves OS in NSCLC patients, efforts should also be taken to improve long-term HRQOL.

Keywords: Quality of life, concurrent chemoradiotherapy, Non-Small Cell Lung Cancer

P1.01-116 EARLY IMMUNE-RELATED ADVERSE EVENTS UNDER PD-1/PD-L1 INHIBITORS PREDICT BETTER PROGRESSION-FREE SURVIVAL IN NSCLC

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Background: Immune checkpoint blockers (ICB) targeting the PD-1/PD-L1 axis improve survival in patients with advanced non-small-cell lung cancer (NSCLC) without oncogenic addiction; however, they are also responsible for immune-related adverse events (irAE) sometimes leading to treatment discontinuation. Despite a clear association with response to ICB in melanoma, the predictive significance of a better outcome for irAE in NSCLC is unclear. **Method:** We retrospectively collected clinical and basic biological data from 160 stage IV NSCLC patients who received nivolumab, pembrolizumab or atezolizumab as second-line single agent in two cancer centers in France between January 2015 and December 2017. All irAE were collected using the Common Terminology Criteria for Adverse Events v5.0 ; general symptoms (*e.g.* fatigue) and cancer-related symptoms were discarded. We used two different statistical approaches to evaluate whether early irAE (≤ 12 weeks) were correlated to a better progression-free survival: i- a 12-week landmark method, including a multivariate Cox proportional hazards model (with ECOG PS and PD-L1 as covariates), ii- a propensity score matching (PSM) method, using PD-L1 level as the matching variable, followed by a Cox proportional hazards model. Finally, we investigated whether grade and number of early irAE were associated with improved PFS. **Result:** Most patients were male (n=107; 66.3%), smokers (n=146; 91.3%) and ECOG PS 0-1 (n=121; 75.7%) and received ICB as second (n=96; 60%), third line (n=38; 23.8%) or more (n=22; 13.8%). Nivolumab was the most used ICB (n=145; 90.6%). Within the first 12 weeks of treatment, 46 irAE occurred in 30 patients (18.8%), including 3 grade 3 irAE (1 pneumonitis, 1 myocarditis, 1 renal failure). Musculoskeletal (8.8%) and skin toxicity (5%) were the most frequent irAE. Clinical baseline characteristics were comparable between patients displaying early irAE (irAE+) and those who did not (irAE-), except for ECOG status (71.5% of PS 0-1 patients in irAE-group versus 93.3% in irAE+, p = 0.023) and PD-L1 level (PD-L1 ≥ 50% in 13.1% of patients in irAE- group versus 30.0% of patients in the irAE+ group, p = 0.016). The 12-week landmark analysis included 80 patients; 23/80 (28.8%) of them experienced at least 1 early irAE. PFS was improved in the irAE+ group in both univariate (HR = 0.24 [0.11-0.53], p < 0.001), and multivariate Cox models (HR = 0.33 [0.14-0.76] p = 0.009). After matching irAE+ and irAE- patients on PD-L1 level, early irAE were still associated with prolonged PFS (HR = 0.29 [0.15-0.57], p = 0.001). In the 12-week landmark population, grade ≥2 irAE were associated with even longer PFS (HR = 0.43 [0.26-0.71], p = 0.0009), and so were multiple co-occurring early irAE (HR = 0.30 [0.15-0.60], p = 0.0007). **Conclusion:** Early occurrence of irAE before 12 weeks appears to be associated with prolonged response to ICBs, independently of PD-L1 baseline expression in advanced NSCLC.

Keywords: adverse event, immune checkpoint blocker, advanced non-small-cell lung cancer

P1.01-117 PULMONARY FUNCTION MONITORING IN PATIENTS WITH OLIGOMETASTATIC NSCLC WHO RECEIVE STEREOTACTIC BODY RADIATION THERAPY

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Background: Patients with early and oligometastatic stage Non-small cell lung cancer (NSCLC) who are non-surgical candidates benefit from new radiation treatment modalities, such as stereotactic body radiotherapy (SBRT). Previously we reported the correlation of lung function decline and the presence of lung toxicity related to concomitant chemo-radiotherapy. This work aims to evaluate lung function performance after SBRT in patients with oligometastatic

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NSCLC. **Method:** A one-year prospective multicentric study was conducted at the Instituto Nacional de Cancerología in Mexico. Twenty-six patients with stage IV NSCLC with a single metastasis considered non-operable were treated with SBRT. Lung function was assessed at the baseline and at one, six, twelve, twenty-four and fifty-two weeks after SBRT, using forced spirometry with a bronchodilator, a carbon monoxide diffusing capacity (DLCO) test and oxygen saturation (SpO_2) measurement. The study was registered in clinicaltrials.gov (NCT01580579). **Result:** Fourteen patients were evaluated with lung function tests, the results were adjusted for the Mexican population. At baseline, the mean for post-bronchodilator (post-BD) FVC (l) was 2.16 (±1.09), for FEV_1 2.25 (±1.06), DLCO (ml/min/mmHg) 20.22 (±8.44) and SpO2 of 94% (±2.81). A reduction of <10% of relative change (max. 294 ml) was observed in lung volume in FEV_1 and FVC (l) post-BD follow-up with non-significant results. A statistically significant reduction in DLCO 18% (*p=0.03*) at week 12 was observed, Fig.1. All patients maintained an oxygen saturation level over 90% during the study. Quality of life reduces significantly at week six after SBRT *(p=0.03),* while respiratory symptoms were non-considerable in the first 12 weeks after receiving SBRT.

Conclusion: Although lung function tests showed a reduction trend, no statistically significant differences were found. The magnitude of lung volume reduction had no significant impact on respiratory symptoms, these findings could suggest that there is less damage in the surrounding tissue after SBRT. This research is an ongoing prospective study of one-year follow-up where several patients continue the be monitored; therefore, we expect to strength our findings by the end of the study.

Keywords: Pulmonary function tests, NSCLC, SBRT

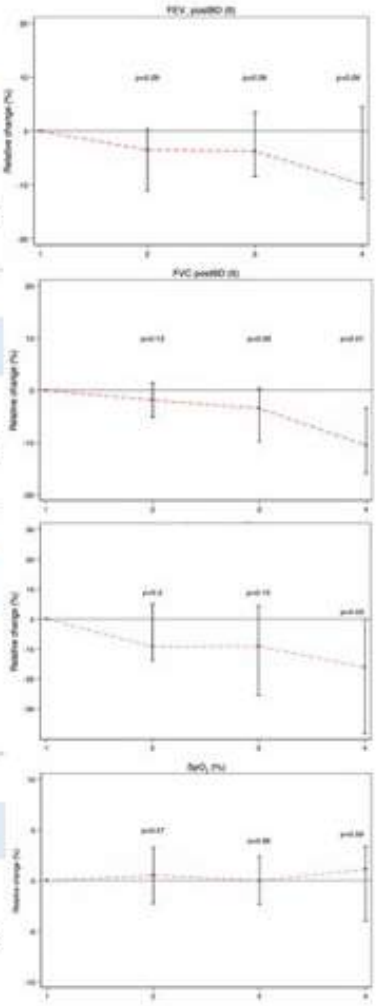
Fig. 1 Relative changes in lung function

Variable, mean [SD]	Baseline	End of RT	p	6 weeks	p	12 weeks	p
Spirometry post-BD	(n=14)	(n=14)		(n=13)		(n=7)	
FEV_1 (l) (absolute change)	-	0.072 [0.22]		0.058 [0.25]		0.168 [0.23]	
FEV_1 (%) (relative change)	-	**-3.26 (9.96)**	0.29	**2.39 (10.45)**	0.09	**-6.09 (7.56)**	0.09

Variable, mean [SD]	Baseline	End of RT	p	6 weeks	p	12 weeks	p
Spirometry post-BD	(n=14)	(n=14)		(n=13)		(n=7)	
FVC (l) (absolute change)	-	0.60 [0.198]		0.127 [0.26]		0.294 [0.18]	
FVC (%) (relative change)	-	**-1.87 (6.35)**	0.13	**-4.18 (7.63)**	0.06	**-9.46 (4.93)**	0.01

Variable, mean [SD]	Baseline	End of RT	p	6 weeks	p	12 weeks	p
DLCO	(n=14)	(n=14)		(n=13)		(n=7)	
DLCO (ml/min/mmHg) (absolute change)	-	1.053 (3.83)		1.872 (4.85)		3.12 (2.72)	
DLCO (%) (relative change)	-	**-4.89 (21.09)**	0.3	**-7.92 (25.5)**	0.15	**-18.01 (15.03)**	0.03

Variable, mean [SD]	Baseline	End of RT	p	6 weeks	p	12 weeks	p
Oxygen saturation	(n=14)	(n=14)		(n=13)		(n=7)	
SpO_2 (%) (absolute change)	-	0.857 (3.69)		0.50 (3.32)		-0.33 (3.74)	
SpO_2 (%) (relative change)	-	**-0.88 (3.956)**	0.57	**-0.49 (3.55)**	0.82	**-0.43 (3.99)**	0.59



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P1.01-118 OVERALL SURVIVAL IN PTS WITH EGFRM+ NSCLC RECEIVING SEQUENTIAL AFATINIB AND OSIMERTINIB: UPDATED ANALYSIS OF THE GIOTAG STUDY

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Background: With three generations of EGFR tyrosine kinase inhibitors (TKIs) now available for the treatment of *EGFR* mutation-positive (*EGFR*m+) NSCLC, it will be important to identify the optimal sequence of EGFR TKIs to maximise survival. The observational GioTag study (NCT03370770) investigated outcomes in patients with *EGFR*m+ NSCLC who were treated with sequential afatinib and osimertinib in a 'real-world' clinical setting, including patients with poor prognosis (ECOG PS ≥2: 15%; stable brain metastases: 10%).[1] Time to treatment failure (TTF) was encouraging (overall: 27.6 months; Del19-positive patients: 30.3 months; Asians: 46.7 months). In this updated analysis, we report OS and updated TTF. **Method:** Data were retrospectively collected between Dec 2017 and June 2018 for 203 pts with *EGFR*m+ (Del19, L858R) NSCLC who had T790M-positive disease after first-line afatinib and subsequently received osimertinib. TTF was the primary outcome; OS analysis was exploratory. Data were collected from electronic health records (EHRs; n=126) or medical charts (n=77). For logistical reasons, this interim analysis includes updated data (as at April 2019) from patients with available EHRs (all from USA; n=94); final analysis incorporating updated data from manual chart reviews is anticipated in early 2020. **Result:** After a median follow-up of 30.3 months, median OS was 41.3 months (90% CI: 36.8–46.3) in the overall dataset (n=203) and 45.7 months (90% CI: 45.3–51.5) in Del19-positive patients (n=149); 80% of patients were alive after 2 years. OS in Asians was immature. Updated median TTF was 28.1 months (90% CI: 26.8–30.3) in the overall dataset, and 30.6 months (90% CI: 27.6–32.0) in Del19-positive patients. Outcomes were not affected by afatinib starting dose. Median TTF with osimertinib was 15.6 months (90% CI: 13.8–17.1) in the overall dataset, and 16.4 months (90% CI: 14.9–17.9) in Del19-positive patients. **Conclusion:** Sequential afatinib and osimertinib is associated with encouraging OS and TTF in pts with *EGFR* T790M-positive NSCLC, especially in Del19-positive patients, indicating that the sequential regimen is a feasible option in this setting. Of note, prior treatment with afatinib did not preclude prolonged TTF with second-line osimertinib (15.6 months overall; 16.4 months in Del19-positive patients). The final analysis will provide further insights into the long-term OS of patients treated with sequential afatinib–osimertinib, including Asians. 1. Hochmair MJ, et al. Future Oncol. 2018;14:2861–74.

Keywords: EGFRm+ NSCLC, Sequential afatinib and osimertinib, GioTag study

P1.01-119 MODIFIED LUNG IMMUNE PROGNOSTIC INDEX (MLIPI) AS A PREDICTIVE TOOL OF NIVOLUMAB OUTCOMES IN ADVANCED NSCLC PATIENTS

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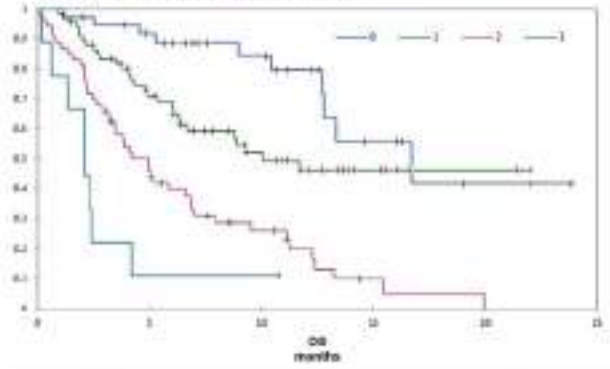
Background: Identification of sub-populations of patients with a greater likelihood of response to anti-programmed death-1 (PD-1) inhibitors in NSCLC continues to be a focus of intense interest. A Lung Immune Prognostic Index (LIPI) has previously been proposed by Mezquita et al. JAMA 2018, based on baseline LDH and dNLR. We have previously presented data on the association between the development of immune mediated Adverse Events (IrAE) with improved outcomes (including median PFS, OS and higher rates of clinical response) and univariate analysis of baseline clinical, biochemical and radiological factors associated with improved outcomes in advanced NSCLC patients treated with Nivolumab across seven oncology institutions in Queensland, Australia. We now propose a modified prognostic index (mLIPI) using baseline performance status (PS), Lactate dehydrogenase (LDH), and Neutrophil to Lymphocyte Ratio (NLR) to better predict patients' likely response to immune checkpoint inhibitors and investigate the relationship between the prognostic index and occurrence of IrAE. In addition, updated survival data for the real world 220 patient cohort, a 12 week landmark toxicity analysis and multivariate analysis will be presented for the first time. **Method:** Multi-institutional retrospective cohort study of 220 patients who received Nivolumab across seven oncology institutions in Queensland, Australia. The mLIPI score was calculated by allocating 1 point for each of the three poor prognostic factors, PS 2-3, NLR >3, and LDH >1.5 x ULN, resulting in 4 groups (good, intermediate, poor and very poor) and was compared against the LIPI score for the same cohort. A multi institutional ethics approval was obtained. **Result:**

Figure 1: Overall Survival by mLIPI Score



Total Points	mLIPI score	mOS	95% CI	HR	Clinical benefit
0	Good	16.73	(12.79 – NR)	49%	81%
1	Intermediate	10.05	(8.38 – NR)	25%	57%
2	Poor	4.93	(3.24 – 6.84)	13%	38%
3	Very Poor	2.08	(1.35 – 2.43)	0%	11%
		p-< 0.001			

The occurrence of IrAE was associated with a lower number of poor prognostic factors at baseline (lower mLIPI score), *P value = 0.013*. **Conclusion:** The mLIPI score correlated with outcomes (median PFS and OS) and was able to better identify those patients likely to obtain benefit from single agent Nivolumab therapy in this cohort when compared against published scores. Patients with a high mLIPI score, indicating a higher number of poor prognostic factors at baseline were less likely to derive a clinical benefit, or develop IrAE.

Keyword: NSCLC, immunotherapy, nivolumab

P1.01-120 IMMUNE CHECKPOINT INHIBITORS VERSUS SECOND LINE CHEMOTHERAPY FOR PATIENTS WITH LUNG CANCER REFRACTORY TO FIRST LINE CHEMOTHERAPY

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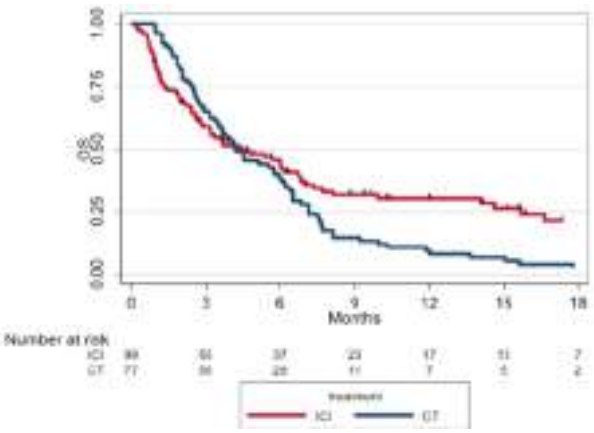
Background: Anti Programmed Death-ligand (PD1/PD-L1) directed immune-checkpoint-inhibitors (ICI) are widely used to treat patients with advanced non-small cell lung cancer (NSCLC) who progress after first line chemotherapy. The best strategy after early progression under first line has not been specifically studied **Method:** We conducted a multicenter, retrospective study including

all consecutive NSCLC patients progressing within the first 3 months following introduction of first-line chemotherapy and being treated with second line ICI monotherapy or chemotherapy between March 2010 and November 2017. We analysed the clinicopathological data and outcome under second line chemotherapy *vs.* second line ICI: progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). **Result:** We identified 176 patients with refractory disease, 99 who received subsequent immunotherapy and 77 undergoing chemotherapy. The 2 populations were comparable regarding the main prognostic criteria, median age was 60, main histology was adenocarcimoma (68,2%). Compared to chemotherapy, ICI treated patients had a superior OS (logrank test, p=0.03) (Median [95% CI] OS 4.6 [2.8-6.7] versus 4.2 months [3.4-5.9] and a non-significant improvement in ORR (17.2% and 7.9%, respectively, p = 0.072). PFS was not significantly different (1.9 [1.8-2.1] versus 1.6 months [1.4- ; 2.0] (p=0.125). Poor performance status (ECOG PS≥2) and a higher number of metastatic sites (≥3) were associated with poorer prognosis. KRAS-mutated patients did not seem to benefit more from ICI than chemotherapy. Table 1 Multivariable analysis of characteristics associated

n= 175	OS		PFS	
Variable	HR [CI 95%]	p value	HR [CI 95%]	p value
Treatment		0.045		0.040
Chemotherapy (ref)	1.00		1.00	
Immunotherapy	0.70 [0.49 ; 0.99]		0.71 [0.51 ; 0.98]	
Number of metastatic location before 2nd line		0.005		0.011
0-1-2 (ref)	1.00		1.00	
3 or +	1.64 [1.16 ; 2.31]		1.52 [1.10 ; 2.10]	
Performance Status		**0.038**		
0 -1	1.00			
2 - 3 - 4	1.46 [1.02 ; 2.09]			

Figure 1: Kaplan Meier curves for Overall Survival for ICI group and CT group



Conclusion: ICI appears to be the preferred second-line treatment for patients who are refractory to first line chemotherapy

Keywords: Immune Checkpoint Inhibitors, Pronosis, Non-Small Cell Lung Cancer

P1.01-121 SUPERIOR OUTCOMES OF 1ST LINE EGFR TKI IN NEXT-GENERATION SEQUENCING IDENTIFIED UNCOMMON EGFR EXON 19DELINS MUTATION NON-SMALL CELL LUNG CANCER

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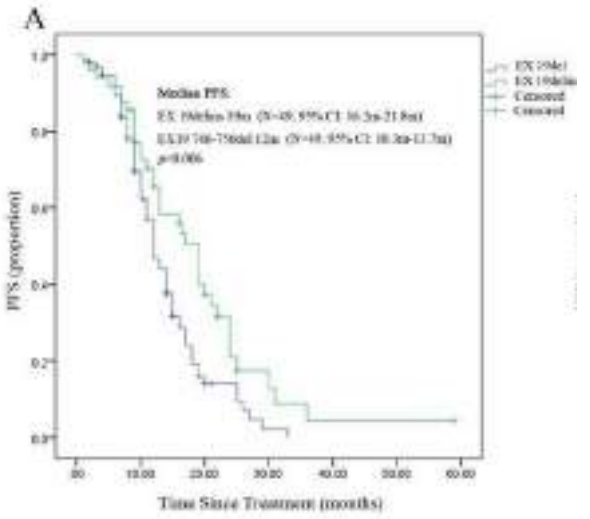
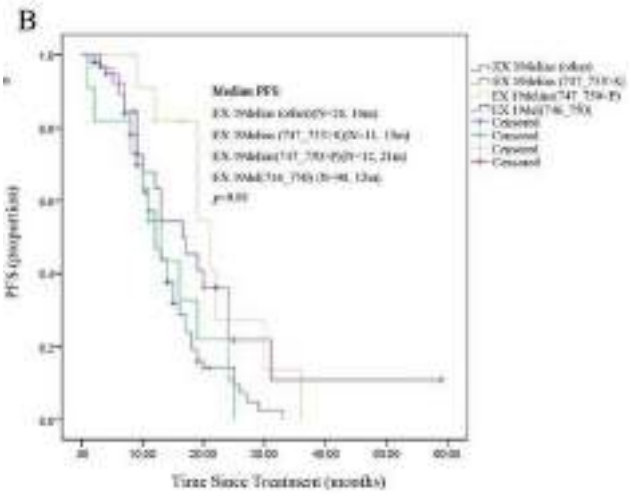
Background: First line EGFR-TKI showed promising efficacy on *EGFR* mutant advanced non-small cell lung cancers (NSCLC). However, the response duration time differs with different mutation variants. The aim of our study was to evaluate the efficacy and resistance mechanism of first-line EGFR TKI in NSCLC patients with uncommon mutation of *EGFR* 19del mutations. **Method:** Among 1530 lung cancer patients who received detection of next generation sequencing (NGS) from Jan, 2015 to Aug, 2018, 49 gefitinib or erlotinib treated EGFR exon 19delins mutant advanced NSCLC patients received NGS of 168 genes panel using tumor tissue in baseline was enrolled in this study for cohort A. Using Propensity Score Matching (Ratio of 1:2), 98 patients carrying *EGFR* sensitive mutation of EGFR exon19del (745-760del) were set as cohort B. EGFR exon 19delins mutation variants in cohort A, clinical outcomes and resistance mechanism for bc





In cohort A, 19 *EGFR* exon 19delins variants were detected and 10 variants were novel. Among exon 19 delins variants, L747-A750delinsP and L747-A753delinsS were the domain variants, contributing to 24.5% (12/49) and 22.5% (11/49) respectively. In cohort A, 38 patients were evaluated with progress disease and 11 patients were ongoing current treatments. In cohort B, 73 patients were evaluated with progress disease and 36 patients were ongoing current treatments. There was no difference between cohort A and B for base characteristics, treatment drugs and response rate. The

median PFS of cohort A and B was 19.0 months *vs.* 12.0 months (p=0.006). In all the 19del variants, the mPFS of L747-A750delinsP subtype was significantly prolong for 21 months (p=0.03). All the progress disease patients received re-biopsy and NGS detection. T790M was defined as the domain acquired resistance mechanism, contributing to 26.3% in cohort A and 45.2% in cohort B, followed by pathology transformation (5.3% *vs* 4.1%) and *MET* amplification (5.3% *vs* 4.1%). **Conclusion:** Our results indicated that patients with EGFR exon 19delins mutation presented with significantly better outcomes for first line EGFR-TKI. Dominate resistant mechanism were still for EGFR exon 20T790M but significantly be decreased in uncommon EGFR mutations.

Keywords: EGFR exon19delins, resistance mechanism, Clinical outcomes

P1.01-122 A CLINICAL UTILITY STUDY OF PLASMA DNA NEXT GENERATION SEQUENCING GUIDED TREATMENT OF UNCOMMON DRIVERS IN ADVANCED NON-SMALL-CELL LUNG CANCERS

H.-Y. Tu[1], C.-R. Xu[1], C. Tong-Li[2], M. Offin[1], P. Razavi[1], E. Schapira[1], A. Namakydoust[1], A. Lee[2], N. Pavlakis[2], S. Clarke[2], C. Diakos[2], D. Chan[2], M. Myers[1], A. Makhnin[1], H. Jain[1], A. Martinez[1], Z. Iqbal[1], A. Adamski[1], H. Li[1], J. Hernandez[3], S. Watford[3], A. Hosseini[3], T. Shaffer[3], L. Lim[3], M. Li[3], A. Drilon[1], M. Ladanyi[1], M. Arcila[1], V. Rusch[1], D. Jones[1], C. Rudin[1], A. Rimner[1], J. Isbell[1], B. Li[1]

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Background: Although EGFR and ALK testing in non-small-cell lung cancers (NSCLC) is now considered standard practice, next generation sequencing (NGS) for extended molecular testing of uncommon drivers is often difficult to perform in the community due to factors surrounding tissue adequacy, availability and turnaround time. We set out to prospectively determine the clinical utility of plasma ctDNA NGS in detecting uncommon actionable drivers and their plasma guided treatment response. **Method:** Patients with advanced NSCLC who were driver unknown after routine EGFR and ALK testing were eligible. Patients were enrolled prospectively at Memorial Sloan Kettering Cancer Center (NY, USA) and Northern Cancer Institute (Sydney, Australia). Peripheral blood (10-20mL) was collected and sent to Resolution Bioscience (*Kirkland, WA*) for targeted ctDNA NGS using a bias-corrected hybrid-capture 21 gene assay in a CLIA laboratory achieving a mean unique read of at least 3000x and sensitivity above 0.1%. Clinical endpoints included detection of uncommon oncogenic drivers defined as actionable alterations in *ROS1*, *RET*, *BRAF*, *MET*, *HER2*, turnaround time, concordance with tissue NGS when available, and plasma guided treatment outcome. **Result:** 614 patients were prospectively accrued. Plasma NGS detected an uncommon oncogenic driver in 7% (45/614) of patients including *ROS1*, *RET* fusions, *BRAF*, *MET* exon 14 and *HER2* exon 20 mutations, of whom 3% (20/614) were matched to targeted therapy producing 12 partial responses. Mean turnaround time for plasma NGS was significantly shorter than tissue NGS (10 vs 25 days, P <0.0001). 399 patients had concurrent tissue NGS results available for concordance analysis; Overall concordance, defined as the proportion of patients for whom an uncommon driver was uniformly detected or absent in both plasma and tissue NGS, was 94.7% (378/399, 95% confidence interval [CI] 92.1 – 96.7%). Among patients who tested plasma NGS positive for uncommon drivers, 87.5% (28/32, 95% CI 71.0-96.5%) were concordant on tissue NGS, and among patients tested tissue NGS positive for uncommon driver, 62.2% (28/45, 95% CI 46.5-76.2%) were concordant on plasma NGS. **Conclusion:** Plasma NGS uncovered uncommon oncogenic drivers with faster turnaround time than tissue NGS, directly matched patients to targeted therapy and produced clinical responses independent of tissue results. A positive finding of an oncogenic driver in plasma is highly specific and can immediately guide treatment, but a negative finding may still require tissue biopsy. Our findings provide prospective evidence to support a "blood first" approach in molecular diagnostics for the care of patients with NSCLC.

Keywords: liquid biopsy, uncommon driver mutation, Non-Small Cell Lung Cancer

P1.01-123 RECENT CLINICAL OUTCOMES OF UPFRONT SURGERY FOLLOWED BY ADJUVANT THERAPY FOR RESECTABLE PATHOLOGICAL N2 NON-SMALL CELL LUNG CANCER

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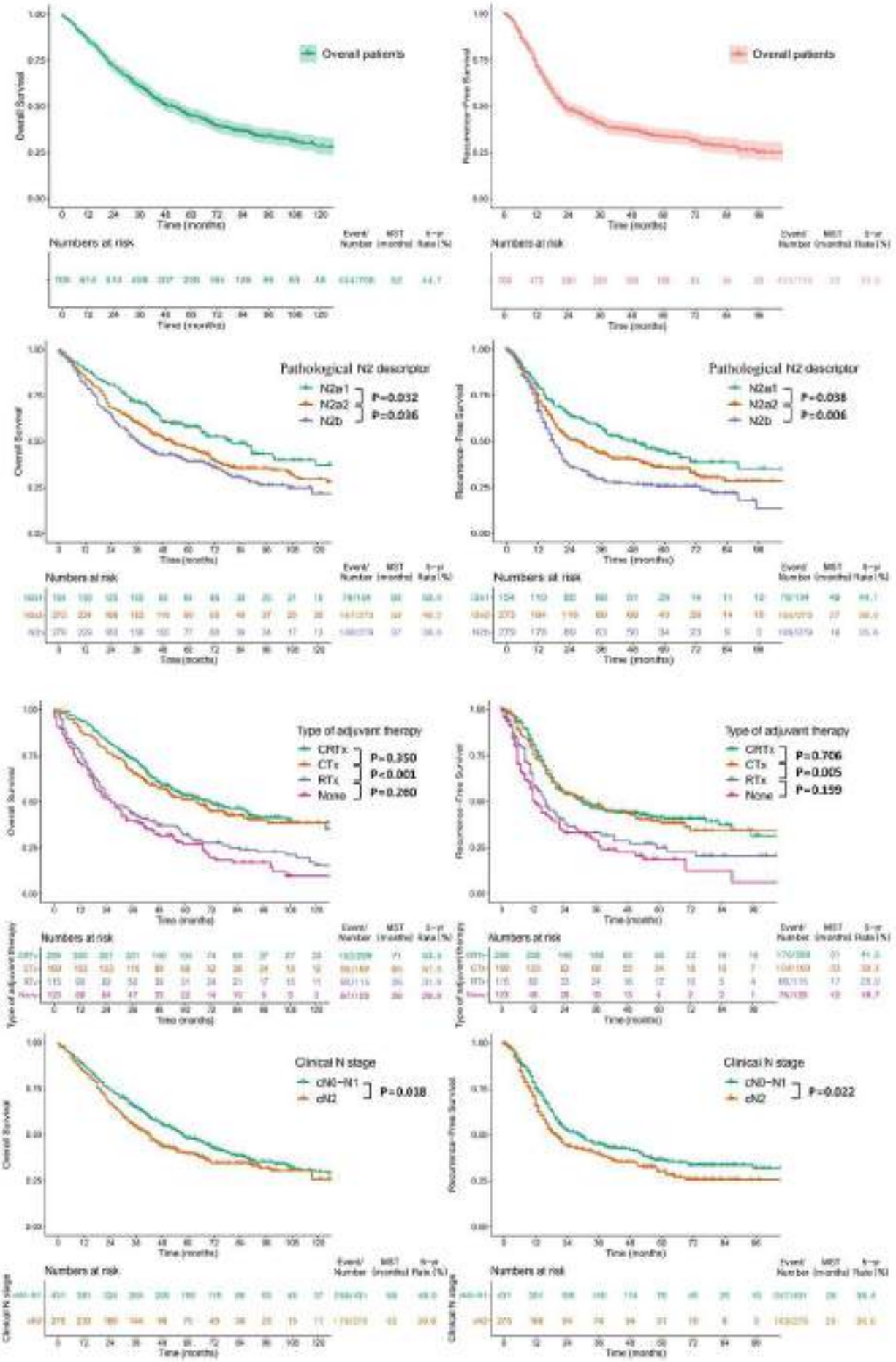
Background: Although definitive treatment with chemoradiotherapy is standard for non-small cell lung cancer (NSCLC) with N2 disease, surgery still has a role in improving the prognosis of patients with resectable tumors. In this study, we evaluated the recent clinical outcomes of upfront surgery followed by adjuvant treatment in pathological N2 (pN2) disease. **Method:** We performed a retrospective analysis of clinical outcomes in patients with pN2 disease who underwent surgery as first-line therapy. Multivariate Cox regression analysis was used to identify the significant factors for overall survival (OS) and recurrence-free survival (RFS). **Result:** From 2004 to 2015, a total of 706 patients who underwent complete anatomical resection were enrolled in this study. With a median follow-up of 40 months, the median OS and RFS times were 52 and 23 months and 5-year OS and RFS were 44.7% and 33.8%. The patients' clinical N stages were: cN0, 308 (43.6%); cN1, 123 (17.4%), and cN2, 275 (39.0%). Adjuvant chemotherapy, radiotherapy, and chemoradiotherapy were administered in 169 (23.9%), 115 (17.4%), and 299 patients (42.4%), respectively. According to subdivided pN2 descriptors, median OS time was 80, 53, and 37 months in patients with pN2a1, pN2a2, and pN2b, respectively. Patients with clinical N0-N1, so-called occult N2 disease, showed better prognosis than those with clinical N2 (P value = 0.018 for OS and 0.022 for RFS). Adjuvant chemotherapy was a significant prognostic factor for both OS and FFR (P value < 0.001 for OS and RFS). **Conclusion:** Recent upfront surgery followed by adjuvant therapy in patients with N2 NSCLC showed favorable outcomes compared to those reported in previous studies. Adjuvant chemotherapy is essential for improving the prognosis in patients undergoing upfront surgery for N2 disease.



Keywords: Lung cancer, N2 node metastasis, initial surgery

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P1.01-124 HEALTH-RELATED QUALITY OF LIFE (HRQOL) DATA IN A PHASE 3 STUDY OF FIRST-LINE BRIGATINIB VS CRIZOTINIB IN NSCLC (ALTA-1L)

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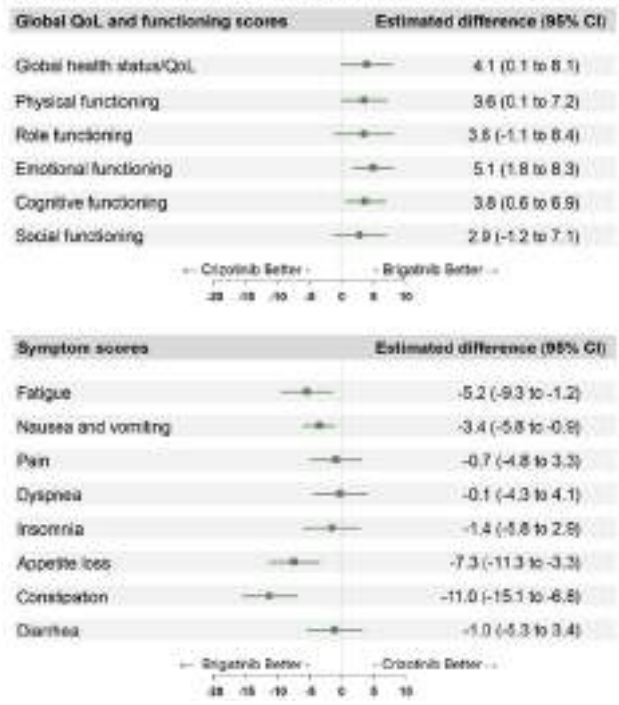
Background: Results from ALTA-1L (NCT02737501) showed that brigatinib vs crizotinib as first-line ALK therapy significantly improves progression-free survival (PFS; HR: 0.49, 95% CI, 0.33, 0.74) in advanced ALK+ NSCLC. HRQoL was evaluated as a secondary objective. **Method:** ALK+ NSCLC patients were randomized 1:1 to brigatinib or crizotinib as first-line ALK therapy. HRQoL was assessed with the EORTC QLQ-C30 and LC13. Change from baseline, duration of improvement, and time to worsening were analyzed in the ITT-PRO population (n=131 for both groups). **Result:** HRQoL compliance was >90% for both groups. Brigatinib substantially improved overall HRQoL vs crizotinib, as demonstrated by the estimated mean difference on change from baseline (4.1, *P*<0.05; Figure 1) and duration of improvement for GHS/QoL (HR=0.16, *P*<0.001; Figure 2), which was also supported by improvement in several functional domains and symptoms (Figure 1). No domains significantly favored crizotinib. Similar results were also observed in patients with baseline CNS metastases.

Figure 1. LS Means of Change from Baseline for EORTC QLQ-C30 Scores



Conclusion: Consistent with the prolongation of PFS seen in first-line treatment of advanced ALK+ NSCLC, brigatinib improved HRQoL and prolonged the duration of improvement in GHS/QoL, and the majority of functional and symptom domains vs crizotinib.

Keywords: brigatinib, Non–small cell lung cancer, Health-related quality of life

P1.01-125 UNIPORTAL VERSUS MULTIPORTAL THORACOSCOPIC LOBECTOMY WITH SYSTEMATIC MEDIASTINAL LYMPHADENECTOMY FOR N2(+) STAGE III NSCLC

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Background: With its growing popularity and potential better outcomes, uniportal(UP) thoracoscopic surgery has been used in the treatment of non small cell lung cancer(NSCLC). In this study,we aimed to evaluate the perioperative and long-term outcomes of uniportal thoracoscopic lobetectomy with systematic mediastinal lymphadenectomy for NSCLC in comparison to multiportal(MP) surgery in our institute. **Method:** A total of 97 consecutive N2(+) stage III NSCLC patients were chosen to undergo thoracoscopic lobetectomy with systematic mediastinal lymphadenectomy in our institute from March 2013 to March 2018. Data such as clinicopathologic characteristics and perioperative outcomes, disease free survival(DFS) and overall survival(OS) were restrospectively reviewed in this article. **Result:** There were 25 patients in the UP group, and 50 patients in the MP group from March 2013 to March 2018.UP group took less time than the MP group in the total operation duration (184.7 ± 69.5 vs 235.5 ± 79.9, P < 0.01). The conversion rate,the average dissected mediastinal lymph node stations,number of mediastinal lymph nodes dissected,the volume of estimated blood loss,volume of thoracic drainage,thoracic tube drainage time,length of postoperative hospital stay,perioperative complication were similar between the two groups(P >0.05). Postoperatively, UP and MP groups showed similar results in terms of disease free survival(DFS) and overall survival(OS). **Conclusion:** In comparison with multiportal thoracoscopic surgery, UP thoracoscopic lobectomy with systematic mediastinal lymphadenectomy showed higher efficiency,and acquired equivalent perioperative short-term and long-term outcomes in the surgical treatment of N2(+) stage III NSCLCs. Further studies based on a larger population and better methodology are required to determine its further benefits towards patients.

Keywords: uniportal thoracoscopic lobectomy, systematic mediastinal lymphadenectomy (SML), advanced non small cell lung cancer

P1.01-126 THE CO-OCCURRING GENOMIC LANDSCAPE OF ERBB2 EXON 20 INSERTION IN NON-SMALL CELL LUNG CANCER (NSCLC) AND THE POTENTIAL INDICATOR OF RESPONSE TO AFATINIB

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POSTERS

Background: Human epidermal growth factor receptor 2 (ERBB2, HER-2) 20 exon insertion (ERBB2ex20ins) has been identified as an oncogenic driver in lung cancer, for which no valid therapy is currently approved. Concurrent alterations may elucidate its refractory features. Previous studies on Afatinib, a pan-ERBB inhibitor, have revealed an inconsistent clinical activity of it for this group of patients. **Method:** Plasma or tissue samples of 112 patients with ERBB2ex20ins were performed next generation sequencing (NGS) for 59 or 1021 cancer-related genes in a Clinical Laboratory Improvement Amendments-certified Laboratory from July 2016 to December 2018. The sequencing data of MSKCC Cohort was downloaded from the public Cancer Genome Atlas Database. The clinical outcomes of 18 patients receiving Afatinib treatment were collected by each contributing doctor in charge and pooled for analysis. **Result:** Among the 112 patients, most of cases were female (54%, 60/112) and adenocarcinoma (68%, 76/112). Considering the insertions sites, three subtypes were A775ins (71%; 79/112), G776indel (17%; 19/112) and P780ins (12%; 14/112) in the order of frequency. 80.4% (90/112) of patients had at least one additional alteration. The most frequent co-occurring genes were TP53 (66.1%, 74/112), LRP1B (18.2%, 10/55), EPHA5 (9.1%, 5/55), MLL3 (9.1%, 5/55) and RB1 (8.0%; 9/112). Putative other driver aberrations were mutually exclusive from ERBB2ex20ins. Furthermore, cell cycle pathway was the most commonly involved pathway (84.0%; 94/112) of all the concurrent genes. No substantial differences of concurrence in genomic or pathway level were observed among the three ERBB2 insertion subtypes. The co-occurring genomic feature of ERBB2ex20ins in Our Cohort of Chinese people had an overall strong concordance with the MSKCC Cohort from the United States (R^2=0.74, P<0.01). For the prognosis, patients had a worse OS when co-occurring mutation in TP53 [median OS:14.5m (95%CI: 12.7m-16.3m) vs 30.3m (95% CI: not reached)], while the OS was not significantly different among three subtypes. The median duration time for patients with disease control of Afatinib was 4.5 months (95%CI: 3.6m-5.4m; range: 2.5m-13.4m). Of note, ERBB2ex20ins in subclonal status was a significantly independent factor relating to shorter PFS of Afatinib [median PFS: 1.2m (95%CI: 0.8-1.6m) vs 4.3m (95%CI: 3.3m-5.3m), P<0.05]. Dynamic detection in two patients found ERBB2 amplification may be a resistance mechanism for Afatinib. **Conclusion:** Concurrence of genetic alterations in NSCLC patients with ERBB2ex20ins was common. The complex genomic characteristic should be fully considered by stratifying patients according to potentially relevant co-mutations other than ERBB2 insertion sites in the designing regimens for them. In addition, the therapeutic effect of Afatinib on patient with ERBB2ex20ins is limited, the clonal status of ERBB2ex20ins may be an important factor with prognosis value.

Keywords: ERBB2 exon 20 insertion, concurrent mutation, Afatinib

P1.01-127 ANTITUMOR ACTIVITY OF THE ORAL EGFR/HER2 INHIBITOR TAK-788 IN NSCLC WITH EGFR EXON 20 INSERTIONS

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Background: We report results of a phase 1/2 open-label, multicenter study of TAK-788 (NCT02716116), an oral investigational EGFR/HER2 inhibitor. **Method:** Patients with advanced, previously treated NSCLC received daily TAK-788 in dose escalation and expansion cohorts based on tumor genotype. Antitumor activity was determined for patients with EGFR exon 20 insertions who received TAK-788 160 mg QD. Safety is reported for all patients across all doses and at 160 mg. To improve gastrointestinal tolerability, food intake instructions in this ongoing study were amended to allow for administration with or without a low-fat meal based on emerging clinical pharmacokinetic data in a healthy volunteer study (data on file). **Result:** As of 14 Sep 2018, 101 patients (median age, 61 y; female, 70%; ≥2 prior anticancer therapies, 76%; brain metastases, 53%) were treated with TAK-788 at 5–180 mg QD. RP2D was determined to be 160 mg QD. 28 patients with EGFR exon 20 insertions were treated with 160 mg QD during dose escalation or in expansion cohort 1 (3.6 months on treatment; 3.8 treatment cycles [medians]); 24 patients remain on treatment. At data cutoff, best response (RECIST v1.1) among 26 patients with ≥1 disease assessment was PR, n=14; SD, n=9; and PD, n=1 (objective response rate, 54%; 95% CI: 33.4%–73.4%); 2 patients were unevaluable. 7/14 objective responses (all PR) were confirmed (6 awaiting confirmation; 1 unconfirmed PR at 160 mg QD); median time to response in these 14 patients was 56 days. 23/26 patients (89%; 95% CI: 69.9%–97.6%) achieved disease control. 23/24 evaluable patients with EGFR exon 20 insertions treated at 160 mg QD had decreased target lesion measurements (median best percent change, -32.6% [-79.1%–3.8%]). Most common TEAEs (≥20%) in patients treated with 160 mg QD: diarrhea (85%), rash (43%), nausea (41%), vomiting (30%), decreased appetite (28%), stomatitis (22%); grade ≥3 TEAEs (≥5%): diarrhea (26%); hypokalemia, nausea, stomatitis (7% each). Among patients treated with 160 mg QD, median dose intensity was 93%, rate of dose reduction due to AEs was 21.7%, and rate of treatment discontinuation due to AEs was 10.9%. There was no clear trend that response to TAK-788 was enriched in any single EGFR exon 20 insertion variant. **Conclusion:** In NSCLC patients with EGFR exon 20 insertions, TAK-788 demonstrated antitumor activity and a safety profile consistent with other EGFR TKIs.

Keywords: EGFR tyrosine kinase inhibitor, EGFR exon 20 mutation

P1.01-128 CHOICE OF POSTOPERATIVE RADIOTHERAPY FOR RESECTED IIIA-N2 NON-SMALL CELL LUNG CANCER: IMPACT OF LOG ODDS OF POSITIVE LYMPH NODES

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Background: Surgical resection alone results in poor survival in patients with stage IIIA-N2 non-small cell lung cancer (NSCLC) owing to high incidence of locoregional recurrence and distant metastasis. One possible way to improve surgical outcome is the administration of postoperative radiotherapy (PORT). However, the benefit and indication of administrating PORT remains controversial for stage IIIA-N2 NSCLC. We aimed to assess log odds of positive lymph nodes (LODDS) as a predictor of the benefit of PORT. **Method:** Patients with resected stage IIIA-N2 NSCLC were extracted from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015. LODDS was defined as $\log_e$[(metastatic nodes count+0.5)/(negative nodes count+0.5)]. X-tile software determined the optimal cut-points for LODDS based on minimal p value method. Survival analyses were conducted with log-rank tests and Cox proportional hazard models. **Result:** Among patients enrolled in this study (n=4197), 1630 (38.8%) received PORT. LODDS was categorized into four groups: LODDS1 (LODDS≤-1.61), LODDS2 (-1.58≤LODDS≤-0.85), LODDS3 (-0.83≤LODDS≤0.00), and LODDS4 (LODDS≥0.01). The median survival in LODDS group 1, 2 ,3, and 4 was 53, 44, 35, and 25 months, respectively. PORT conferred significant improved survival for stage IIIA-N2 NSCLC. According to multivariate Cox regression analyses, PORT and LODDS were both identified as independent prognostic factors. When analyzed by LODDS group, the benefit of PORT was limited to patients with LODDS4 (LODDS≥0.01), whereas the PORT benefit was not observed in LODDS1-3.

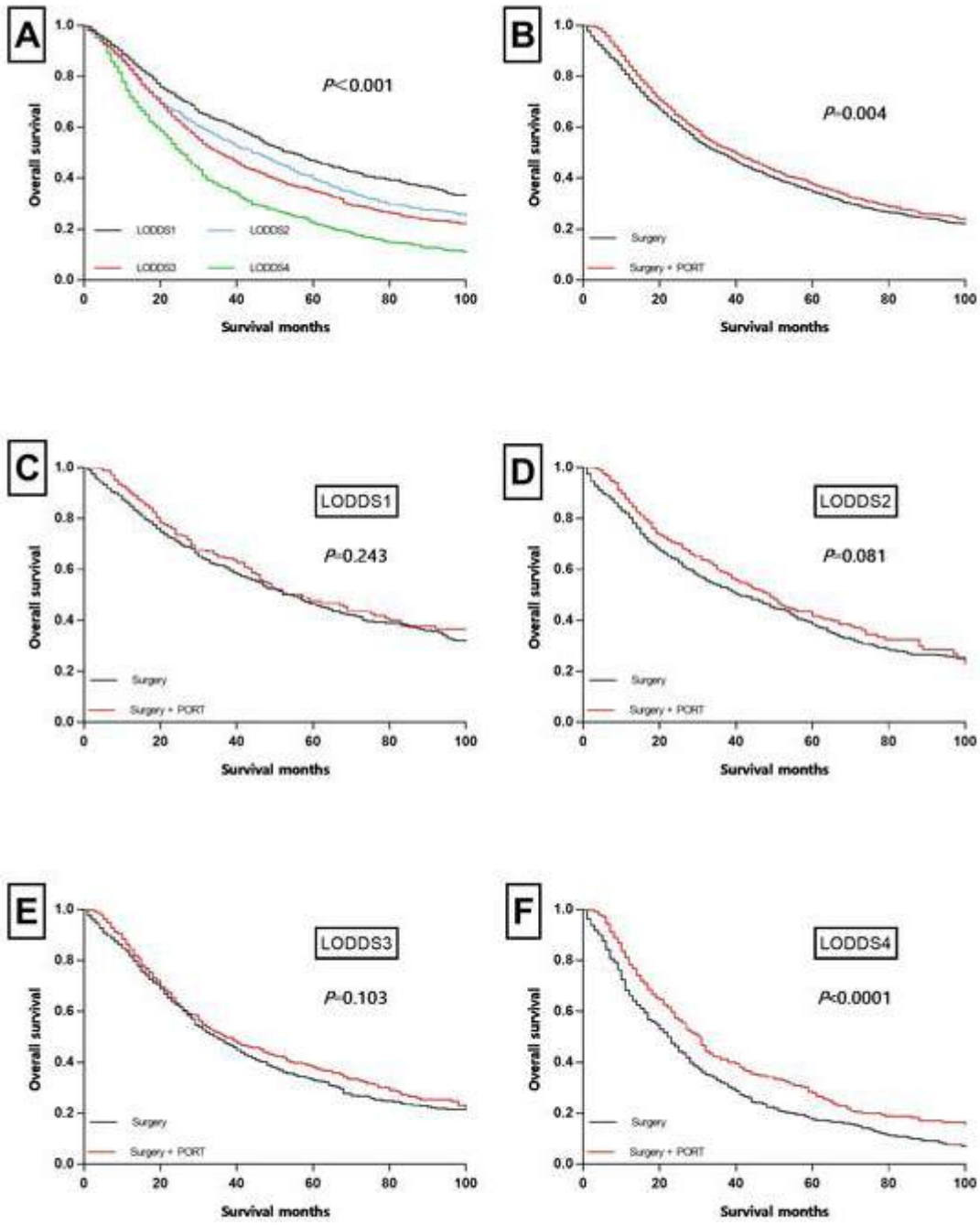

Figure 1 Survival curves stratified by (A) LODDS Categories, (B) treatment modality in whole cohort, (C) treatment modality in LODDS1, (D) treatment modality in LODDS2, (E) treatment modality in LODDS3, and (F) treatment modality in LODDS4.

Conclusion: Our study validates LODDS as a significant prognostic factor in stage IIIA-N2 NSCLC. It is worth noting that LODDS may predict which group of patients could benefit from PORT.

Keywords: Non-Small Cell Lung Cancer, radiotherapy

P1.01-129 PRECLINICAL GENETIC EVALUATION OF ALTERNATING ALK TKI THERAPY VERSUS CONTINUOUS DOSING IN ALK NSCLC TO INFORM THE ALKTERNATE CLINICAL TRIAL

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Background: Despite recent advances in the management of advanced *ALK*-rearranged NSCLC, with high objective response rates to ALK TKI therapy and survival gain, resistance to TKIs remains inevitable. Mechanisms of *ALK*-dominant and non-dominant resistance are being increasingly recognized, although in a many patients the underlying cause of drug resistance is unexplained. ALKternate is a clinical trial recruiting pre-treated patients, testing the hypothesis that with fixed alternating TKI therapy, the emergence of ALK resistant clones can be suppressed through applying variable selection pressure compared to continuous treatment with a TKI. This has been tested pre-clinically with a human cell line to complement the clinical trial in progress, ALKternate (Abstract #2043). Proteomic pathway profiling to complement these data are presented in #2072. **Method:** The H3122 human cell line (EML4(13)-ALK(20) variant 1 fusion) was treated with continuous ceritinib to induce resistance as confirmed by triplicate cytotoxicity assays. Once ceritinib resistance had developed, treatment continued with either continuous lorlatinib ('CONT' arm) or alternating continuous lorlatinib intercalated with crizotinib ('ALT' arm) to recapitulate ALKternate. Treatment continued for 17 cycles. Total nucleic acid was extracted from cells after cycles 5,11 and 17 of treatment and targeted next generation sequencing performed using the Oncomine Lung total nucleic acid assay on the Ion S5 system (Thermo-Fisher Scientific). Results were compared between treatment arms and over time. **Result:** The genetic changes are detailed in Figure 1. The number of mutations identified increased with treatment duration.

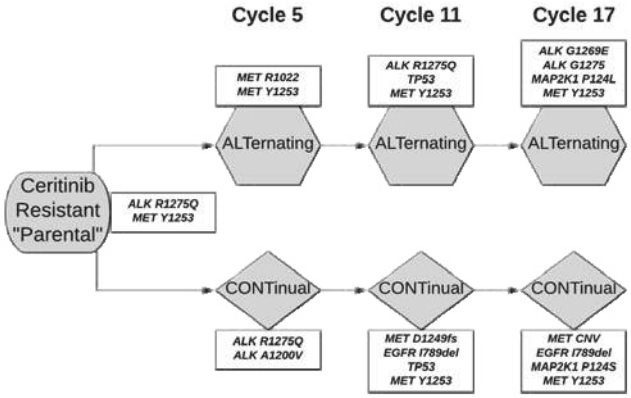

Figure 1: Mutations and copy number gains (CNV) identified. **Conclusion:** In keeping with the hypothesis, the genetic profiles identified demonstrate the emergence of different clones over time and between treatment strategies. This supports further investigation into the novel strategy of alternating therapy as planned in the ALKternate trial.

Keyword: NSCLC, ALK, genetic

P1.01-130 CLINICAL EXPERIENCE WITH NINTEDANIB IN PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER IN SPAIN: A RETROSPECTIVE MULTICENTER STUDY

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Background: Lung cancer is the leading cause of cancer deaths worldwide. Nintedanib is a triple angiokinase inhibitor approved with docetaxel for non-small cell lung cancer after chemotherapy. The aim of this study is to analyze the efficacy and safety of nintedanib in combination with docetaxel in patients treated in various Spanish centers. **Method:** We conducted a retrospective multicenter study, which included all patients with non-small cell lung cancer who received nintedanib with docetaxel in second o third line of treatment. **Result:** We enrolled 124 patients from ten different Spanish centers. The male –female ratio was 3:2, with an average age of 62 years. 82,7% were smokers, 12,2% never smokers and 5,7% former smoker. The most frequent histology was adenocarcinoma (97,6%) and respect mutational state only 5 patients were EGFR mutate and 1 patient presented ALK translocation. PDL1 status was unknown in 46,3% of cases, negative in 32,5% and positive in 21,1%. The majority of patients were diagnosis in stage IV (74%) and in stage III (13,8%). In the first line, 98,4% had received platinum-based chemotherapy and 40,7 % had received previous bevacizumab therapy with an average of 4,1 cycles. The average of nintedanib cycles was 6 and the median time of treatment was 496 days. 65,9% of patients included had progressed to the first line in less than 9 months. The disease control rate was 61% (25,2% stable disease, 34,1% partial response and 1,6% complete response). Progression free-survival was 4,1 months and the overall survival was 26,9 months. The most common adverse events were: fatigue (82,1%), diarrhea (63,4%), nausea (32,5%), neutropenia (33,3%) and cough (18,2%). Thirty-one patients (25,2%) required dose adjustment (15 patients decrease to 200 mg daily and 18 patients to 300 mg daily). **Conclusion:** The efficacy and safety of nintedanib in our cohort is similar to the previously reported. Nintedanib in combination with docetaxel is an effective treatment option for patients with advanced non-small cell lung cancer.

Keyword: non-small cell lung cancer, nintedanib.

P1.01-131 THE COMPARISON BETWEEN NON-INTUBATED AND INTUBATED ANESTHESIA VIDEO-ASSISTED THORACOSCOPIC SURGERY: A META-ANALYSIS

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Background: It remains unclear whether the feasibility and safety of non-intubated VATS under LA is comparable or advantageous compared with conventionally intubated VATS under GA in different thoracic diseases. Consequently, a meta-analysis was conducted with the aim of assessing whether non-intubated VATS offered better perioperative outcomes over intubated VATS in terms of diverse thoracic diseases, including pulmonary nodules, spontaneous pneumothorax, and malignant pleural effusion. **Method:** A comprehensive search of online databases was performed. Intraoperative and postoperative variables were compared between the subgroups. The odds ratio (OR) or SMD and its 95% CI was calculated using a random effects model. Heterogeneity across studies was examined by the Cochran Q chi-square test and the I^2 statistic. **Result:** A total of 15 eligible studies including 1964 patients were recruited. Each included study had comparable baseline characteristics and the same surgical procedures except for the regimens of anesthesia and ventilation. Non-intubated anesthesia VATS was performed on 959 patients, whereas the other 1005 patients underwent intubated VATS. In the overall analysis, patients who underwent non-intubated surgery associated with significant shorter postoperative hospital stays (SMD=-0.36, p<0.001), postoperative fasting time (SMD=-2.80, p<0.001) and anesthesia time as well as lower rates of mortality, postoperative overall, respiratory, and cardiovascular complications. Patients underwent non-intubated surgery also manifested a trend toward shorter operative time and less blood loss with no significant significance. **Conclusion:** Non-intubated VATS was confirmed as a safe and feasible alternative to intubated VATS and potentially provided a more rapid postoperative rehabilitation than intubated VATS overall and specifically in the management of pulmonary nodules, spontaneous pneumothorax, and malignant pleural effusion. Future large-scale multicenter studies are supposed to focus on prospective validation of feasibility and safety and immunological changes for non-intubated thoracoscopic approach

Keywords: Thoracoscopic Surgery, non-intubated, video-assisted

P1.01-132 CLINICOPATHOLOGICAL AND GENOMIC COMPARISONS BETWEEN DIFFERENT HISTOLOGIC COMPONENTS IN COMBINED SMALL CELL AND NON-SMALL CELL LUNG CANCER

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Background: Histologic transformation from adenocarcinoma to small cell lung cancer (SCLC) is one of the mechanisms of acquired resistance after epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. Furthermore, de novo combined SCLC/non-small cell lung cancer (NSCLC) have occasionally been reported; however, their mutational statuses and clinicopathological features have not yet been elucidated. In this study, we aimed to profile the genetic backgrounds of these 2 different histologic components by investigating patients with de novo combined SCLC/NSCLC as well as those with lung adenocarcinoma who experienced SCLC transformation after TKI treatment. **Method:** Four patients with de novo combined SCLC/NSCLC were investigated, as were 4 other patients with lung adenocarcinoma who experienced SCLC transformation after TKI treatment. The different histologic components of the tumors in each patient were tested for thyroid transcription factor-1, p40, synaptophysin, chromogranin A, p53, retinoblastoma protein (Rb), and achaete-scute homolog 1 (ASCL1) via immunohistochemistry, and were macroscopically dissected for mutational analysis using next-generation sequencing with the Oncomine Focus Assay and Comprehensive Assay panel. **Result:** Our study comprised two groups of patients: the first group were patients with de novo combined SCLC/NSCLC and the second group were lung adenocarcinoma with SCLC transformation after TKI treatment. De novo combined SCLC/NSCLC patients have poor prognoses and poor responses to EGFR TKI. In both groups, identical EGFR/TP53/RB1 mutations and p53/Rb expression patterns were observed in both SCLC and NSCLC components. A high frequency of activating mutations involving PI3K/AKT1 signaling pathway was observed in de novo combined SCLC/NSCLC and also in the SCLC component of the second group after TKI treatment. Nuclear ASCL1 expression was present in SCLC but absent or barely present in adenocarcinoma in 7 cases. **Conclusion:** Our data imply that inactivation of TP53/RB1 function is a possible early event in the histogenesis of synchronous and metachronous SCLC/NSCLC. Moreover, the non-adenocarcinoma (SCLC) component might arise from the adenocarcinoma (NSCLC) component through a mechanism that involves the activation of the ASCL1 and PI3K/AKT1 signaling pathways.

Keywords: lung adenocarcinoma, small cell lung cancer, Next-generation sequencing

P1.01-133 RANDOMIZED OPEN-LABEL STUDY OF BINTRAFUSP ALFA (M7824) VS PEMBROLIZUMAB IN PATIENTS WITH PD-L1 EXPRESSING ADVANCED 1L NSCLC

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Background: Transforming growth factor β (TGF- β) promotes tumor progression via immune- and non–immune-related processes. Bintrafusp alfa* (M7824) is an innovative first-in-class bifunctional fusion protein composed of 2 extracellular domains of TGF-βRII (a TGF-β "trap") fused to a human IgG1 monoclonal antibody against PD-L1. Targeting these independent and complementary pathways may restore and enhance antitumor responses. An expansion cohort of the NCT02517398 study of patients with advanced NSCLC (n=80) treated with bintrafusp alfa in the second-line setting presented at ESMO 2018 showed an objective response rate of 86% in the subgroup with high PD-L1 tumor expression at the recommended phase 2 dose (1200 mg intravenously [IV] every 2 weeks [Q2W]). Observed data support the hypothesis that bintrafusp alfa may be superior to other PD-(L)1 inhibitors, including pembrolizumab, for the treatment of NSCLC. Based on the promising antitumor activity and manageable safety profile, this study will evaluate bintrafusp alfa treatment in patients with advanced NSCLC in the 1L setting. **Method:** Here we present a global, randomized trial comparing bintrafusp alfa vs pembrolizumab in the 1L treatment of patients with metastatic NSCLC with high PD-L1 expression levels. Patients in this study must have a histologically confirmed diagnosis of advanced NSCLC with high PD-L1 expression on tumor cells (defined as either ≥80% by the Dako 73-10 pharmDx kit or ≥50% by the Dako 22C3 pharmDx kit since both assays are expected to select a similar patient population at their respective cut-offs). ECOG performance status must be 0 or 1. Patients must not have received prior systemic treatment for advanced NSCLC. Patients with tumors with actionable mutations (for which targeted therapy is locally approved) are not eligible. Patients will receive 1200 mg Q2W or pembrolizumab 200 mg Q3W as an IV infusion until confirmed disease progression, unacceptable toxicity, or trial withdrawal. Dual primary endpoints are progression-free survival and best overall response; key secondary endpoints include overall survival, duration of response, and safety. Estimated enrollment is 300 patients. Clinical trial information: NCT03631706. *Proposed INN. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: bintrafusp alfa, M7824, NSCLC

P1.01-134 SAVANNAH: PHASE II TRIAL OF OSIMERTINIB + SAVOLITINIB IN EGFR-MUTANT, MET-DRIVEN ADVANCED NSCLC, FOLLOWING PRIOR OSIMERTINIB

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Background: The toxicity profile of the third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) osimertinib makes it an attractive backbone for combination with other targeted agents, possibly overcoming acquired resistance mechanisms. Combination with a MET-inhibitor is an intuitive approach as *MET*-amplification was identified as the most common mechanism of resistance to osimertinib in preliminary ctDNA data from the Phase III FLAURA (15% of patients) and AURA3 (19% of patients) studies. Savolitinib (AZD6094, HMPL-504, volitinib) is an oral, potent and highly selective MET-TKI that had an acceptable safety profile when combined with osimertinib in the Phase Ib TATTON study, providing the basis for this Phase II SAVANNAH study (NCT03778229). Other mechanisms of acquired resistance to osimertinib, including secondary *EGFR* mutations (e.g. C797S), RAS/RAF activation, and oncogenic gene fusions, provide additional opportunities for developing osimertinib-based combinations. **Method:** Eligible patients will have histologically or cytologically confirmed *EGFR*-mutant, locally advanced or metastatic non-small cell lung cancer (NSCLC), and *MET*-driven (MET+) disease by central fluorescence *in situ* hybridization (FISH), central immunohistochemistry (IHC), or local next-generation sequencing (NGS; retrospectively confirmed by central FISH/IHC). Patients must have documented radiological progression following 1–3 lines of prior therapy (must include osimertinib). Patients will receive osimertinib plus savolitinib in 28-day cycles. The primary objective is efficacy (RECIST 1.1) by overall response rate (ORR) in patients who are MET+ by central FISH. Secondary endpoints include: ORR (MET+ by central IHC and all patients); progression-free survival, overall survival, duration of response, percent change in tumor size, HRQoL, and *EGFR* mutation ctDNA clearance (MET+ by central FISH, central IHC, and all patients); safety, and pharmacokinetics (all patients). Based on the TATTON study, we anticipate enrolling ~172 patients with MET+ disease, to include ≥117 patients with MET+ disease by central FISH. Enrolment began in Q1 2019. Ongoing development of complementary trials targeting other osimertinib resistance mechanisms will also be discussed. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Non-Small Cell Lung Cancer, resistance, MET

P1.01-135 SALVAGE CHEMOTHERAPY AFTER IMMUNOTHERAPY FAILURE IN NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Objective response rate (ORR) to salvage chemotherapy (sCT) in non-small-cell lung cancer (NSCLC) patients failing upfront platinum-based doublets is limited (≈5-15%). Recently, unexpected favorable outcomes have been reported for sCT upon progression to immune checkpoint inhibitors (ICIs) as compared to historical data, with ORR observed in up to 53% and 27% in Asian and Caucasian patients respectively. Few data are available regarding prior response to ICIs and sCT performance, especially in Caucasian patients. **Method:** All consecutive patients with advanced NSCLC who started ICIs at our institution from Apr 2013 to Dec 2018 were retrospectively reviewed. Patients who underwent sCT after progression to ICIs and had at least one radiological response assessment were included. ORR was calculated as the percentage of complete or partial responses according to RECIST 1.1 as best response. Survivals were estimated with Kaplan-Meier method. Correlation was assessed using Spearman's test. **Result:** Out of 283 patients included, 43 received sCT after ICIs. Among them, 29 (67%) had adenocarcinoma and 14 (37%) squamous cell carcinoma. 11 (26%) patients received sCT as second line therapy and 32 (74%) as third or more advanced treatment. sCT regimens included platinum based doublets (14; 32.5%), docetaxel or paclitaxel (20; 46.5%), and other monotherapies such as gemcitabine or vinorelbine (9; 21%). ORR to sCT was 30%. Median progression free survival and overall survival were 3.6 and 8.4 months, respectively. All patients receiving taxanes as sCT had already been treated with platinum based therapy and their ORR to sCT was 40%. ORR to upfront chemotherapy was 50%, while ORR to the last chemotherapeutic regimen prior to ICIs was 35%. ORR to sCT in pretreated patients was non-inferior to that observed in chemo-naïve ones (31% and 27%, respectively). High ORR (25%) was observed even in patients receiving sCT beyond third line. Neither response to ICIs (P=0.36) nor to prior chemotherapeutic regimens (P>0.05) were associated to the likelihood of achieving tumor response to sCT. **Conclusion:** We provide further evidence that NSCLC patients progressing to ICIs might still benefit from sCT even if heavily pretreated, regardless of sensitivity to ICIs or previous chemotherapy regimens. Further investigations are needed for uncovering bases of increased sensitivity to genotoxic agents in patients with innate or acquired resistance to ICIs and exploiting optimal treatment sequence.

Keywords: Lung cancer, salvage chemotherapy, Immunotherapy

P1.01-136 UNCOMMON EGFR MUTATIONS IN NON-SMALL CELL LUNG CANCER: A SYSTEMATIC LITERATURE REVIEW OF PREVALENCE AND CLINICAL OUTCOMES

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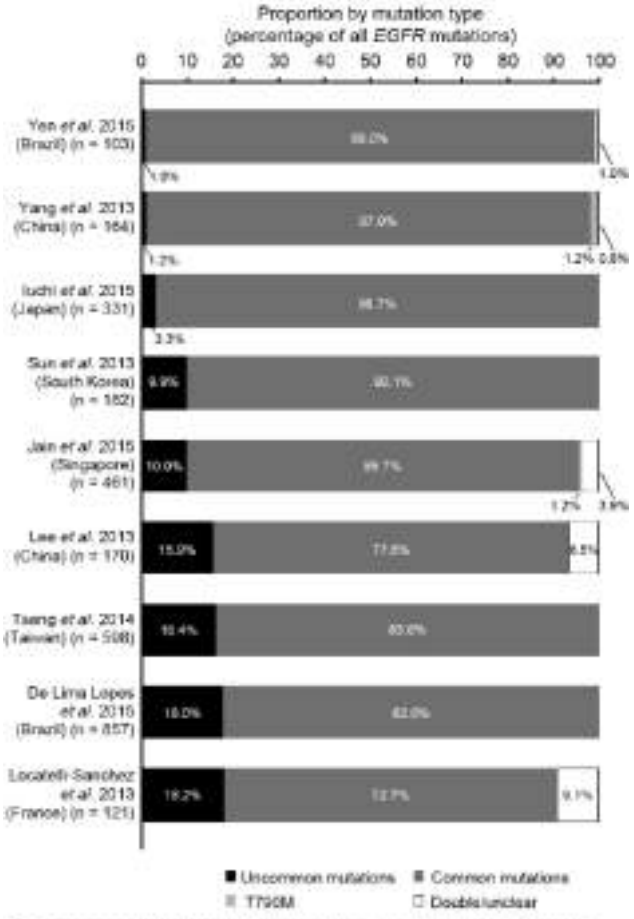
Background: Mutations in exons 18–21 of the epidermal growth factor receptor gene (*EGFR*) can confer sensitivity to tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). About 90% of detected mutations are either deletions in exon 19 or the exon 21 L858R substitution. Comparatively few data are available on the prevalence, treatment sensitivity or clinical outcomes associated with the remaining 10%, termed 'uncommon mutations'. To collate available published evidence, we conducted a systematic literature review (SLR) focussing on these uncommon *EGFR* mutations in metastatic and locally advanced NSCLC. **Method:** Embase, MEDLINE and the Cochrane Library were searched using terms for NSCLC and *EGFR*; abstracts from relevant congresses were also reviewed. Screening identified clinical trials and observational studies published 2012–2019 that included patients with uncommon *EGFR* mutations (all mutations except exon 19 deletions, L858R and T790M). For prevalence data, only studies in which exons 18–21 were sequenced in their entirety were considered relevant; studies that used targeted methods to detect *EGFR* mutations were not included. We assessed the overall prevalence of uncommon *EGFR* mutations, and also compared response to treatment and progression-free survival (PFS) in patients with common and uncommon mutations. **Result:** In total, 20 epidemiology and 90 clinical studies met the inclusion criteria, with broad variation in geography and study population. The prevalence of uncommon mutations varied widely across studies, between 1.0% and 18.2% of all *EGFR* mutations (Figure). The most frequently reported uncommon mutations, either singly or occurring in double/triple mutations, were G719X (0.9–4.8% of all EGFR mutations), exon 20 insertions (0.8–4.2%), L861X (0.5–3.5%) and S768I (0.5–2.5%). Patients with common mutations typically experienced better treatment response and longer PFS than patients with uncommon mutations when receiving TKIs. However, there was considerable heterogeneity across studies, which is likely to result partly from variations in TKI-sensitivity between different types of *EGFR* mutations and disparities in the uncommon mutation types represented in each study. In several studies, exon 20 insertions were associated with worse outcomes than other uncommon mutations, particularly mutations in exon 18.

Figure. Uncommon *EGFR* mutation rates in the prevalence studies identified in the systematic review.



Studies reporting data that allowed calculation of the overall prevalence of common and uncommon EGFR mutations are included. The study of Yang *et al.* (2013) did not differentiate between common and uncommon exon 21 mutations, and therefore the proportion of uncommon mutations may be an underestimate.

Conclusion: This comprehensive SLR indicates that uncommon mutations may comprise a clinically significant proportion of the *EGFR* mutations occurring in NSCLC worldwide. As there are apparent disparities in TKI-sensitivity between some of the most frequently reported uncommon mutations, assessment and reporting of outcomes by specific mutation type will prove invaluable in identifying the most appropriate treatment strategy in each case.

Keywords: EGFR, uncommon mutations, Survival

POSTERS

P1.03-01 POLYMORPHISMS IN GLYCOLYSIS-RELATED GENES ARE ASSOCIATED WITH CLINICAL OUTCOMES OF PACLITAXEL-CISPLATIN CHEMOTHERAPY IN NSCLC

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Background: The shift from oxidative phosphorylation to glycolysis is a hallmark of cancer cells. Rapidly proliferating cells, such as cancer cells, exhibit increased glucose uptake, enhanced glycolysis, and reduced oxygen consumption even in the presence of a normal oxygen supply, leading to the accumulation of lactate. This phenomenon, commonly referred to as the Warburg effect, is thought to occur because cancer cells must deal with increased needs for both energy and biosynthetic intermediates to support their growth and invasiveness . In this study, we hypothesized that polymorphisms in genes involved in glycolysis affect energy production, macromolecular biosynthesis, and other non-glycolytic functions in cancer cells, thus influencing the clinical outcomes of chemotherapy in patients with NSCLC. To test this hypothesis, we evaluated the association of genetic variants in the glycolytic pathway with the chemotherapy response and survival of patients with NSCLC undergoing first-line paclitaxel-cisplatin chemotherapy. **Method:** A total of 377 patients with NSCLC were enrolled. Fifty-seven single-nucleotide polymorphisms (SNPs) in 25 genes involved in the glycolytic pathway were investigated. The association of the SNPs with the chemotherapy response and overall survival (OS) were analyzed. **Result:** Among the 57 SNPs investigated, PFKL rs2073436C>G and GPI rs7248411C>G were significantly associated with clinical outcomes after chemotherapy in multivariate analyses. PFKL rs2073436C>G was significantly associated with a worse response to chemotherapy (adjusted odds ratio [aOR] = 0.64, 95% CI = 0.45–0.90, P = 0.01) and with worse OS (adjusted hazard ratio [aHR]= 1.35, 95% CI = 1.14–1.61, P = 0.001). GPI rs7248411C>G was significantly associated with both a better chemotherapy response (aOR= 1.58, 95% CI = 1.07–2.23, P = 0.02) and better OS (aHR= 0.80, 95% CI = 0.66–0.98, P = 0.03). When stratified by tumor histology, PFKL rs2073436C>G was significantly associated with OS only in squamous cell carcinoma, whereas GPI rs7248411C>G exhibited a significant association with the chemotherapy response and OS only in adenocarcinoma. **Conclusion:** This result suggests that the PFKL rs2073436C>G and GPI rs7248411C>G polymorphisms are useful for predicting the clinical outcome of first-line paclitaxel-cisplatin chemotherapy in NSCLC.

Keywords: Chemotherapy response, Polymorphism, Glycolysis

P1.03-02 NINTEDANIB SELECTIVELY INHIBITS ANGIOGENESIS INDUCED BY THE CONDITIONED MEDIUM OF LUNG ADENOCARCINOMA TAFS IN VITRO

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Background: Nintedanib is an antifibrotic and antiangiogenic drug that was clinically approved to treat EGFR-wild-type lung adenocarcinoma (ADC) patients based on the positive therapeutic results elicited in combination with docetaxel in the LUME-Lung1 clinical trial in ADC but not in squamous cell carcinoma (SCC) patients. However, the mechanisms underlying the selective therapeutic effects of nintedanib in ADC remain poorly understood. Tumor-associated fibroblasts (TAFs) are the most abundant stromal cell type and have been implicated in all steps of tumor progression, including growth, angiogenesis, invasion, metastasis and resistance to therapies. Of note, we recently reported that nintedanib elicits larger antifibrotic effects in ADC-TAFs compared to SCC-TAFs *in vitro*. However, the antiangiogenic effects of nintedanib in TAFs remain unknown. **Method:** ADC-TAFs and SCC-TAFs were activated with TGF-β1 in the presence or absence of nintedanib, and the corresponding conditioned medium was used to stimulate endothelial cells (HUVECs and HMVECs) to either migrate or form vascular networks on Matrigel. **Result:** Our results showed that the conditioned medium from ADC-TAFs and SCC-TAFs induced an increase in human endothelial cell migration. In contrast, the conditioned medium from ADC-TAFs promoted an increase in angiogenesis that was selectively inhibited by nintedanib, whereas such inhibition was not observed in SCC-TAFs. **Conclusion:** Our results reveal that nintedanib inhibits the pro-angiogenic effects elicited by factors secreted by ADC-TAFs but not SCC-TAFs, thereby supporting that angiogenesis may be regulated by TAFs through distinct mechanisms in ADC and SCC.

Keyword: Angiogenesis, TAFs, nintedanib

P1.03-03 INHIBITION OF H1299 LUNG CANCER CELL PROLIFERATION AND SURVIVAL BY ROSEMARY EXTRACT IS ASSOCIATED WITH AMPK ACTIVATION

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Background: Non-small cell lung cancer (NSCLC) represents around 80% of all lung cancer cases and is characterized by low survival rates due to chemotherapy and radiation resistance. New treatments to inhibit NSCLC cell proliferation and survival are urgently needed. The energy sensor AMP-activated protein kinase (AMPK) is a serine/threonine kinase that plays a critical role in cancer cell metabolism, proliferation and survival. Activated AMPK leads to downstream inhibition of the mammalian target of rapamycin (mTOR) and p70S6K resulting in inhibition of protein synthesis and proliferation. Compounds of plant origin have attracted scientific attention for use as agents for cancer prevention and treatment. Rosemary extract (RE) has been shown to have anti-cancer effects. The objectives of the present study were to examine the effects of RE on H1299 human NSCLC cell proliferation and survival, and to investigate its effects on AMPK and its downstream signaling pathways which regulate cell growth and survival. **Method:** Cell proliferation was measured using the crystal violet assay, clonogenic assays were performed to examine the effects of RE on cell survival and immunoblotting with specific antibodies was performed to examine signaling events. **Result:** RE dose-dependently inhibited H1299 cell proliferation and survival. Maximum inhibition of H1299 cell proliferation (30.7±3.0% of control, p<0.001) was seen with 25μg/mL of RE. In addition, significant inhibition (42.3±1.9 % of control, p<0.001) of cell survival was seen with 2.5 μg/mL RE while 10 μg/mL RE caused near complete inhibition of survival (0.8±0.6% of control, p<0.001). AMPK phosphorylation levels were significantly increased by RE treatment. **Conclusion:** Our data indicate that treatment with RE significantly inhibits NSCLC cell proliferation and survival. AMPK phosphorylation/activation is significantly increased by RE treatment and the effects on signaling molecules downstream of AMPK are under investigation. Overall, our data suggest that RE may have potent anticancer properties in NSCLC and warrants further investigation.

Keywords: Survival, NSCLC, proliferation

P1.03-04 USE SUPERNATANT OF MALIGNANT PLEURAL EFFUSION TO IDENTIFY DRIVER MUTANTS AND MONITOR RESPONSE TO TARGETED THERAPY

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Background: Malignant pleural effusion (MPE) from patients with non-small cell lung cancer (NSCLC) is useful for genetic testing due to advantages including availability, less-invasiveness, and less-heterogeneity. Generally, cell pellets of MPE are used. This study is to further address whether supernatant of MPE is a suitable source to identify key oncogenic mutants in NSCLC patients and provide evidence for clinical molecular testing. **Method:** MPE samples from 12 NSCLC patients were centrifuged to obtain supernatants and cell pellets, and DNA were extracted. The DNA samples were analyzed by next generation sequencing (NGS) panels using Illumina HiSeq platform. **Result:** First, MPE samples with the corresponding cancer tissues were collected from 3 NSCLC patients and analyzed with a 500-gene comprehensive cancer panel. Nine mutants were identified

in both the paired MPE and cancer tissue samples. We then analyzed nine more NSCLC patient samples using an 18-gene panel to detect key oncogenic mutants; in total, 8 mutants including EGFR L858R, 19DEL, or T790M were identified in the MPE samples. For all of the 17 mutants from the 12 MPE samples, 10 mutants were observed in both the supernatants and pellets of the matched sample sets, of which more pairs (6 out of 10) had supernatants with higher abundance of mutants than the corresponding cell pellets. Importantly, 7 of the 17 mutants were detected only in the supernatants but not the pellets of the paired MPE samples. These results suggest that supernatant of MPE is a better source to detect key oncogenic mutants of NSCLC. Interestingly, 2 patients had both sensitive and resistant mutants to EGFR tyrosine kinase inhibitor (TKI) detected in supernatants of MPE; both patients had treated with EGFR TKI previously, suggesting the development of TKI resistant mutant and supporting the usage of MPE supernatants in monitoring TKI resistance. **Conclusion:** This study demonstrates that supernatant of MPE is a suitable source for identifying key oncogenic driver mutants for NSCLC and can also be used to monitor response to targeted therapy. The study provides evidence of using supernatant of MPE as an alternative for molecular testing and thus direct precise targeted therapy and surveillance of the therapy effect.

Keywords: Pleural effusion, supernatant, mutant

P1.03-05 COMMD4 IN LUNG CANCER: TOWARDS A NEW THERAPEUTIC TARGET AND DIAGNOSTIC BIOMARKER

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Background: Lung cancer has the highest incidence and mortality among all cancers. As resistance to the current therapies are inevitable, there is a great need to identify new therapeutic targets. In order to prevent cancer, cells possess a complex network of signalling pathways called the DNA damage response, which is involved in the detection, signalling, and subsequent repair of DNA. Failure of the DNA damage response results in cancer and tumorigenesis. The aims of this study were to investigate the therapeutic potential of COMMD4, a new protein within the DNA damage response, in lung cancer. **Method:** The expression of COMMD4 in squamous and nonsquamous non-small cell lung cancer was investigated using bioinformatics, qPCR, lung cancer TMAs and immunoblotting experiments from immortalised human bronchial epithelial cell (HBEC) and lung cancer cell lines. We investigated the function of COMMD4 using *in vitro* assays in HBEC and lung cancer cells that were depleted of COMMD4 using siRNA. **Result:** The *COMMD4* gene was found to be upregulated in lung cancer cells compared with the non-malignant tissue. High levels of *COMMD4* correlated with poor patient prognosis. Additionally, COMMD4 protein levels were upregulated in some lung cancer cells compared with the control HBEC cell line and COMMD4 protein was increased in NSCLC tissue. The depletion of COMMD4 markedly reduced the proliferation of NSCLC cells and not the control cell line. Furthermore, COMMD4-depleted cells were hypersensitive to DNA damaging chemotherapeutic agents which are currently used in the clinic and these agents lead to the induction of apoptosis and mitotic catastrophe in COMMD4-depleted cells. **Conclusion:** Taken together, our data suggests COMMD4 as a potential therapeutic target and diagnostic biomarker in lung cancer, through the induction of cell death and inhibition of tumour growth.

Keywords: DNA damage response, Lung cancer, COMMD4

P1.03-06 INTEGRATIVE OMICS ANALYSIS REVEALS IMPORTANT ROLES OF ADENOSINE DIPHOSPHATE IN HAEMOSTASIS AND PLATELET ACTIVATION IN NSCLC

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Background: Lung cancer is the leading cause of cancer-related deaths in the world. The most prevalent subtype, accounting for 85% of cases, is non-small cell lung cancer (NSCLC). Lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) are the most common subtypes. Despite recent advances in treatment, the low 5-year survival rate of NSCLC patients (approximately 13%) reflects the lack of early diagnostic biomarkers and incomplete understanding of the underlying disease mechanisms. **Method:** We hypothesised that integration of metabolomic, transcriptomic and genetic profiles of tumours and matched normal tissues could help to identify important factors and potential therapeutic targets that contribute to tumorigenesis. We integrated omics profiles in tumours and matched adjacent normal tissues of patients with LUSC (N = 20) and LUAD (N = 17) using multiple system biology approaches. **Result:** We confirmed the presence of previously described metabolic NSCLC pathways, particularly those mediating the Warburg effect. In addition, through our combined omics analyses we found that metabolites and genes that contribute to haemostasis, angiogenesis, platelet activation and cell proliferation were predominant in both subtypes of NSCLC. **Conclusion:** The important roles of adenosine diphosphate (ADP) in promoting cancer metastasis through platelet activation and angiogenesis suggests this metabolite could be a potential therapeutic target.

Keywords: NSCLC, Metabolomic, Transcriptomic

P1.03-07 ADVANTAGES AND SETBACKS OF EGFR MUTATION TESTING FROM LIQUID BIOPSY OF ADVANCED LUNG ADENOCARCINOMA PATIENTS IN SERBIA

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Background: With approximately 8000 newly diagnosed cases in 2018, lung cancer has become the most common malignant disease in Serbia. *EGFR* gene mutation testing as companion diagnostic for treatment with tyrosine kinase inhibitors (TKIs) has been introduced in 2011 in Serbia only for advanced lung adenocarcinoma patients. In 2016. additional *EGFR* mutation testing was employed from liquid biopsy samples of patients who have progressed on TKIs or whose biopsies were unavailable for initial testing. **Method:** *EGFR* mutation testing was performed from FFPE tumor samples or glass slides of advanced lung adenocarcinoma patients (stage IIIB or IV, and ECOG performance status 0, 1 or 2,) using the Cobas® EGFR Mutation Test. Patients with sensitizing *EGFR* mutations were treated with first generation TKIs until progression. Resistance to TKI was tracked from liquid biopsy samples (10 mL of plasma) of patients who progressed in the first three months of first-line TKI treatment. **Result:** In the period between 2011-2018, 4750 *EGFR* mutation analyses were performed, with around 11% of mutated samples detected, which is in good accordance with literature data for the Caucasian population. Although *EGFR* mutation testing has been successfully implemented in routine management of lung cancer patients in Serbia with an average turnaround time of 5 working days, we still had approximately 3% of tumor samples with insufficient material for successful DNA isolation. In such cases, 124 plasma samples were tested, and 9 mutations were detected (7.3 % of total) with a turnaroud time of 2 days, and a 99.2 % testing success rate. Testing liquid biopsy samples of 104 patients who progresses on first-line TKIs showed an accordance rate of 93 % with driver mutations, and 34 patients (33% of total) had the T790M mutation which rendered them eligible for third-generation TKIs in Serbia. Additional 2 patients who tested *EGFR* wt from plasma and were rebiopsied proved to have the T790M mutation as well. **Conclusion:** In developing countries, testing from circulating tumor DNA, as an alternative sample source for patients with scarce biopsy material or without any at all is an acceptable cost/benefit option. However, routine monitoring of molecular disease progression from liquid biopsy before clinical progression occurs has still not been implemented in Serbia for economic reasons.

Keywords: lung adenocarcinoma, EGFR, liquid biopsy

P1.03-08 RNF43 UBIQUITINATES AND DEGRADES PHOSPHORYLATED E-CADHERIN BY C-SRC TO FACILITATE EPITHELIAL-MESENCHYMAL TRANSITION IN LUNG ADENOCARCINOMA

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Background: In epithelial cells, tyrosine kinases induce tyrosine phosphorylation and ubiquitination of the E-cadherin complex, which is responsible for the epithelial-mesenchymal transition (EMT). However, the precise mechanisms remain unclear. **Method:** Protein antibody microarray was applied to identify the potential E3 ligase to downregulate E-cadherin. EMT was determined by morphology, epithelial-mesenchymal markers and aggressive behavior *in vivo*with the lung adenocarcinoma cell lines and tissues. The molecular biological methods including western blotting, immunoprecipitation, MALDI-Mass, immunohistochemistry, et al were applied to explore the signaling of RNF43-mediated EMT. **Result:** Protein antibody microarray and E3 ligase profiling revealed that RING finger protein 43 (RNF43) is linked with E-cadherin downregulation within the context of c-Src activation in lung adenocarcinoma tissues. In addition, c-Src-Caspase-8 interaction markedly increased c-Src activity. Activated c-Src phosphorylated E-cadherin at the tyrosine 797 site to initiate RNF43-mediated E-cadherin ubiquitination at lysine 816 and subsequent degradation, thus freeing β-catenin into the nucleus to upregulate Vimentin and RNF43 in lung adenocarcinoma cell. Decreased E-cadherin and increased Vimentin induced EMT phenotype and promoted tumor metastasis. Frizzled 8 (Frz8)-RNF43 induced ubiquitination of phosphorylated E-cadherin was blocked by monoclonal antibody against the cysteine-rich domain (CRD) of Frz8 but not by antibodies against the protease domain (PA) of RNF43. **Conclusion:** Our data suggest that RNF43 participates in the regulation of EMT in the metastasis of lung adenocarcinoma, through ubiquitination and degradation of phosphorylated E-cadherin by activated c-Src.

Keywords: Caspase-8, RNF43, c-Src

P1.03-09 ATYPICAL UBIQUITIN AS A MOLECULAR TARGET IN LUNG CANCER

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Background: Atypical ubiquitin is a newly identified type of posttranslational modification. Although the role of most atypical ubiquitins remains unknown, linear ubiquitin (M1Ub) was shown to regulate activation of NFkB signaling. M1Ub is specifically assembled by an enzyme complex known as linear ubiquitin chain assembly complex (LUBAC), composed of the proteins HOIP, HOIL-1L, and Sharpin. Since the role of M1Ub and LUBAC in lung cancer is unclear, our study aimed to identify the potential value of LUBAC as a molecular target in lung cancer. **Method:** We searched for lung cancer cell lines with high LUBAC expression. We inhibited LUBAC activity by siRNA or CRISPR/Cas9 and analyzed effect on tumor proliferation, migration, and tumor formation. We also analyzed prognostic impact of LUBAC expression in lung cancer patients and searched for mutations known to activate LUBAC activity. **Result:** Several adenocarcinoma cell lines showed high LUBAC expression. LUBAC inhibition resulted in lower proliferation, migration, and tumor formation, partly via activation of NFkB and ERK signaling. LUBAC knockdown also showed increased apoptosis via activation of caspases. The expression of LUBAC was a significant prognostic factor in survival of lung adenocarcinoma patients. Few patients were identified with a mutation of HOIP related to LUBAC formation, resulting in high LUBAC expression. **Conclusion:** We identified that LUBAC components regulate proliferation, migration, and apoptosis in certain lung cancer cell lines. LUBAC expression was also associated with prognosis of lung cancer. LUBAC components may become a potential treatment target in lung cancer.

Keywords: Lung cancer, ubiquitin

P1.03-10 HIGH-RISK GROWTH PATTERNS OF LUNG ADENOCARCINOMA SHOW DISTINCT MODES OF METASTASIS AND RECURRENCE

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Background: Following curative surgery for non-small cell lung cancer, around half of patients ultimately succumb to recurrent/metastatic disease. This may occur in many ways, such as recurrence at the surgical site, within the pleura, or by metastatic spread via lymphatics or blood vessels. This study aims to identify tumour-intrinsic pathological risk factors which predict particular modes of recurrence of lung adenocarcinoma, to improve our understanding of both the clinical course of disease and the biology underlying tumour recurrence. **Method:** A single-centre cohort of 1025 patients who had surgically resected primary lung adenocarcinoma between the years of 1998 and 2015 was used. Full clinicopathological data were collected from patient records and slide review. All available radiology image data were examined to identify first recurrence site(s) for each case; these were grouped as surgical site, ipsilateral lung, ipsilateral pleura, nodal recurrence and distant recurrence. 824 cases with complete recurrence data were included in the final analysis. Univariate and multivariate Cox models of time to recurrence after surgery for each recurrence site were constructed. Depending on recurrence site, models included growth pattern (predominance or presence), tumour size, nodal involvement, vascular invasion, pleural involvement, surgical procedure and R stage. **Result:** 408 patients (49.5%) had recurrent disease, with 200 (24.2%) patients showing simultaneous recurrence at multiple sites. Of the patients who developed recurrences, 99 (24.3%) recurred at the surgical site. 118 (28.9%) patients recurred within the ipsilateral lung and 75 (18.4%) within the ipsilateral pleura. There were 168 instances of nodal recurrence, most often within N2 lymph nodes (n=95, 56.5%). 316 cases of distant recurrence were reported, with the most common sites being the contralateral lung (n=110, 34.8%), bone (n=71, 22.5%) and brain (n=67, 21.2%). Distant recurrence is associated with significantly shorter post-recurrence survival (PRS) than locoregional recurrence (50% PRS 7.9 vs. 11.1 months, P=0.008). Surgical site recurrence is related to subanatomical wedge resection (HR=4.98, 95% CI: 2.45-10.12, P<0.001), tumour size (HR=1.01, 95% CI: 1.00-1.03, P=0.042) and positive resection margins (HR=4.05, 95% CI: 2.01-8.15, P<0.001). Ipsilateral pleural recurrence is strongly predicted by advancing PL stage (PL2 vs. PL0, HR=2.61, 95% CI: 1.18-5.77, P=0.018; PL3 vs. PL0, HR=3.74, 95% CI: 1.64-8.51, P=0.002). Notably, recurrence in the ipsilateral lung (HR=2.08, 95% CI: 1.29-3.35, P=0.003) and nodal recurrence (HR=2.11, 95% CI: 1.29-3.46, P=0.003) are both independently predicted by the presence of any micropapillary component of tumour growth. In contrast, distant recurrence is related to solid pattern predominance (HR=2.50, 95% CI: 1.43-4.35, P=0.001) univariately, and with near independence in multivariate analysis (HR=1.79, 95% CI: 0.99-3.24, P=0.054). In multivariate models, only solid-predominant tumours are significantly associated with recurrence in the brain (HR=8.52, 95% CI: 1.13-64.01, P=0.037). **Conclusion:** We present evidence that the two high-risk patterns of tumour growth, solid and micropapillary, have predilections for recurrence/metastasis via haematogenous and lymphatic vascular systems respectively. This distinction raises important biological questions about mechanisms of tumour spread, and may help to inform future treatment and prevention strategies.

Keywords: Non small cell lung cancer, site-specific recurrence, Growth pattern

P1.03-11 MOLECULAR TESTING OF SMALL BRONCHOSCOPY SPECIMENS USING NANOSTRING TECHNOLOGY

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Background: Molecular testing for driver variants in oncogenes is crucial for NSCLC management to predict response to targeted therapy. In the majority of cases, NSCLC is diagnosed by trans-thoracic needle aspiration or more commonly bronchoscopy techniques resulting in small diagnostic tissue biopsies or cytological samples. As such specimens may be inadequate for molecular testing, we tested the accuracy of a novel digital molecular barcoding

assay to detect actionable mutations in a single-centre cohort. **Method:** A consecutive cohort of 46 specimens (19 endobronchial biopsy, EnBx; 18 transbronchial biopsy, TBBx; seven bronchoalveolar lavage, BAL; and two transbronchial needle aspirate, TBNA) were obtained ancillary to primary diagnostic specimens from 36 patients undergoing EBUS-guided bronchoscopy at The Prince Charles Hospital. Specimens containing at least 5ng DNA after standard column-based extraction methods were analysed using the NanoString SNV Solid Tumour Panel for testing of 104 somatic variants across 25 genes of clinical significance. NanoString variants calls were compared with routine clinical testing results from the primary diagnostic sample. Agreement analyses for variants common to both methods revealed the positive, negative and overall percentage agreement (PPA, NPA, OPA). One discordant case was validated using droplet digital PCR. **Result:** Using NanoString, molecular analysis was feasible for 60.1% (28/46) of specimens. At least one variant was identified in 8/28 (28.6%) cases (Table 1). Two (7.1%) cases harboured dual mutations. *KRAS* mutations were detected in six (21.4%) cases, and *EGFR* in two (7.1%). Two patients would be eligible for targeted therapy. Agreement analysis for the two methods revealed PPA, NPA and OPA of 100%, 88.9% and 92.3%. In one discordant case, NanoString identified a *KRAS* G12C mutation and was confirmed by ddPCR with a mutant allele frequency of 5.5%. The mean time for reporting clinical mutation test results was 19.6 days. Of the 18 excluded cases with insufficient DNA, five had routine testing results for comparison however 3/5 cases cited insufficient DNA for reliable *EGFR* testing.

Table 1: Clinical and molecular characteristics of bronchoscopy samples used for molecular testing

				Clinical molecular testing			NanoString	Concordance
Case no.	**Sample type**	**Histological classification**	**DNA yield (μg)**	**Mutation testing result (MAF)**	**Mutation testing method**	**TAT to result (days)**	**SNV panel result**	**Agreement (Yes/No)**
1	BAL	No evidence of malignancy	2.81	Not performed	N/A	N/A	WT	NCA
2	TBNA	AC	4.39	Not performed	N/A	N/A	WT	NCA
3	TBBx	SCC	0.39	Not performed	N/A	N/A	*KRAS* G12R	NCA
4	TBBx	AC	1.82	*EGFR* exon 19 (L747_P753>S) del (24%)	NGS TruSight	21	*EGFR* exon 19 (L747_P753>S) del	Yes
5	TBBx	No evidence of malignancy	1.24	Not performed	N/A	N/A	WT	NCA
6	TBBx	No evidence of malignancy	0.62	Not performed	N/A	N/A	WT	NCA
7	EnBx	AC	1.41	WT for *EGFR*, *KRAS*, *NRAS*, *BRAF*	NGS TruSight	13	WT	Yes
8	EnBx	SCC	0.57	Not performed	N/A	N/A	WT	NCA
9	TBBx	SCC	0.53	Not performed	N/A	N/A	WT	NCA
10	TBBx	AC	0.51	WT for *EGFR*, *KRAS*, *NRAS*, *BRAF*	NGS TruSight	20	*KRAS* G12C	No*
11	TBBx	AC	0.31	*EGFR* L858R (12%), *EGFR* T790M (6%)	NGS TruSight	13	*EGFR* L858R, *EGFR* T790M	Yes
12	TBBx	No evidence of malignancy	0.69	Not performed	N/A	N/A	WT	NCA
13	TBBx	NSCLC	4.26	WT for *EGFR*	castPCR	48	WT	Yes
14	EnBx	AC	1.37	*KRAS* G12C (10%)	NGS TruSight	23	*KRAS* G12C	Yes
15	EnBx	NSCLC	19.6	*KRAS* G12A (25%)	NGS TruSight	20	*KRAS* G12A	Yes
16	EnBx	Carcinoid	1.16	Not performed	N/A	N/A	WT	NCA
17	TBBx	SCC	5.4	Not performed	N/A	N/A	WT	NCA
18	EnBx	AC	4.03	WT for *EGFR*, *KRAS*, *NRAS*, *BRAF*	NGS TruSight	19	WT	Yes
19	EnBx	SCC	2.12	Not performed	N/A	N/A	WT	NCA
20	TBBx	AC	3.85	WT for *EGFR*	castPCR	14	*KRAS* G12C, *NRAS* Q61K	NCA
21	EnBx	SCC	6.4	Not performed	N/A	N/A	WT	NCA
22	TBBx	AC	1.63	WT for *EGFR*	castPCR	20	*KRAS* G12C	NCA
23	EnBx	AC	0.234	WT for *EGFR*, *KRAS*, *NRAS*, *BRAF*	NGS TruSight	16	WT	Yes
24	BAL	AC	0.871	*BRAF* G466V (12%)	NGS TruSight	24	WT	Yes
25	TBBx	AC	0.0918	*BRAF* G466V (12%)	NGS TruSight	N/A	WT	Yes
26	TBBx	AC	0.893	WT for *EGFR*	castPCR	13	WT	Yes
27	TBBx	SCC	0.66	Not performed	N/A	N/A	WT	NCA
28	EnBx	AC	4.4	WT for *EGFR*	castPCR	10	WT	Yes
Mean			2.58			19.6		

Conclusion: The performance of the NanoString platform for SNV characterisation was highly concordant with alternate clinical testing methods for those with sufficient DNA. Advantages of NanoString include its multiplex capacity, high sensitivity, low nucleic acid input, reduced turn-around time (<24hr) compared to alternate testing methods. The NanoString platform is a robust method for identification of actionable variants in NSCLC where at least 5ng of DNA is available.

Keywords: single nucleotide variants, mutation profiling, Non-Small Cell Lung Cancer

P1.03-12 PRECLINICAL VALIDATION OF AN EPIGENETIC PANEL OF SEVEN MIRNAS AT EARLY STAGES NSCLC PATIENTS AND ITS PROGNOSTIC IMPLICATIONS

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Background: Despite radical intent, many patients in early stages of NSCLC will recur. There is a need to find novel biomarkers able to help to identify patients in higher risk. Previous results from our group provide a miRNA signature from "*in vitro*" studies that might be involved in worst prognosis in NSCLC patients (PMID: 29158814). The main objective of this work is to analyse and compare the miRNA seven-panel signature in paired plasma (CIRmiARN) and tumor tissue samples (TmiARN) obtained from early stages NSCLC patients and to study the clinical implications. **Method:** We conducted a descriptive study including 16 paired samples of patients diagnosed with early stage NSCLC. Both RNA from fresh tissue and plasma were extracted and the seven mRNAs levels were measured by qRTPCR(miR-7, -132, -335, -148, -10a, -124 and -9). Association between qualitative variables was analyzed using the chi-square test or Fisher's exact test. Mann-Whitney U test and the t-student test were used for qualitative and quantitative data comparison. A Kaplan Meier survival analysis (log-rank analysis) was carried out to study the overall survival and progression-free survival. Patients were also clustered in terms of tissue and plasma values, and then subgroups analyzed in terms of Survival. Difference between groups was analyzed with Cox Regression. **Result:** There was no association between CIRmiARN and TmiARN expression levels and between clinical parameters. We found significant data associated with three miRNAs. There were significant differences ($p<0.05$) with low TmiR-132 expression level and worse survival and also a clear trend towards the group of patients with high levels of CIRmiR-7 and CIRmiR-124 and worst survival. Interestingly, we found an inverse correlation between CIRmiARN-132 and -124($p<0.05$). Patients clustered regarding TmiR132 and CIRmiR-124 and -7levels, segregate in three clusters statistically significant in terms of survival ($p<0.005$), identifying a group of patients with a reduced risk of 78,6% (Hazard Ratio of 0.214 p<0,005). **Conclusion:** Many patients diagnosed in early stages of NSCLC present a tumor relapse during the first 5 years. Genetic and epigenetic profiles help us to identify tumors with a greater risk of recurrence. In our study, we have identified three potential molecular candidates, both in liquid and tissue biopsies, which could have potential clinical use stratifying patients with higher risk of recurrence. Further studies will be needed to gain insight into the prognostic impact of these biomarkers in early and advanced stages NSCLC patients.

Keyword: Epigenetic, Early stages NSCLC, Recurrence

P1.03-13 GENOMIC LANDSCAPE OF BRAZILIAN NON-SMALL CELL LUNG CANCER

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Background: Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer with low survival rates. Therefore, NSCLC patients may be benefited by tailored treatment based on genomic profiling. However, the genomic landscape of Brazilian NSCLC remains unknown. Thus, our aim was to evaluate the genomic profiling of NSCLC of a Brazilian series. **Method:** We analyzed 96 NSCLC patients from Barretos Cancer Hospital, Brazil. Exome sequencing of paired tumor/blood DNA was performed by Illumina HiSeq2500™ and VarScan was applied for germline alterations exclusion, variant calling, and annotation. Cancer Genome Interpreter was employed for identification of driver genes. Mutational Signatures were performed using Somatic Signature. Copy Number Variations (CNV) were determined using Circular Binary Segmentation. Gene expression analysis was assessed by NanoString and pathway enrichment was performed using KEGG. **Result:** Overall, 61 cases were adenocarcinomas, 34 squamous cell carcinomas and 1 was adenosquamous (I, n=19; II, n=14; III, n=23; IV, n=40). Regarding smoking, 82 patients were current/former smokers and 12 patients were never smokers and most of the cases presented the mutational signature 4. More than 30,000 mutations were identified and 733 were classified as drivers (known: 90; predicted: 643). *TP53* gene was the most recurrently mutated gene (56% of the cases). Besides of *TP53* gene, recurrent mutations were found in *KRAS* (23%), *EGFR* (12.5%), *NFE2L2* (9%), *HERC2* (9%), *STK11, ROS1, PIK3CA and CDKN2A* (8%). *KRAS*, *EGFR, STK11* and *ROS1* mutations were mutually exclusive. CNV gain was observed in 1q21.3, 1q22, 3q26, 31q29, 7q11.21, 7p11.1-q11.1, 8p11.1-q11.1, 19q13. Downregulation of *DKK1, IBSP, LAMC2, NGFR* and *LAMB3* and upregulation of *LAMC3, MAPK8IP1, IL5RA, NR4A1, AXIN2, PLA2G4E, COL6A6, CACNA2D2, LRP2, NR4A3, FOS, BMP5*, and *FGFR2* were observed in disease stages I/II indicating enrichment of PI3K-Akt, MAPK, Ras, Rap1 and Wnt signaling pathways. Downregulation of *MCM2, VEGFA, E2F1, HMGA1, CCNE1, CHEK1, RAD51, FOSL1, CCNB1, GNG4, IL11* and *IL8* and upregulation of *WNT10B, MAPK10, GNG7, WNT4, IL7R, PIK3CG*, and *FGFR2* were observed in never smokers indicating enrichment of Cell cycle, Pathways in cancer and PI3K-Akt signaling. Differential expression of *KRAS*-mutated tumors indicated enrichment of ECM-receptor interaction, Focal adhesion, and PI3K-Akt pathway and *TP53*-mutated tumors indicated enrichment of Cell Cycle. **Conclusion:** The genomic profiling of Brazilian NSCLC indicated remarkable driver mutations and genomic amplifications. Gene expression profiling indicates the enrichment of key pathways enrolled in *TP53*- and *KRAS*-driven tumors. Our results may contribute for improving the knowledge about the molecular pathogenesis of Brazilian NSCLC.

Keywords: NSCLC, genomic landscape, driver genes

P1.03-14 HLA-E AND FAT1 IN HEAD AND NECK AND LUNG CANCER. THE EFFECT OF OSIMERTINIB OR OLMUTINIB WITH ARTESUNATE (DIHYDROARTEMISININ)

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Background: Cisplatin and cetuximab have little effect in head and neck squamous cell carcinoma (HNSCC) and lung squamous cell carcinoma (LSCC). HLA-E expression suppressed the cetuximab effect and HLA-E is overexpressed in both HNSCC and LSCC. In addition, FAT1 inactivating mutations are present in 30% of HNSCCs and 19% of LSCCs. Dihydroartemisinin (DHA) inhibits STAT3 and increases cisplatin effect in HNSCC. Osimertinib and olmutinib increase intracellular accumulation of doxorubicin by blocking the efflux function of ABC transporters. We posit that osimertinib or olmutinib, plus DHA, could have activity in the HNSCC cell lines, FaDu and CAL27, with loss of FAT1 expression. **Method:** Osimertinib and olmutinib plus DHA were tested in the FaDu and CAL27 cell lines. Tumor cell proliferation assays (MTTs) and mouse xenografts were performed, and western blotting analysis was carried out. FaDu CTXR clone #3 (cetuximab-resistant, a gift from Bhola) and SCCNC4

(EGFR exon 20 S768_D770 dup, a gift from Hermsen) were also examined. **Result:** 1. DHA decreased HLA-E protein levels in a dose dependent manner in the FaDu CTXR. 2. DHA was able to induce the expression of FAT1 in FaDu and CAL27 cells. 3. Osimertinib plus DHA had a synergistic effect (<1, Combination index (CI)=0.468 and 0.593 in FaDu and CAL27, respectively). Olmutinib with DHA was also synergistic (CI=0.773 and 0.762 in FaDu and CAL27). 4. Osimertinib plus DHA was validated in vivo in FaDu and CAL27 mice xenografts with significant tumor regression. 5. Osimertinib plus DHA suppress the expression of onco-effectors: STAT3, Src, YAP and AXL. 6. Osimertinib plus DHA was also synergistic in SCCNC4 (CI=0.596). **Conclusion:** The findings indicate that DHA can revert resistance to cetuximab by repressing the expression of HLA-E. The combination of DHA plus osimertinib was active in the parental FaDu, but not in FaDu CTXR. For tumors with lack of FAT1 expression, the use of DHA reactivates FAT1 and YAP1 inhibition was noted. DHA has been tested for the treatment of systemic lupus erythematosus (SLE), orally, daily for 2 years. The results encourage development of clinical trials with DHA to re-sensitize HNSCC and LSCC cells to cetuximab-based therapy.

Keywords: dihydroartemisinin, head and neck, Lung cancer

P1.03-15 NON-INVASIVE DETECTION OF SECONDARY RESISTANCE MUTATIONS IN ALK-POSITIVE NSCLC PATIENTS BY NEXT-GENERATION SEQUENCING

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Background: ALK inhibitors have led to important improvements in ALK-positive non-small cell lung cancer (NSCLC) patient's survival and quality of life. However, despite the good responses, resistance mutations inevitably emerge. Several resistance mutations in ALK domain have been describe. Remarkably different mutations can confer different sensitivities to different ALK inhibitors. However, 2nd and 3rd line treatment is often prescribe empirically without knowing the molecular mechanism underlying treatment failure. **Method:** 21 samples from ALK-positive NSCLC patients were collected at disease progression. Circulating Nucleic Acids were isolated from platelets, exosomes and plasma. Libraries were prepared using 20ng of template and Oncomine™ Pan-Cancer Cell-Free Assay. Samples were sequenced on an Ion GeneStudio S5 Plus System. Sequencing data was first analyzed using Torrent Suite software. Subsequently variant calling, annotation and filtering was performed on the Ion Reporter (v5.10) platform using the Oncomine TagSeq Pan-Cancer Liquid Biopsy w2.1 workflow. **Result:** In 14 (67%) patients a somatic mutation was identified in the plasma sample collected at disease progression. The average number of mutations detected per sample was 2.6. Noteworthy, 14 mutations were found in oncogenes that have been previously associated with ALK inhibitors resistance (5 mutations in ALK locus, 4 mutations in PIK3CA, 1 mutation in EGFR, 1 mutation in KIT, 1 mutation in KRAS, 1 mutation in MTOR and 1 mutation in MYC). The rest of mutations (N=21) were found in TP53 gene. Secondary resistance mutation in ALK locus occurred in 24% of the cases. Specifically, p.G1269A (N=2), p.G1202E (N=1), p.R1275Q (N=1) mutations were found in ALK-positive NSCLC who had progressed on crizotinib and p.G1202R mutation was found in 1 ALK-positive NSCLC who had progressed on ceritinib. **Conclusion:** Secondary ALK-TKI resistance mutations could be detected using liquid biopsies in a high proportion of patients. Non-invasive molecular profiling of samples collected at disease progression is feasible being useful for further treatment selection in ALK-positive NSCLC patients.

Keywords: ctDNA, liquid biopsy, ALK

P1.03-16 ANTI-TUMOR EFFECT OF PAN-RAF INHIBITOR IN NSCLC CELLS HARBORING BRAF MUTATION

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Background: *BRAF* mutation occurs in 0.5-3% of lung adenocarcinoma and acts as an oncogenic driver. Dabrafenib (BRAF inhibitor) combined with trametinib (MEK inhibitor) has shown substantial antitumor effect in patients with non-small-cell lung cancer (NSCLC) harboring *BRAF* V600E mutation. However, in patients with NSCLC harboring *BRAF* non-V600E mutation, there are few reports of effective targeted therapy. LY3009120, a newly discovered pan-RAF inhibitor, showed strong anti-tumor effect in *BRAF*-mutant cancers, such as melanoma, colorectal and pancreatic cancers in preclinical studies. In this study, we evaluated the anti-tumor effect of LY3009120 in *BRAF*-mutant NSCLC cells. **Method:** We examined the sensitivity of LY3009120 against normal bronchial cells BEAS-2B which ectopically overexpressing wild-type or mutant *BRAF*. Human cDNAs encoding full-length *BRAF* (wild-type and its variants V600E and G469V) were inserted into the pIDT-SMART (C-TSC) vector, pCMViRTSC. In addition, we treated four *BRAF*-mutant NSCLC cell lines, one *BRAF*-mutant colorectal cancer cell line, and one *KRAS*-mutant cell line with LY3009120. The type of *BRAF* mutation consisted of V600E, L597V, G469A, and G466V. We determined cell proliferation by MTS assay and calculated the IC50 values. We also performed Western blotting to investigate downstream signaling pathways. **Result:** BEAS-2B cells ectopically overexpressing wild-type BRAF or mutants (V600E and G469V) showed constitutive auto phosphorylation of BRAF and activation of downstream signaling by Western blotting. The IC50 values in *BRAF* mutant cell lines ranged from 9.4nM to 1,193nM, which suggests strong anti-tumor effect of LY3009120. This effect was observed regardless of the type of *BRAF* mutation, including non-V600E mutation. On the other hand, LY3009120 did not show anti-tumor effect in *KRAS*-mutant cell (IC50 value, 6,948nM). LY3009120 suppressed the phosphorylation of downstream MEK and ERK activation in *BRAF*-mutant cell lines by Western blotting. **Conclusion:** LY3009120 showed strong anti-tumor effect in NSCLC cells harboring *BRAF* mutation regardless of the type of mutation, suggesting that LY3009120 can be a promising therapeutic option in the treatment of NSCLC harboring *BRAF* mutation.

Keywords: Non-Small Cell Lung Cancer, BRAF mutation, pan-RAF inhibitor

P1.03-17 FUNCTION OF ANTISENSE LNCRNA RP11-539E17.5 AND FAM83A-AS1 UP-REGULATING FAM83A IN LUNG ADENOCARCINOMA TUMORIGENESIS AND DEVELOPMENT

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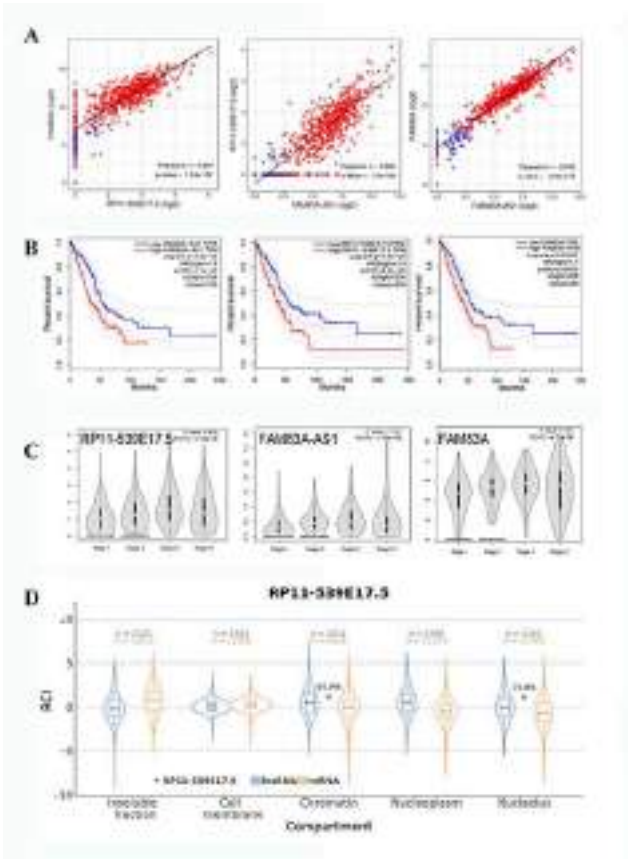
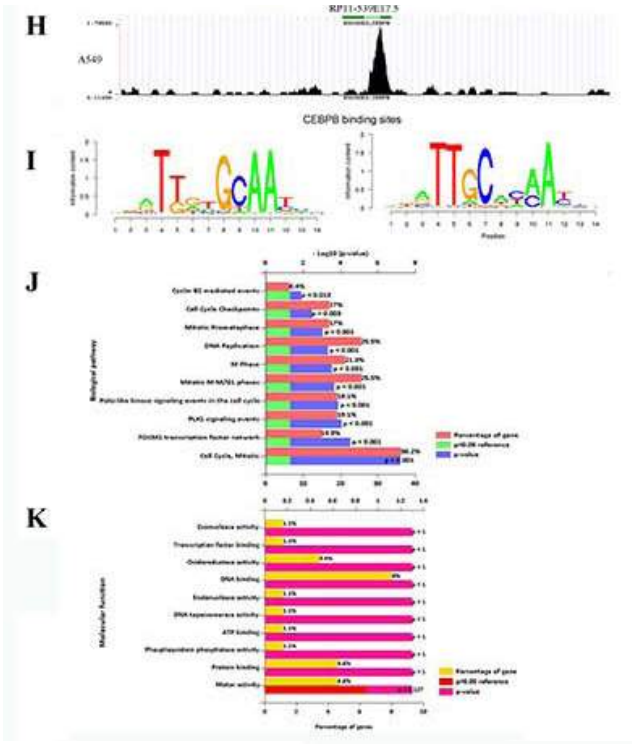
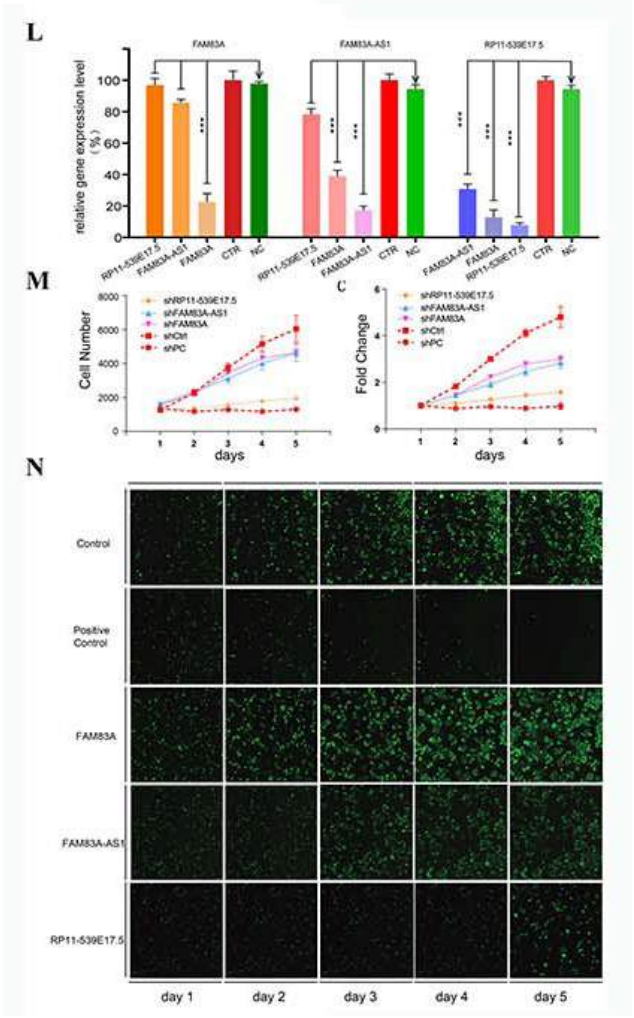
Background: Chromosome 8q24 lies in a gene desert with only a few predicted coding genes, but its variation is associated with multiple tumors. FAM83A in this region activates both PI3K/AKT/TOR and RAS/MAPK signaling cascades downstream of EGFR. The contribution of long noncoding gene in the antisense chain of FAM83A (RP11-539E17.5 and FAM83A-AS1) to the risk of lung adenocarcinoma (LUAD) need to be studied. **Method:** We use systematic informatics method to identify the differential expression genes of the Cancer Genome Atlas (TCGA) LUAD transcriptome sequencing data. Then use data mining method to analysis the lncATLAS, USCS, Cistrome, and ENCODE database to infer the biological role of these two lncRNAs. Significant analysis of gene ontology (GO) terms enrichment analyzed the co-expression genes of RP11-539E17.5 in the LUAD and adjacent tissues. At last we use cell experiment to verify the lncRNA function. **Result:** FAM83A-AS1 and RP11-539E17.5 located in Chromosome 8q24 were significantly different expressed between cancer and adjacent tissues (log2foldchange>5, p<0.05). The two lncRNA expression levels had notable correlation with FAM83A expression (coR> 0.8, P<0.005) and were significantly associated with patient overall survival and clinical stage (p<0.05). RP11-539E17.5, located in the enhancer element GH08J123181,belong to the enhancer lncRNA group. lncRNA subcellular localization data (lncATLAS) results showed that RP11-

539E17.5 transcripts in K562 cells is mainly distributed in the nucleus, and most around the nucleolus and chromosomes. USCS, Cistrome, and ENCODE data mining identified four transcription factors (FOSL2, CTBP2, CEBPB, and MAFK) have significant correlation with the expression of FAM83A-AS1 and RP11-539E17.5. In K562 cell line with high expression of FAM83A-AS1, RP11-539E17.5 and FAM83A showed that expanded regions of RP11-539E17.5 gene sequence were marked by enhancer-specific modifications (H3K27ac domains and H3K4me3 domains). This region also showed an excellent source of DNase sensitive site, and with several binding sites for CTCF, FOSL2, CTBP2, CEBPB and MAFK. In addition, RP11-539E17.5 gene also with enriched DNA methylation feature. RP11-539E17.5 and FAM83A-AS1 knocked down both inhibited the expression of FAM83A the proliferation of PC9, and RP11-539E17.5 gene owning a more significant effect. GO terms enrichment analysis of the co-expressed genes with RP11-539E17.5 showed that the most significantly activated biological pathways is involved with Cell cycle,and cell mitotic signaling pathway, while the molecular function involved with transcription factor binding, DNA binding, ATP binding, endonuclease activity, DNA topoisomerase activity.







Conclusion: We found a LncRNA RP11-539E17.5 with enhancer character up regulate FAM83A expression in LUAD. These results can lay a theoretical foundation for LUAD corresponding countermeasures.

Keywords: LncRNA RP11-539E17.5 and FAM83A-AS1, FAM83A, lung adenocarcinoma (LUAD)

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P1.03-18 OCIAD2 IMPAIRS MITOCHONDRIA-MEDIATED APOPTOSIS THROUGH SUBSTANTIAL ALTERATION OF CRISTA STRUCTURE IN LUNG ADENOCARCINOMA

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Background: Lung cancer is one of the leading causes of cancer-related death worldwide. However, the mechanisms that trigger the progression of early-stage lung cancer remain unclear. Our group has identified a novel cancer-specific protein localized in mitochondria, ovarian carcinoma immune-reactive antigen domain 2 (OCIAD2), which shows significantly higher expression in invasive adenocarcinoma than in adenocarcinoma *in situ* (Ishiyama T *et al*. 2007). Although several reports have focused on OCIAD2 expression in malignant tumors, the roles of OCIAD2 remain unknown. Here we show that OCIAD2 is associated with mitochondrial morphology, including mitochondrial distribution and crista formation. We have also revealed that OCIAD2 regulates mitochondrial crista formation in lung adenocarcinoma by interacting with optic atrophy 1 (OPA1). **Method:** The effects of siRNA transfection on the expression of OCIAD2 mRNA and protein in a lung adenocarcinoma cell line (A549) were examined by real-time RT-PCR and Western blotting. Cellular proliferation was assessed by the WST-8 assay and apoptosis was examined by Western blotting using apoptosis-related proteins such as cleaved caspase -3, -9, and PARP. Moreover, using transmission electron microscopy (TEM), we investigated alterations of mitochondrial morphology in A549 cells after OCIAD2 knockdown. Endogenous and exogenous binding of OCIAD2 and OPA1 were then confirmed by co-immunoprecipitation and Western blotting. **Result:** We confirmed that OCIAD2 expression was downregulated at both the mRNA and protein levels in A549 cells after siRNA-OCIAD2 transfection. Cellular proliferation was significantly decreased after OCIAD2 knockdown. Moreover, suppression of OCIAD2 induced mitochondria-dependent apoptosis by activating cleavage of caspase -3, -9, and PARP. In addition, suppression of OCIAD2 led to alterations of mitochondrial morphology such as crista destruction. Moreover, we confirmed endogenous and exogenous binding of OCIAD2 and OPA1 in A549 cells

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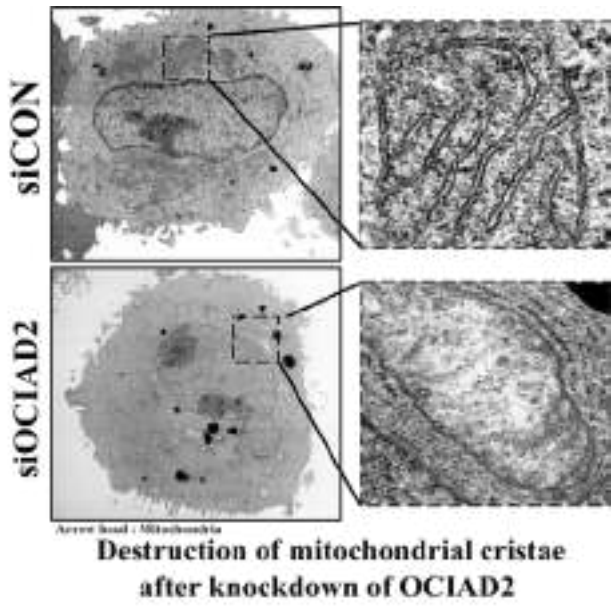

Conclusion: OCIAD2 contributes to the imbalance of cellular proliferation and apoptosis in lung adenocarcinoma. Overexpression of OCIAD2 might prevent tumor cell apoptosis through substantial crista formation by interacting with OPA1. Since OCIAD2 is a tumor-associated protein and is not expressed in normal cells, we believe that OCIAD2 could be a promising therapeutic target for lung adenocarcinoma.

Keywords: OCIAD2, lung adenocarcinoma, Mitochondria

P1.03-19 CIRCULATING TUMOUR CELLS IN NON-SMALL CELL LUNG CANCER

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Background: Metastasis in cancer patients is reflected by measurable levels of circulating tumour cells (CTCs) in the blood of cancer patients. CTCs represent cancer cells from the primary and metastatic sites, thereby providing a comprehensive representation of the tumour burden of an individual patient. **Method:** Our study was designed to use microfluidic devices for the capture and characterization of CTCs in non-small cell lung cancer (NSCLC) patient samples (n=105). **Result:** We demonstrated a higher CTC capture efficiency using microfluidic CTC enrichment platforms. Using a novel multi-flow microfluidic device, we demonstrated label free CTC capture with high purity (>87%) and high recovery rate (>93%) with clinically relevant CTC concentrations. Molecular alterations present in the primary tissue were confirmed in the CTCs by 3D DNA FISH (ALK-translocations) and Immunohistochemistry (EGFR mutations, PD-L1). The presence of CTC clusters asssociated with poorer patient outcomes. **Conclusion:** Our data suggests that PD-L1 is frequently expressed in NSCLC CTCs and an immunoscore may be able to identify patients likely to benefit from immunotherapy. The isolation and characterisation of CTCs by a simple blood draw provides a non-invasive means by which to sample the tumour dynamics prior to treatment and over the course of therapy.

Keywords: Non-Small Cell Lung Cancer, circulating tumour cells, ALK

P1.03-20 EXPLORING DRIVER MUTATIONS IN NON-CODING RNAS IN LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma (LUAD) is the most frequent subtype of lung cancer, which is the leading cause of cancer death worldwide. Unraveling the molecular mechanisms of LUAD is crucial for identifying novel biomarkers and molecular targets for the diagnosis, prognosis and treatment of LUAD. One of the main molecular mechanisms responsible for LUAD and other cancers is the accumulation of driver somatic mutations, which undergo positive selection. However, driver mutations only represent a small proportion of the total mutations in a tumor and identifying true drivers can be challenging, especially in non-coding regions. Non-coding RNAs are RNA molecules that do not code for protein. Increasing evidence suggests that many non-coding RNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play critical roles in most, if not all hallmarks of cancer. However, very little is known about the driver mutations that affect non-coding RNAs in cancer and, in particular, in lung adenocarcinoma (LUAD). **Method:** We performed targeted next-generation sequencing on genomic DNA from 70 LUAD primary tumors, focusing on 1470 miRNAs and 913 lncRNAs. We developed a novel bioinformatics pipeline to identify somatic mutations by combining three state-of-the-art mutation calling tools, and then we prioritized the high-confidence somatic mutations based on various published functional impact metrics specifically designed for miRNAs and for lncRNAs. In addition, we further validated our pipeline and our results using whole-genome sequencing data from 59 LUAD primary tumors from The Cancer Genome Atlas (TCGA). **Result:** We identified 193 miRNA mutations in our cohort of 70 LUAD primary tumors. These included 16 mutations affecting seed regions and 48 mutations affecting mature miRNAs. Using miRNA target prediction tools, we identified one somatic mutation that affected the seed of a well-known miRNA and that significantly altered the predicted targets of the miRNA. In lncRNAs, we found 2004 mutations in out cohort, out of which 565 passed preliminary filters based on the predicted functional impact. Of those mutations, 91 were recurrent in more than one patient, and some affected well-known lncRNAs such as HOTAIR and PVT1. The

results from our internal cohort differed greatly from those obtained from TCGA patients. Future work will focus on refining the mutation prioritization pipeline and experimentally validating the most significant results. **Conclusion:** Our novel pipeline may aid in the identification of novel driver mutations in non-coding RNAs, which may reveal novel biomarkers and molecular targets for the diagnosis, prognosis and treatment of LUAD.

Keywords: Non-coding RNA, DNA mutational analysis, lung adenocarcinoma

P1.03-21 EPIGENOME-WIDE ASSOCIATION STUDY OF CANCER ASSOCIATED FIBROBLASTS-INDUCED ONCOGENIC TRANSFORMATION OF LUNG EPITHELIAL CELLS

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Background: Cancer-associated fibroblasts (CAFs) provide a microenvironment suitable for tumor development. CAFs have been shown to hold the capacity to facilitate carcinogenesis, drug resistance, tumor recurrence and metastasis through the signaling networks. Most studies investigating the impact of CAFs have focused on the cancer cells. The issue that how CAFs could induce carcinogenesis in the adjacent normal tissues, including genetic and epigenetic changes; however, attracts less attention. We aimed to characterize CAF-driven molecular changes in non-tumorous epithelial cells by genome/epigenome-wide study. **Method:** We primary cultured CAFs from NSCLC patients and co-cultured CAFs with normal human epithelial cells (BEAS2B). We performed *in vitro* soft agar assay and processed the established cocultured clones onto the methylome and transcriptome high-throughput platforms. **Result:** We found that the CAF-BEAS2B coculture could form colonieson the soft agar while CAFs or BEAS2B alone could not. Following isolation, the cells of cocultured clones developed more colonies than the parental BEAS2B by colony formation assay. The absence of CAF marker CD90 staining indicated no CAF contamination in the cocultured clones. In addition, DNA methylation profiling integrated with gene expression identified clusters (eg. ROBO1) that could discriminate cocultured clones from parental BEAS2B cells. The results of this study showed that CAFs could induce normal epithelial cells to undergo oncogenic transformation via DNA methylation regulation, suggesting the pro-tumorigenic potency of CAFs. **Conclusion:** Exploring the molecular interaction between CAFs and surrounding normal cells could help clarify the role of CAFs predisposed in the microenvironment in transforming normal cells epigenetically.

Keywords: oncogenic transformation, Cancer-associated fibroblasts, Epigenome-wide association study

P1.03-22 A NOVEL METHOD FOR DETECTING LOW ABUNDANT MUTANTS IN THREE TYPES OF LIQUID BIOPSIES BY CAPTURING MUTANT-ALLELES

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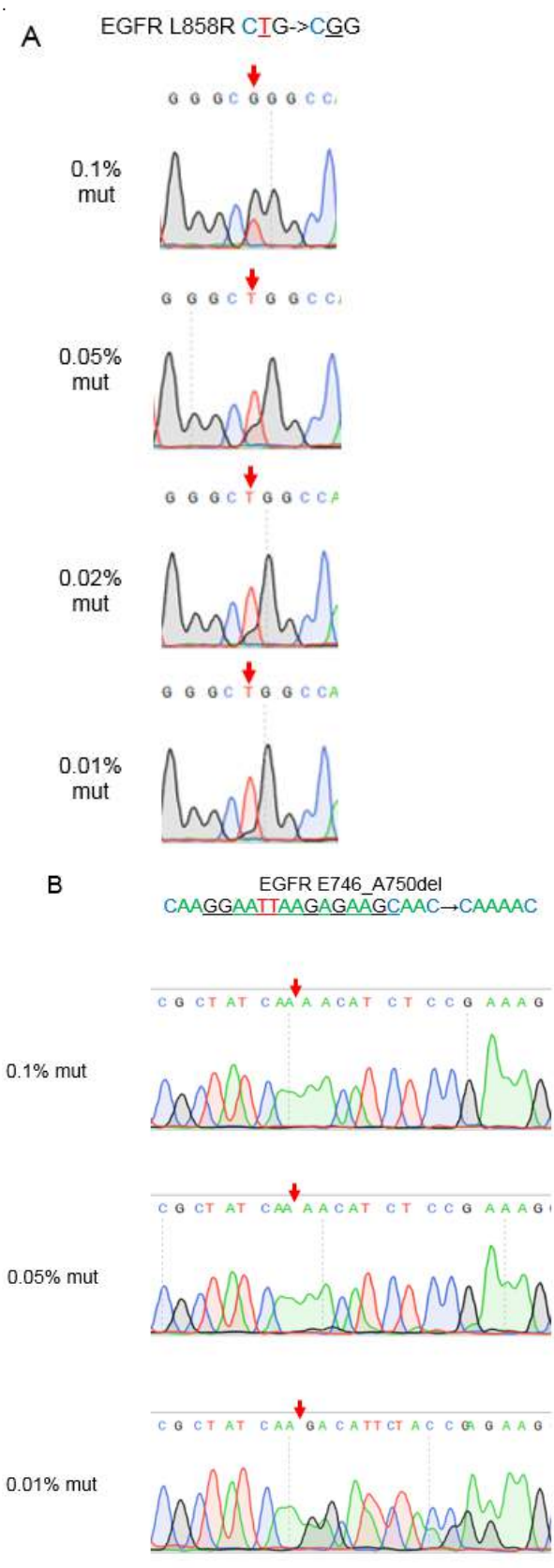
Background: Liquid biopsy can facilitate early detection of cancers, treatment selection, and disease monitoring. Improved methods to detect low abundant circulating tumor DNA (ctDNA) are needed for clinical samples including plasma, pleural effusion, and cerebrospinal fluid that carry a large amount of wild-type DNA. **Method:** We have developed a novel method, namely PEAC, with an ultra-high sensitivity to detect low abundant mutants from ctDNA through mutant capturing followed by Sanger sequencing or next-generation sequencing (NGS). This novel approach combines the high discrimination power of locked–nucleic acid (LNA) modified nucleotide sequence and short probes as bait to capture mutant fragment under an optimized temperature. Mutant fragments bound by biotin-labelled, LNA-modified probes are enriched by streptavidin beads and amplified by PCR, and then sequenced for detection. **Result:** Using circulating cell-free DNA (cfDNA) reference standards, we demonstrated that PEAC technology can enrich mutants up to 5000-fold (panel B of the figure below) and empower to detect clinically relevant EGFR mutants such as L858R, 19Del, and T790M mutant at the abundance as low as 0.01-0.1% by Sanger sequencing or NGS analysis. The clinical implications of PEAC technology were further validated using ctDNA from liquid biopsy specimens of non-small cell lung cancer (NSCLC) patients. EGFR L858R, 19DEL or T790M mutants were detected at the abundance >50% after PEAC enrichment from plasma samples of NSCLC patients, whereas the corresponding ctDNA samples without PEAC enrichment were undetectable by Sanger sequencing and hardly detected by NGS analysis. One cerebrospinal fluid and two pleural effusion samples had dominated 19DEL, L858R and T790M peaks after PEAC enrichment, respectively, but exhibited almost the background signal levels prior to PEAC



Conclusion: PEAC technology can enrich ctDNA from body fluids of cancer patients to detect ultra-low abundant clinically relevant mutants. Combined with other methods including NGS, the technology may serve as an attractive detection method in clinical practice.

Keywords: liquid biopsy, novel method, EGFR

P1.03-23 DELTA-LIKE 1 HOMOLOG (DLK1) EXPRESSION IN NON-SMALL-CELL LUNG CANCER AND THE DEVELOPMENT OF RADIOIMMUNOTHERAPY TARGETING DLK1

H. Takagi[1], S. Zhao[2], S. Muto[1], H. Mine[1], M. Watanabe[1], Y. Ozaki[1], N. Okabe[1], T. Hasegawa[1], Y. Shio[1], M. Aoki[2], C. Tan[2], S. Shimoyama[2], K. Nakamura[3], A. Inano[2], H. Suzuki[1]

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Background: Currently, treatments for advanced non-small-cell lung cancer (NSCLC) have progressed with the development of molecular targeted drugs and immune checkpoint inhibitors. However, most tumors have become resistant to these treatments. In small cell lung cancer (SCLC), the Notch receptor ligand family, which regulates cell proliferation, is expected to be a therapeutic target. Among this family, Rovalpituzumab is an antibody-drug conjugate directed against Delta-like ligand 3 (DLL3) and showed promising effects in phase 1 trials. However, in NSCLC, clinical impact of this Notch ligand family is still unknown. We therefore focused on Delta-like 1 homolog (DLK1), a noncanonical Notch ligand, which is not also yet fully understood in lung cancer. **Method:** We assessed the correlation between clinical features and DLK1 expression in resected specimens from 101 NSCLC patients who had undergone complete resection in the Fukushima Medical University Hospital between January 2012 and January 2017, and were available for analysis. We assessed DLK1 expression on tumor cells using immunohistochemistry with anti-DLK1 antibody (clone DI-2-20, IgG1). Moreover, cell and animal experiments were performed for the development of radioimmunotherapy using this anti-DLK1 antibody. **Result:** In 101 patients with NSCLC, 17 (16.8%) had DLK1 positive tumors. There was no association between DLK1 expression and pathological staging. DLK1 expression was associated with recurrence-free survival ($p<0.01$) but not overall survival. In addition, iodine-125 labeled anti-DLK1 antibody (HuBA-13D) was specifically incorporated into DLK1 on the tumor cell membrane in cell lines of human SCLC and human neuroblastoma. Furthermore, the complex was specifically incorporated into tumor tissue in a mouse model with human neuroblastoma. **Conclusion:** The results of the present study indicate that DLK1 expression could be a promising prognostic factor for recurrence in patients with resected NSCLC. In addition, DLK1 could be a therapeutic target for radioimmunotherapy for NSCLC by using our DLK-1 antibody.

Keywords: Notch ligand, DLK1, Radioimmunotherapy

P1.03-24 THORACIC INJECTION OF PD-1 BLOCKING ANTIBODY IMPROVES THE MURINE MODEL OF MALIGNANT PLEURAL EFFUSION

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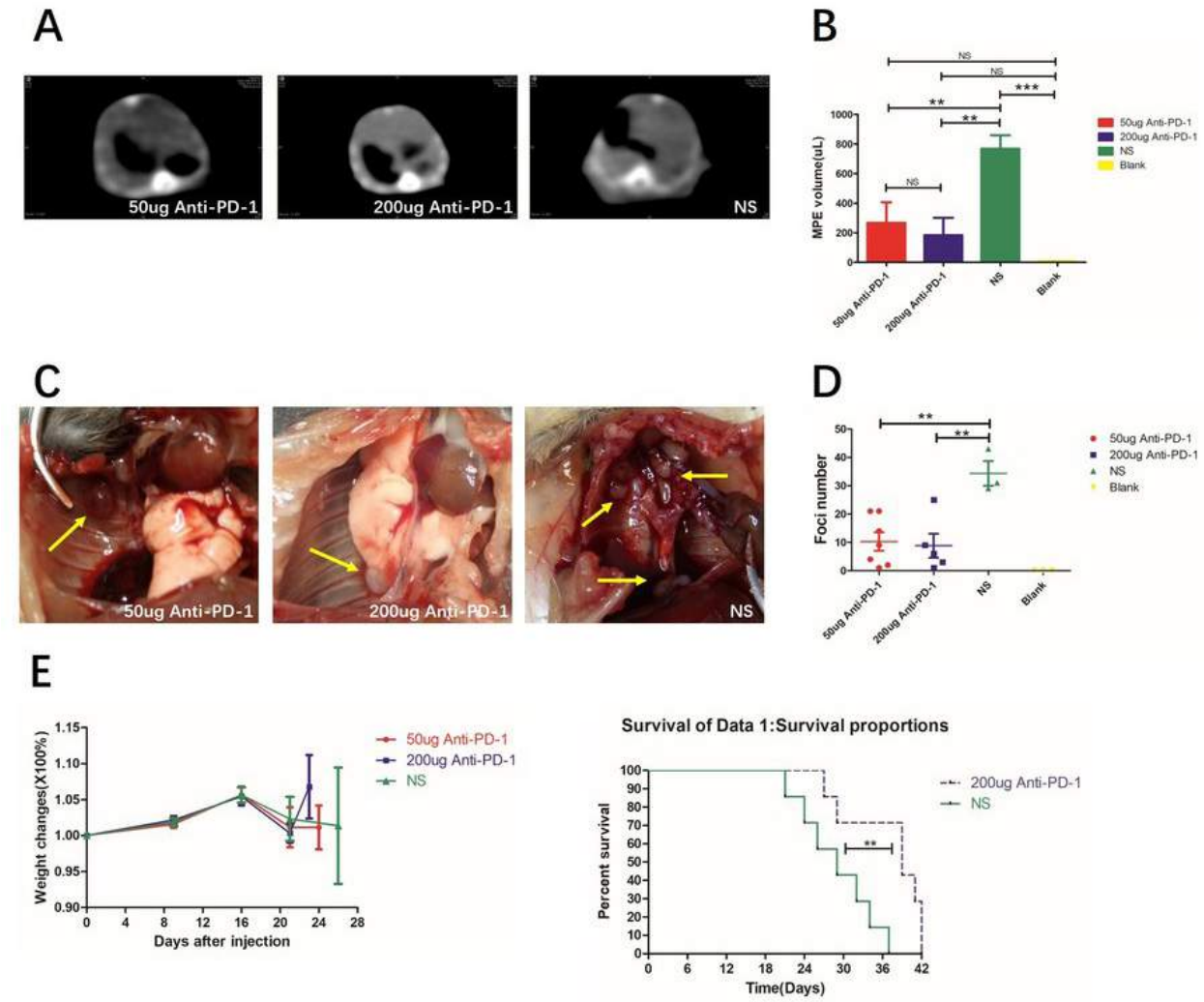
Background: Malignant pleural effusion (MPE) occurs as a common complication of lung cancer with poor prognosis. It should be mainly attributed to pleura metastasis and lymphatic obstruction by cancer cells. Despite that intravenous immune-checkpoint inhibitor (ICIs) shows remarkable therapeutic capacity, the effect of thoracic injection of anti-PD-1 antibodies remains undefined. **Method:** MPE xenografts mice model was established by intralumen injection of Lewis lung carcinoma (LLC) cells and randomly divided into three groups: high dose of anti-PD-1 monoclonal antibody (200ug), low dose of anti-PD-1 monoclonal antibody (50ug) and an equal volume of saline. Drugs were injected into the pleural cavity on Day 7 and Day 14. Computed tomography (CT) was performed 14 days after LLC injection. All mice were sacrificed on day 21 and the volume of pleural effusion, the number of pleural nodules were quantitatively recorded. Expression of PD-1, PD-L1, $CD8^+$ and CD31 in tumor and normal pleural tissues were evaluated by western blot and immunohistochemical staining (IHC). Flow cytometry was performed on mice spleen after grinding. Weight and survival were recorded. **Result:** The volume of pleural effusion, the number of pleural tumor foci and the proportion of $CD8^+$ T cells in the spleen of mice were significantly reduced in both high and low dose of anti-PD-1 antibody treatment groups. Western Blot results showed that the expression of PD-1 in tumor and adjacent pleura was significantly inhibited after anti-PD-1antibody treatment. IHC results showed that $CD8^+$ T cells in tumor area of mice in high dose anti-PD-1 monoclonal antibody group were significantly less than those in low dose group, and the expressions of PD-1 and PD-L1 were significantly increased. Anti-PD-1 monoclonal antibody treatment was associated with much longer survival ($p=0.0098$). Median survival in the anti-PD-1 antibody treated group was 39 days, versus 29 days in the control group.



Conclusion: Intralumen delivery of anti-PD-1 antibody could significantly reduce MPE volume and improve survival by inhibiting the expression of PD-1, reducing the number of $CD8^+$ T cells in the tumor region and spleen, and affecting angiogenesis.

Keywords: Malignant pleural effusion, pd-1, thoracic injection

P1.03-25 SYNERGISTIC LETHALITY OF FERROPTOSIS INDUCER-DISULFIRAM/COPPER COMPLEX AND WEE1 KINASE INHIBITOR FOR RAS/TP53 MUTANT NSCLC

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Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai/China

Background: Co-mutation of RAS and TP53 is prevalent in NSCLC but with no reagents targeting this specific subtype. Drug synergy is a feasible approach in targeting the tumor with the multi-site mutation. In this study, the synergistic lethality of disulfiram/copper complex (DSF-Cu) and WEE1 kinase inhibitor, and its association with RAS/TP53 status were interrogated in NSCLC. **Method:** DSF was approved by the FDA for alcoholism treatment for decades, and its role in cancer therapy arose extensive interest recently with uncertain mechanisms. Three $RAS^{mut}/TP53^{mut}$ NSCLC cell lines [H1299, TP53-knockout A549 (A549-KOTP53), TP53-knockout H460 (H460-KOTP53)], two $RAS^{mut}/TP53^{wt}$ NSCLC cell lines (A549, H460), and one $RAS^{wt}/TP53^{mut}$ cell line (H522) were used to examine the anti-cancer effect of DSF-Cu complex, which was tested with MTT and colony formation assay. The mechanism of DSF-Cu's anti-tumor effect was determined by flow cytometry, western blot and ferroptosis staining. The synergistic lethality effect of DSF-Cu and WEE1 inhibitor was estimated under 2D and 3D cell culture systems. **Result:** The anti-tumor effect of DSF-Cu was more evident in $RAS^{mut}/TP53^{mut}$ NSCLC than in $RAS^{mut}/TP53^{wt}$ or $RAS^{wt}/TP53^{mut}$ NSCLC. We firstly found that the anti-tumor effect of DSF-Cu was associated with ferroptosis accompanied by lipid peroxidation of cell membrane (Figure 1A, 1B). DSF-Cu also inhibited WEE1 sumoylation (Figure 1C) to induce G2/M checkpoint arrest by eliciting oxygen radicals in $RAS^{mut}/TP53^{mut}$ NSCLC cell lines. A WEE1 kinase inhibitor, Adavosertib combined with DSF-Cu showed synergistic lethality in $RAS^{mut}/TP53^{mut}$ NSCLC cell lines compared with other non-co-mutation NSCLC cell lines (Figure 1D, 1E).

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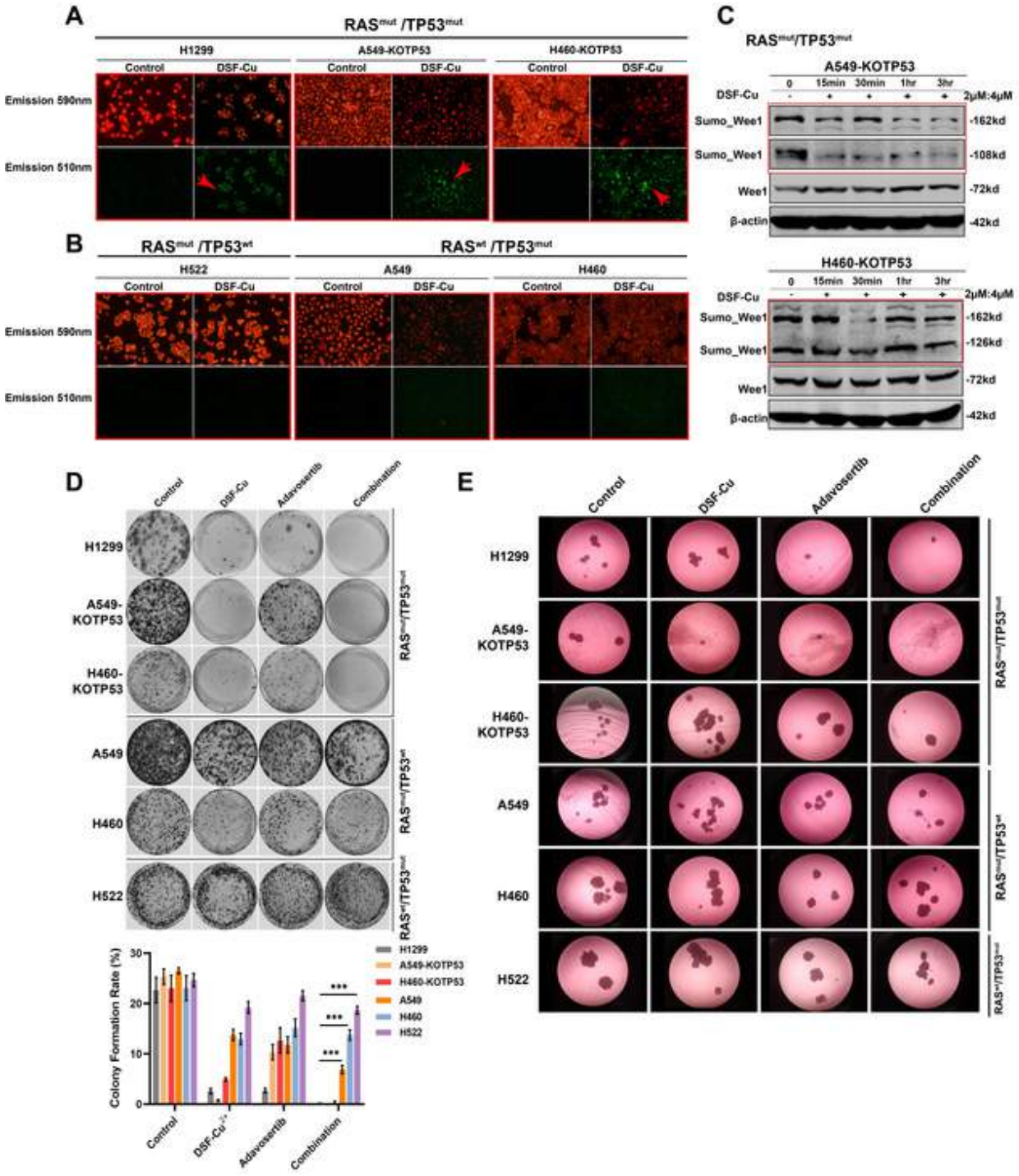

Figure 1

Conclusion: Our study elucidated a novel mechanism of the anti-tumor effect of DSF-Cu, that the subsequent elicitation of oxygen radicals can induce both WEE1 sumoylation inhibition and ferroptosis, especially in the RAS^{mut}/TP53^{mut} NSCLC. The synergistic lethality of DSF-Cu with adavosertib may be a promising treatment strategy for RAS^{mut}/TP53^{mut} NSCLC.

P1.03-26 GENETIC AND MOLECULAR PROFILING OF NON-SMOKING RELATED LUNG ADENOCARCINOMAS

E. Pros[1], M. Saigi[1], J.J. Alburquerque-Béjar[1], M.J. Pajares[2], B. Martínez-Delgado[3], J. Carretero[4], R. Tonda[5], A. Esteve-Codina[5], S. Verdura[1], I. Català[6], N. Reguart[7], O. Juan[8], E. Nadal[9], E. Felip[10], L. Montuenga[2], M. Sanchez-Cespedes[1]

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Background: The etiology and many details of the genomic profile and molecular basis of lung adenocarcinomas (LuADs) in nonsmoker patients remain elusive. Further, the scarcity of primary cultures available from non-smoking related lung adenocarcinomas (NSK-LuADs) contributes to hamper our biological understanding of these tumors. **Method:** We established patient-derived cancer cell (PDCs) cultures from NSK-LuADs, and performed whole exome sequencing (WES) and RNA sequencing (RNA-seq) analysis to delineate their genomic architecture. For validations, we analyzed independent cohorts of LuADs. **Result:** The analysis revealed non-smoker related alterations such as those at the growth factor receptors *RET, ALK, EGFR* and *ERBB2.* There were also mutations affecting signal transduction molecules such as *AKT1, BRAF* and *KRAS*, and mutations in tumor suppressor genes, including *TP53, CDKN2A*, *RB1, ARID1A, ATM* and *STK11.* We also identified new fusions and recurrent mutations in some genes, one of them, a possible regulator of gene expression, affecting ten percent of the LuADs, thus constituting a potentially relevant tumor suppressor gene. We also report a predominance of *RB1*-inactivation, mostly complex intragenic rearrangements (homozygous deletions or duplications) in *EGFR*-mutant tumors. Three *EGFR-/RB1*-mutant tumors, treated with EGFR-TKIs, and one *EGFR*-wild type tumor, treated with standard chemotherapy, developed small cell lung cancer and/or squamous cell carcinoma transformation, evident in the re-biopsies and/or PDCs. Finally, we found pathogenic germ-line mutations at genes associated to familiar-cancer syndromes, especially the *TP53*-associated Li Fraumeni syndrome, affecting ten percent of *EGFR*-mutant LuADs patients, underscoring a genetic predisposition origin for a subset of NSK-LuADs. **Conclusion:** The recurrent gene inactivation found in candidate gene in LuADs heralds a tumor suppressor role which deserves further exploration. The pre-existent inactivation of *RB1* predominates in *EGFR*-mutant tumors and may underlie an extremely ductile nature, albeit additional gene alterations are required to overcome sensitivity to the TKIs. Given their potential clinical and therapeutic implications, testing for *RB1*-alterations and for the Li-Fraumeni syndrome in *EGFR*-mutant LuADs patients may need to be incorporated in the clinical settings.

Keywords: Non-smoking related lung adenocarcinomas, Next generation sequencing, EGFR

P1.03-27 ASPIRIN OVERCOMES ACQUIRED RESISTANCE TO OSIMERTINIB IN HUMAN LUNG CANCER CELLS VIA BIM-DEPENDENT APOPTOSIS INDUCTION

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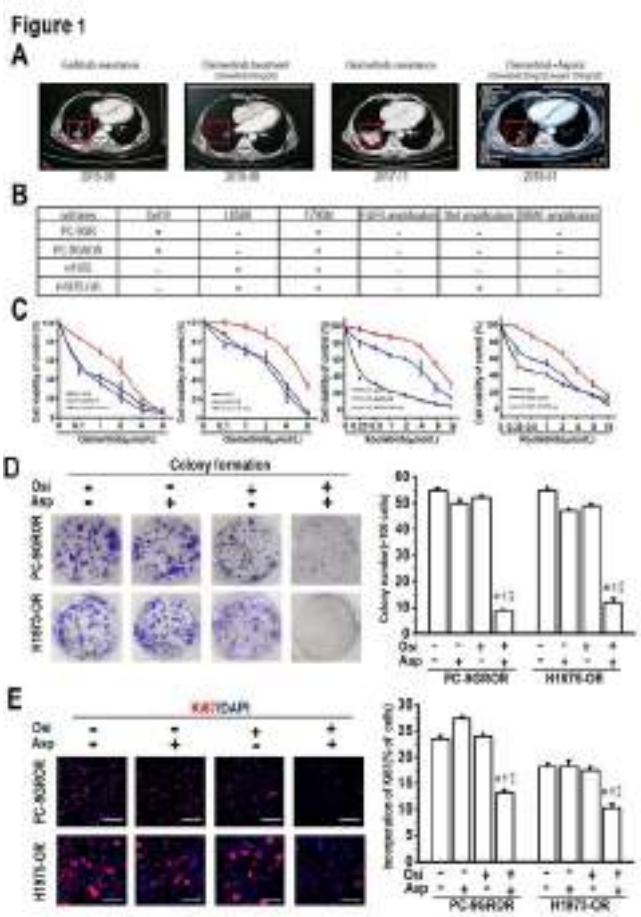
Background: Osimertinib, a third-generation irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), provides remarkable clinical benefit for patients with EGFR-TKI sensitizing and/or EGFR T790M resistance mutations. Unfortunately, osimertinib can be changed to acquired resistance eventually occurs, which limits its clinical effects. There is currently no effective method to overcome this acquired resistance. The current study aims to identify a new method to overcome acquired osimertinib resistance. **Method:** The effects of combination treatment with osimertinib and aspirin on osimertinib-resistant non-small cell lung cancer (NSCLC) cell lines (PC-9GROR and H1975-OR) were assayed using MTT and Ki67 incorporation assays, flow cytometry, immunofluorescence staining, Western blotting analysis, and xenograft tumor implantation. Data of NSCLC patients who received osimertinib treatment in Daping hospital between January 2015 and January 2019 were reviewed retrospectively. **Result:** Two patients with NSCLC who were gradually developing resistance to osimertinib began aspirin for thrombosis; a partial anti-tumor response was unexpectedly observed. The combination of osimertinib and aspirin induced strong anti-proliferative and pro-apoptotic effects in osimertinib-resistant NSCLC lines through inhibition of Akt/FoxO3a signaling phosphorylation and increased Bim expression. Furthermore, siRNA knockdown of Bim expression significantly attenuated the ability of aspirin to re-sensitize osimertinib. In vivo, the combination of aspirin and osimertinib significantly decreased tumor growth of xenografts based on the PC-9GROR cell line through inhibition of Akt/FoxO3a signaling phosphorylation and elevation of Bim. The retrospectively analyze clinical data of 45 cases of NSCLC patients showed the median progression-free survival (PFS) in osimertinib plus aspirin group patients were significantly longer than those in osimertinib alone group patients.

Figure 1



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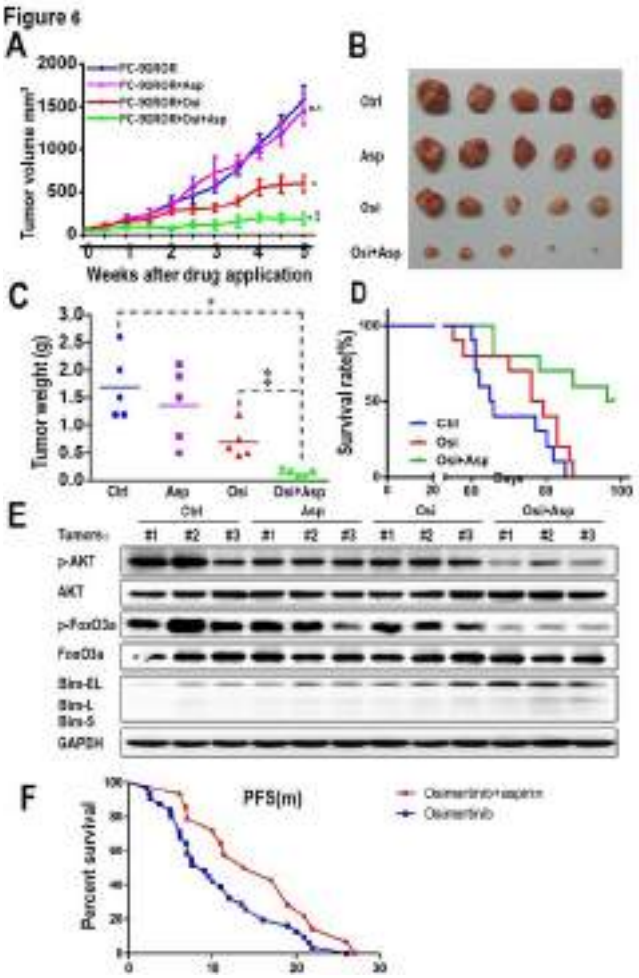

Conclusion: Aspirin, a generally safe and inexpensive drug, has synergistic effects with osimertinib via modulation of Bim-dependent apoptosis in osimertinib-resistant NSCLC cell lines and xenografts. It may be an effective strategy for overcoming acquired resistance to osimertinib and prolonging survival in patients with NSCLC.

Keyword: osimertinib, aspirin, resistance

P1.03-28 PROGNOSTIC VALUE OF ESTROGEN RECEPTOR BETA TUMOR EXPRESSION IN NON-SMALL CELL LUNG CANCER PATIENTS AFTER RADICAL SURGERY

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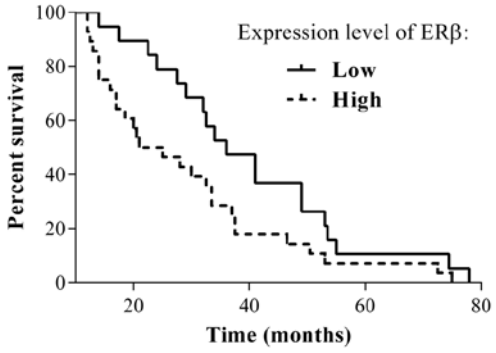
Background: Estrogens play significant role in development and progression of non-small cell lung cancer (NSCLC), but prognostic value of estrogen receptors (ERα and ERβ) in cancer tissue are controversial. Moreover, there is no accurate information about frequency of ERs expression in tumor cells as the key for antiestrogens which is a promising NSCLC therapy. Therefore, *we aimed to 1) evaluate expression of ERβ in NSCLC cancer tissue and 2) estimate prognostic value of ERβ on survival of patients.* **Method:** Expression of ERβ in 125 surgical NSCLC samples was evaluated quantitatively by immunofluorescent assay and flow cytometry. The primary anti-ERβ (14C8, ab288) and secondary (DyLight650, ab98510) antibodies were used. The level of ERβ expression was calculated as the ratio (%) of specifically fluorescent cells to the control (incubation with the secondary antibody only). The prognostic value of ERβ expression in tumor tissue was studied in 49 patients without neoadjuvant therapy who died in 6.5 years after radical surgery. There was division into two level expression groups: high – ERβ were revealed in ≤40% and low – >40% cells. Statistical analysis was performed by Kaplan-Meier curves analysis (log-rank test) and Cox-regression in software packages: GraphPad Prism 7.0 and SPSS 22.0. **Result:** 1. Expression of ERβ was revealed in all the investigated NSCLC samples. Significant heterogeneity of the marker expression level was shown: the mean and median of the marker index were 42.3%±15.6 and 44.0% respectively. 2. It was shown in comparison of Kaplan-Meier curves in patients with low vs high level of ERβ expression (see Fig.1) that the survival median of the patients who died in 6.5 years after radical surgery was more than 1.5 times greater in the group with the low vs high level of ERβ expression: 36.0 and 22.0 months respectively (p=0.04). The risk of death in follow-up period after radical surgery was 2.0 times greater in the group classified as high level of tumor ERβ expression: hazard ratio has been statistically significant – 1.8 (95% CI: 1.1–6.4, p=0.05).

Fig. 1. Kaplan-Meier survival curves of NSCLC patients with low and high level of ERβ expression



Conclusion: 1. ERβ tumor expression has prognostic value in NSCLC patients, namely, the high level of ERβ (in more than 40% tumor cells) is a negative prognostic marker. 2. The fact of ERβ expression in all the NSCLC specimens investigated has shown that hormonal antiestrogen therapy could be a promising option for all the NSCLC patients.

Keywords: Estrogen receptors beta, Non-Small Cell Lung Cancer, flow cytometry

P1.03-29 CELLULAR BIOLOGY DETERMINES ABILITY OF XIST TO ACT AS A MIRNA SPONGE IN NON-SMALL CELL LUNG CANCER

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Background: XIST, the female-specific lncRNA canonically involved in silencing the X chromosome, has been suggested by many studies to function as a miRNA sponge. This sponge mechanism has been suggested to affect many cancer types, including lung adenocarcinoma (LUAD). However, determination of miRNA:lncRNA interaction is largely based on sequence homology, impeding the identification of functional gene pairs. The sex-specificity of XIST provides the opportunity to study the biological relevance of these interactions. Here we take a comprehensive approach by considering factors that affect preferential regulation through XIST-miRNA sponging in LUAD. **Method:** Sequencing data from 568 LUAD and non-malignant samples (304 female and 264 male) were downloaded from CancerBrowser and processed to provide gene expression for mRNAs, miRNAs, and XIST. 3'UTR sequences of all candidate genes were run through the miRanda binding prediction algorithm. Spearman's tests were performed to identify positively correlated candidate sponged genes. **Result:** To identify the best sponge-regulated candidates, we considered genes that (1) were positively correlated with *XIST* expression and (2) are targeted by shared miRNA with XIST, and (3) expressed in lung adenocarcinoma. This revealed a robust set 128 of genes potentially positively regulated by *XIST* through the sequestration of 804 shared miRNAs. As *XIST* is sex-specific, we compared the changes in miRNA-target gene relationships in *XIST*-high and *XIST*-low systems to identify a high-confidence set of 13 miRNA-gene pairs. In order to interact with the exclusively nuclear expressed *XIST,*miRNAs must also be expressed in the nucleus. We validate the

nuclear presence of several of these high confidence miRNAs using RT-qPCR, confirming the co-localization required for *XIST* to interact with these species. **Conclusion:** We use a biology-driven approach to identify genes defended from miRNA-based inhibition by the lncRNA *XIST* in LUAD. Importantly, we identify that the miRNAs that mediate the *XIST*-target gene axis are enriched in the nucleus, co-localizing with XIST in lung cancer cell models. Our results reinforce the necessary consideration of biological features in future studies of lncRNA:miRNA interactions.

Keywords: Non-coding RNA, miRNA sponge, gene regulation

P1.03-30 TRANSCRIPTOME SIGNATURES OF TOBACCO CARCINOGENS ON LUNG ADENOCARCINOMA CELL LINES

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Background: Lung adenocarcinoma (LUAD) sequencing studies and carcinogens induced LUAD in animal models show how different mutational processes leave their specific signatures in the genome. Unluckily those signatures were obtained from heterogeneous tissues containing tumor and stromal cells. Moreover, whole-genome analyses provide a comprehensive collection of genome alterations but tend to lose specificity in the signature that affects the coding region of cancer genomes. AIM: To address the importance of mutational signature in the transcriptome of carcinogens induced LUAD cell lines. **Method:** We investigated the raise of mutations and the changes in the transcriptome profiles of ten different carcinogen-induced LUAD cell lines derived from three different mouse strains and induced with urethane or diethyl-nitrosamine. Data were analyzed for transcripts abundance, sequences alignments, pathways and geneset enrichment, and analyzed the single nucleotide variations (SNV) effect on the three-dimensional structure of proteins and on their functions. **Result:** The LUAD cells gene expression profiles show classical hallmarks of cancer, where proliferation pathways are up-regulated and adhesion control pathways are down-regulated. Among those altered pathways in LUAD cell lines transcriptome profiles, we observed a clear reprogramming of the metabolism through the up-regulation of the nucleotides synthesis and a contemporary down-regulation of the amino acids synthesis as a switch in the metabolic usage of glucose across the glycolytic pathway. We detected in our LUAD cell lines an average of 10000 SNV. When we focused on the flanking bases of those SNV, we noticed a pure tendency in two specific transitions, A>G and T>C, where the dominant 5´ flanking nucleotide is C and the dominant 3´ is G. We investigated the distribution of common SNV across the chromosomes to highlight mutational hotspots. In *Kras*-mutant LUAD cell lines, we observed that both carcinogens tend to leave their specific mutational fingerprints with a major density in the terminal regions of the chromosomes. When we compared the specific genomic position of every induced SNV and correlated it with the different levels of heterogeneity in LUAD cell lines, we observed in all of them 15 common SNV in 11 different genes. Among those genes, we pinned two key genes of the glycolytic pathway: *G6pd2* and *Aldort1*. **Conclusion:** From the tobacco carcinogens transcriptome signatures of LUAD cells, we propose here an uncharted role of two altered forms of *G6pd2* and *Aldort1*. Their corresponding proteins: G6PD2 and ALDOA, are able to drive the glucose usage toward the nucleotide synthesis, resulting in an enhancement of the tumor cells proliferation and in the LUAD pathogenicity. We believe that those two proteins could be more investigated as novel pharmacological targets for human LUAD treatment

Keywords: Metabolic Reprogramming, Next generation sequencing, LUAD

P1.03-31 BRAF MUTATIONS: CLASSES I, II AND III IN NSCLC PATIENTS INCLUDED IN THE SLLIP TRIAL, TARGETED TREATMENT ACCORDING TO CLASS

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Background: BRAF V600 mutations have been found in 2% of non-small cell lung cancer (NSCLC) patients, with FDA approved treatment of dabrafenib plus trametinib and progression free survival (PFS) of 10.9 months. However, 50-80% of BRAF mutations in lung cancer are non-V600, and can be class 2, with intermediate to high kinase activity and RAS independence, or class 3, with impaired kinase activity, upstream signaling dependence and consequently sensitivity to receptor tyrosine kinase (RTK) inhibitors. Non-V600 tumors require combinatory therapy with RAF/MEK inhibitors and blockers of RTK signaling, like SHP2 (PTPN11) inhibitors. **Method:** Plasma DNA of 185 newly diagnosed advanced lung adenocarcinoma patients was examined for BRAF and other mutations with a clinically validated cell-free DNA (cfDNA) assay (Guardant360, Guardant Health Inc. CA, U.S), and results were correlated with patient outcome. In addition, two NSCLC cell lines and one Triple Negative Breast Cancer (TNBC), H1395 (class 2 BRAF mutation), H1666 (class 3 BRAF mutation) and MDA-MB-231 (class 2 BRAF mutation) were treated with single or combined BRAF, MEK and SHP2 inhibitors and cell viability was assessed. **Result:** BRAF mutations were found in 17/185 (9%) and BRAF amplification in five patients (3%). Three patients had BRAF V600E mutations (2%) and 14 patients non-V600 BRAF mutations (8%), including four class 2 and four class 3 mutations. Patients were treated with chemotherapy and/or immunotherapy, or targeted therapy for other co-alterations. PFS was 1.8, 6.1, 5.0, 5.3 and 5.3 months for Class 1, 2, 3, other BRAF, and BRAF amplification, respectively. These low survival rates indicate that new treatment options are urgently needed. *In vitro* results confirm sensitivity of class 3, and resistance of class 2 BRAF mutations to single SHP2 inhibition with RMC-4550 and SHP099, with similar results in TNBC and lung cancer cells. Combined dabrafenib and trametinib treatment indicated antagonistic effects, especially in the class 3 BRAF mutant cell line. Concomitant MEK and SHP2 inhibition was synergistic in both class 2 and 3 BRAF mutations. **Conclusion:** It is evident that different classes of BRAF mutations require distinct treatments, which could even outweigh tumor type. Therefore, we should examine BRAF class in daily clinical practice. Upfront targeting of the MAPK signaling pathway combined with SHP2 inhibitors reveals synergistic interactions, and additional inquisition may pave the way for new treatment options in the most frequently found mutations in BRAF patients.

Keywords: NSCLC, SLLIP trial, BRAF mutations

P1.03-32 KNOCKDOWN OF CENPF GENE INHIBITS THE PROGRESSION OF LUNG ADENOCARCINOMA MEDIATED BY ERβ2/5 PATHWAY

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Background: The signal transduction pathway of estrogen receptors (ER) mainly includes gene and non-gene pathways. Studies have shown the gene pathway of ER is related to expression of nuclear proteins, and our previous research showed that estrogen promotes progression of lung cancer via ERβ. Four GEO datasets (two NSCLC, two lung adenocarcinomas (LUAD)) were analyzed and found elevated expression of the nuclear protein gene, human centromere protein F (CENPF) in LUAD. This study explores the relationship between ERβ and CENPF in lung cancer. **Method:** We verified the above phenomenon by analysis of Oncomine database, specimen transcriptome and protein mass spectrometry in LUAD patients. Co-expression of CENPF and ERβ in the nucleus of LUAD cells were

confirmed by cellular immunofluorescence and tissue microarray analysis. This result was also verified by analysis of GEPIA and TCGA databases. Finally, cell culture and animal models of lung cancer were treated with a CENPF knockdown gene and/or combination with fulvestrant (ERβ inhibitor) and assessed for cell survival and tumor volume. Mechanism was assessed with markers of ER β2/5 or surrogates of other signaling pathways. **Result:** The high expression of CENPF was associated with high TNM stage (*p <0.001, Figure 1A), low overall survival (OS, p =0.01, Figure 1B) and low disease-free survival (PFS, p =0.027) in LUAD. CENPF and ERβ2/5 were highly co-expressed and this co-expression positively related with high TNM stage in LUAD patients (p <0.001). Knockdown of CENPF gene significantly inhibited the biological effects of LUAD cells (p <0.05, Figure 1 C-D), tumor growth in mice (p <0.05, Figure 1 E, F, H), and the expression of ERβ2/5 (p <0.05, Figure 1 G).* **Conclusion:** Both CENPF and ERβ2/5 play important roles in the progression of LUAD, and knockdown of the CENPF gene can inhibit the progression of LUAD by inhibiting the expression of ERβ 2/5.

Keywords: estrogen receptor beta 2/5, lung adenocarcinoma, human centromere protein F

P1.03-33 ANALYSIS OF LIPID METABOLISM GENES IN ADVANCED SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer death worldwide. Although most of the knowledge about metabolic dysregulation in cancer focuses on carbohydrates, the importance of alterations related to lipid metabolism is starting to be recognized. There is increasing data on lipid metabolism and non-small lung cancer, but much less is known about this in small cell lung cancer (SCLC). In order to improve our knowledge of these alterations we evaluated a genetic profile related to lipid metabolism and studied clinical outcomes **Method:** We performed a retrospective analysis of 22 genes related to lipid metabolism in 37 tumoral tissue samples of SCLC patients and evaluated clinical features and outcomes. Advanced SCLC patients enrolled from November 1, 2008 through December 31, 2015 were included in this analysis. Clinical data were collected from medical records at the time of enrollment. The study was approved by an Ethics Comittee and all patients signed an Informed Consent form. We used formalin-fixed, paraffin- embedded tumor tissue. Samples were deparaffinated and total RNA was extracted. A Taq-Man Low Density Array (Applied Biosystems) was specifically designed and gene-expression assays were performed in a HT-7900 Fast Real time PCR. RT-StatMiner software was used to detect and determine the quality control and differential expression analyses of data. **Result:** We included 37 patients, 73 % males and 27 % women, with a median age of 62. 29 patients (78%) had stage IV tumor and nearly all of them (92%) were treated with platinum- based chemotherapy. 11 % (4/37) received thoracic radiotherapy and 5% (2/37) received whole brain radiotherapy. 6 patients (16%) were on chronic treatment with metformin and 15 (40%) on statins. We performed a multivariable analysis and found that overexpression of two metabolic genes (a mitochondrial enzyme and a lipid metabolism regulator) led to longer overall survival. (HR 0.13 (0.04-0.42), p 0.0019, $p_{adjusted}$ 0.04 and HR 0.11 (0.03-0.35) p 0.0006, $p_{adjusted}$ 0.01, respectively). **Conclusion:** These genes contribute to normal functioning and regulation of lipid metabolism and could be considered as potential prognostic biomarkers. There is no previous evidence of association between levels of expression of these genes and overall survival in SCLC. Validation in a larger series of patients is ongoing.

Keywords: lipid metabolism, small cell lung cancer, prognostic biomarker

P1.03-34 THE LNCRNA NEAT1 PROMOTES RADIORESISTANCE VIA THE MIR-491-5P/CAPG AXIS IN NSCLC

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Background: Long noncoding RNAs (lncRNAs) have been implicated in various biological processes and pathological conditions in cancer. However, the exact roles of LncRNA NEAT1 and its underlying mechanisms in radioresistance of non-small cell lung cancer (NSCLC) remain largely unclear. **Method:** The expression of LncRNA NEAT1 was measured in NSCLC tissues and cell lines by reverse transcriptionquantitative polymerase chain reaction (RT-qPCR). The radiosensitivity of NSCLC cells including H358, H226, HCC827, H1975, H1395 and H23 were detected by colony formation. Lentivirus-mediated short hairpin RNAs were used to knock down NEAT1 expression in H358 cells. Furthermore, the role of NEAT1 on tumor cell biological behavior and radioresistance were explored through MTT, colony formation, transwell migration, and invasion assays *in vitro*. Luciferase reporter assay was used to verify interaction between miR-491-5p and NEAT1, CAPG. The potential mechanism of LncRNA NEAT1 was identified by Western blot. Additionally, the association between the survival time and miR-491-5p expression in lung adenocarcinoma patients were evaluated based on the TCGA data. **Result:** NEAT1 was highly expressed in NSCLC tissues and cell lines. NEAT1 was up-expressed in radiosensitive NSCLC cells and low-expressed in radioresistant NSCLC cells. Conversely, miR-491-5P was low-expressed in radiosensitive NSCLC cells and up-expressed in radioresistant NSCLC cells. In addition, we revealed a reciprocal repression between NEAT1 and miR-491-5P. CAPG was identified as a down-stream target of miR-491-5P. Further experiments revealed that lncRNA NEAT1 silencing inhibited cell proliferation, invasion and radioresistance *in vitro*. Overexpression of CAPG rescued the effects of NEAT1 downregulation on proliferation, invasion and radioresistance. In addition, mechanistic analysis showed that lncRNA NEAT1 upregulated the miR-491-5p-targeted gene CAPG through acting as a competitive "sponge" of miR-491-5p. By cox regression analysis, a tendency towards a survival benefit in patients with high miR-491 expression was observed in 430 lung adenocarcinoma patients of the TCGA database. **Conclusion:** Our findings suggest that NEAT1 regulated proliferation, invasion and radioresistance by modulating the miR-491-5p/CAPG axis in NSCLC.

Keywords: NSCLC, NEAT1, miR-491

P1.03-35 ANALYSIS OF TET2 GENE ABERRATIONS IN EAST ASIAN NON-SMALL-CELL LUNG CANCER PATIENTS AND EVALUATION OF THEIR PROGNOSIS

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Background: Ten-eleven translocation 2 (*TET2*) enzymes are frequently deregulated in cancer, but the genetic spectrum of *TET2* mutation non-small cell lung cancer patients (NSCLC) patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *TET2* mutations. **Method:** A total of 895 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *TET2* mutations and other genes were detected by next generation sequencing. **Result:** *TET2* gene mutation rate was 1.90% (17/895) in non-small cell lung cancer, including G126W (1 patient), E1477* (1 patient), I1871Nfs*4 (1 patient), T665K (1 patient), Y60F (1 patient), D932H (1 patient), M533I (1 patient), R1262W (1 patient), N71Kfs*5 (1 patient), Q769* (1 patient), W1198C (1 patient), Y1645Ifs*16 (1 patient), Q1532* (1 patient), R369W (1 patient), D648Y (1 patient), G1370V (1 patient) and T344K (1 patient), and median overall survival (OS) for these patients was 19.0 months. Among them, all patients were *TET2* gene with co-occurring mutations. Briefly, patients with (n=15) or without (n=2) co-occurring *TP53* mutations had a median OS of 19.0 months and 4.0 months respectively (P<0.01); patients with (n=3) or without (n=10) co-occurring *CTNNB1* mutations had a median OS of 13.0 months and 19.0 months respectively (P=0.90); patients with (n=3) or without (n=10) co-occurring *NF1* mutations had a median OS of not up to now

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months and 13.0 months respectively (P=0.87), patients with (n=3) or without (n=10) co-occurring *KDM5C* mutations had a median OS of not up to now months and 13.0 months respectively (P=0.75). **Conclusion:** *TET2* oncogenic activation through mutation defines a novel and distinct subset of NSCLC. *CTNNB1*, *NF1* and *KDM5C* gene accompanied may have less correlation with *KIT* mutation in NSCLC patients. *TP53* accompanied mutations might play a good prognosis in *TET2* gene mutation non-small cell lung cancer.

Keywords: non-small-cell lung cancer, TET2 mutation, prognosis

P1.03-36 CELL-FREE DNA LEVELS IN LIQUID BIOPSY FROM PATIENTS WITH NON-SMALL CELL LUNG CANCER AND ASSOCIATION WITH CLINICAL PARAMETERS AND DISEASE OUTCOME

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Background: Patients with non-small cell lung cancer (NSCLC) are constantly submitted to invasive biopsies for clinical management and for guiding tailored treatment based on molecular targets. The liquid biopsy is a minimally invasive collected sample that contains cell-free circulating DNA (cfDNA), which may reflect clinical conditions and outcome based on their levels. Thus, the aim of this study was to assess the cfDNA levels in liquid biopsy samples from NSCLC patients and to correlate with the clinical parameters, overall survival, and disease outcome. **Method:** cfDNA was manually isolated from the liquid biopsies NSCLC patients (n=38) employing MagMax Cell-free cfDNA Isolation Kit. The cfDNA levels were checked by fluorometry and fragments size were evaluated by TapeStation. The cfDNA levels were associated with clinical parameters from NSCLC patients and disease outcome. **Result:** Overall, 18 cases were adenocarcinomas and 20 squamous cell carcinomas. Regarding smoking, 34 patients were current or former smokers and 4 patients were never smokers. cfDNA was successfully isolated from 31 cases, whose presented detectable levels of cfDNA (median: 0.862 ng/μL; range 0.144– 4.36 ng/μL), and 7 cases presented undetectable levels of cfDNA. All cfDNA fragments were successfully confirmed by TapeStation. Of note, patients with detectable levels of cfDNA were diagnosed at stages I (n=2), II (n=4), III (n=10), IV (n=14). However, disease staging at diagnosis was not associated with cfDNA levels (Kruskal-Wallis p=0.54). cfDNA levels were not associated with overall survival (Log-Rank p=0.86). Nonetheless, detectable levels of cfDNA were associated with unfavorable outcome (Qui-Square test p=0.03). **Conclusion:** Our results may reassure the use of liquid biopsy in personalized medicine, although these results should be confirmed in a larger series. Our results show that liquid biopsy is a useful non-invasive tool for prognostication of NSCLC patients.

Keywords: NSCLC, cfDNA, liquid biopsy

P1.03-37 IMPACTS OF DSB REPAIR PROTEIN, NBS1, ON LUNG CANCER

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Background: The maintenance of genomic integrity is essential for cell survival and normal function, while genomic instability has been demonstrated in the development and progression of multistep cancers including lung cancer. Double strand breaks (DSB) repair protein, Nijmegen breakage syndrome 1 (NBS1), play a critical role in sensing DNA lesions, arresting cell cycle and repairing damages via forming a complex with Mre11 and Rad50 protein. Controversially, elevated NBS1 protein levels have frequently associated with the resistance to chemotherapy/radiotherapy in certain cancers. This study aims to investigate if NBS1 aberrations may contribute to NSCLC. **Method:** Immunohistochemistry was used to analyze the distribution patterns of NBS1 protein in lung cancer (n=127) and the results were further statistically correlated with clinicopathological characteristics and survival rate. XTT, invasion assay and immunoblotting were used to explore a part of bioimpacts and underlying mechanisms of the NBS1 and its interplay with nicotine in lung cancer cells. **Result:** The Kaplan–Meier plotter shows that 1926 lung cancer patients, regardless of tissue types, with high NBS1 mRNA levels will have an improved overall survival rate (p=0.004). Further immunohistochemistry showed that Increased nuclear NBS1 frequency was inversely correlated with LN metastasis (p=0.044). The significant survival difference between smoker and non-smoker (p<0.001) was lost when they presented high nuclear NBS1 frequency (p=0.095). In addition, the significant survival difference seen in relapse and relapse-free patients (p<0.001) was lost in adenocarcinoma cases when they presented with high NBS1 expression frequency (p=0.658). Intriguingly, a short term nicotine treatment increased NBS1 expression but did not significantly increase proliferation rate of the parental A549 cells. Nevertheless, the A549N cells that had been treated with nicotine for 6 months not only maintained increased NBS1 expression but also had increased cisplatin-sensitiveness. **Conclusion:** Our results showed that reduced nuclear frequency of NBS1 might be required for cigarette carcinogenic content-mediated advanced development. In addition, NBS1 might play a role in the treatment response of lung adenocarcinoma.

Keyword: Double strand breaks repair protein, Nijmegen breakage syndrome 1, lung adenocarcinoma

P1.03-38 EGFR MUTATION STATUS AS A PROGNOSTIC MARKER IN STAGE 1 LUNG ADENOCARCINOMA AFTER DEFINITIVE SURGICAL RESECTION

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Background: With tumor molecular genetics at the forefront of precision medicine, EGFR mutation status has been paramount for predicting response to therapy in advanced and metastatic NSCLC. However, little is known about the implications of EGFR mutation status in stage 1 disease following definitive surgical therapy, particularly in regard to prognosis and disease recurrence. **Method:** We retrospectively studied the clinical outcomes in 101 EGFR-positive patients and 97 age-matched EGFR-negative controls with stage 1 lung adenocarcinoma who underwent definitive surgical resection +/- chemoradiation. EGFR status was determined by pathologic molecular testing performed at time of diagnosis and TNM stage was determined at time of treatment. These cases were then followed for pathologically confirmed cases of recurrence and assessed for stage at recurrence, time elapsed since definitive treatment, and disease-free survival at 1, 2 and 5 years. **Result:** EGFR-positive disease demonstrated higher rates of metastatic recurrence with 15% vs 3% in controls (p=0.007). Median time to progression among those who progressed, defined as time to recurrence or death, was significantly shorter in EGFR-positive cases (82 weeks vs 158 weeks, p=0.048). There was no significant difference in rates of recurrence (p=0.32) between both groups. Disease-free survival in EGFR-positive cases was most notably lower at 2 years, with 0.86 (0.78-0.94) vs 0.94 (0.89-0.99).

	EGFR	Non-EGFR	P-value for comparison
Number in each group	101	97	-
Recurrence rate, N (%)	16 (16%)	10 (10%)	0.32 (chi-square)
Metastatic recurrence rate overall, N (%)	15 (15%)	3 (3%)	0.007 (chi-square)
Time to progression among those who progressed (weeks), Median (IQR)	82 (42, 130)	158 (75, 182)	0.048 (Wilcoxon rank sum test)
Progression free survival rates, based on Kaplan-Meier method (95% CI):			
1 year (52 weeks)	0.92 (0.86, 0.98)	0.98 (0.95, 1.00)	
2 years (104 weeks)	0.86 (0.78, 0.94)	0.94 (0.89, 0.99)	
5 years (260 weeks)	0.70 (0.58, 0.84)	0.69 (0.56, 0.86)	

Conclusion: This study suggests that EGFR-positive disease may be associated with a higher risk of metastatic recurrence and decreased time to progression in individuals who ultimately progress. EGFR molecular testing may be a promising tool for risk stratification and surveillance following definitive management for stage 1 disease. Future prospective modeling may be indicated in this disease.

Keywords: EGFR, Stage I NSCLC, Recurrence

P1.03-39 INTRA-TUMORAL CD61+ MEGAKARYOCYTES PREDICTS POOR PROGNOSIS IN NON-SMALL CELL LUNG CANCER

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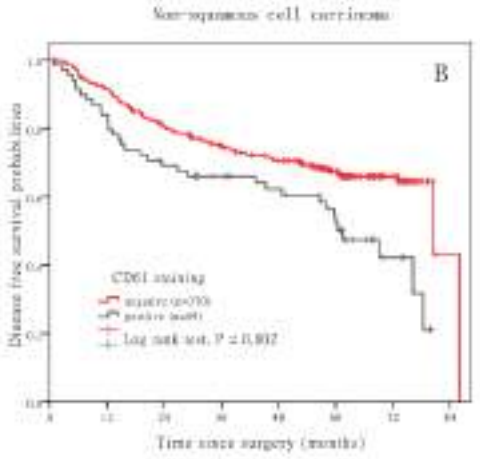
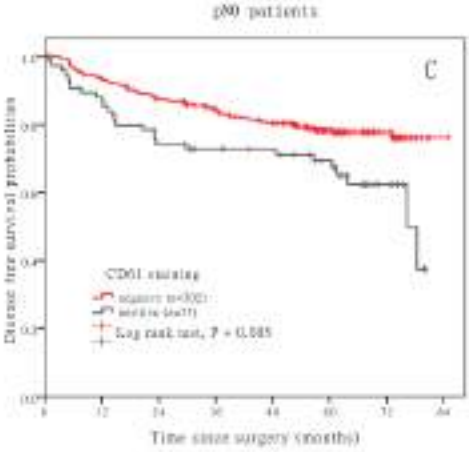
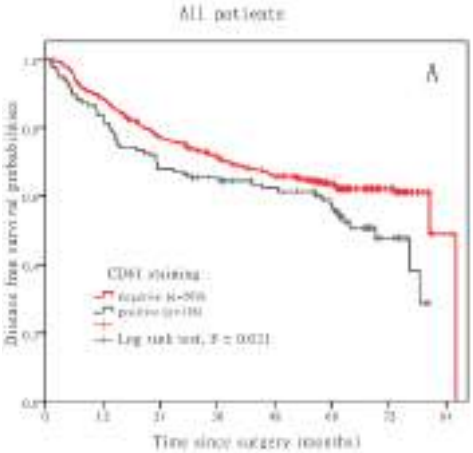
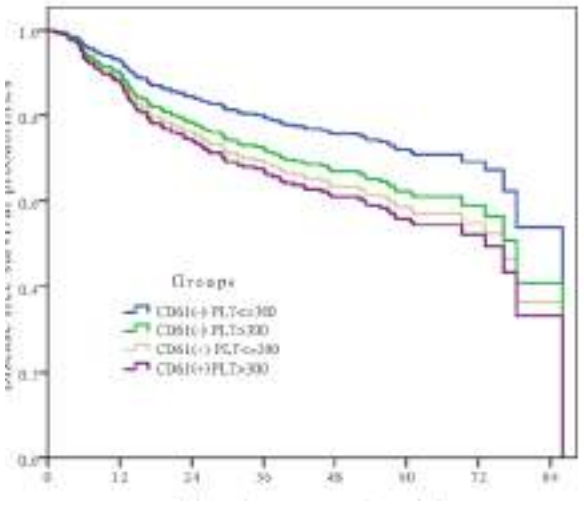
Background: Lung is a reservoir for MKs to produce platelets. The aim is to investigate relationship between intra-tumoral MK with the recurrence of NSCLC. **Method:** The tissue sections of 629 patients with resected NSCLC were stained with hematoxylin, anti-CD61, anti-CD34 and stromal cell-derived factor-1 (SDF-1). CD61+ giant cells localized in CD34+ capillaries were identified as MKs. The impact of MKs and DFS was investigated. **Result:** Overall, 18.9% of patients were positive for the presence of MKs. In univariate analysis, the median DFS of the MK+ group was shorter than the median DFS of the MK- group (69.1 vs. 80.5 months; *P*=0.021). Multivariate analysis indicated that MKs in tumor tissue was an unfavorable prognostic factor for DFS (HR 1.351, *P*=0.065), the impact of which was more significant in non-squamous cell carcinoma (NSCC) (HR 1.710, *P*=0.008) and in patients with N0 (HR 1.883, *P*=0.009). Although systemic platelet count of the MK+ group was significantly higher than the MK- group (270.6 vs. 243.6 $\times 10^9$/L, *P*=0.007), the stratified subgroup DFS curves (*P*=0.003) showed that the effect of MKs on prognosis was independent of the blood platelet count. In addition, the positive association of SDF-1, CD61 and microthrombi indicated a potential mechanism by which increased MKs facilitate blood metastasis.









Conclusion: CD61+ MKs in tumor tissue predict unfavorable prognosis in NSCLC. The prognostic impact of MKs in addition to that of systemic platelet count implies that regional MK-producing platelets in tumors might contribute to NSCLC metastasis.

Keywords: Non-Small Cell Lung Cancer, Megakaryocyte, prognosis

P1.03-40 USING MODEL SYSTEMS TO IMPROVE OUTCOMES FOR EARLY STAGE NSCLC

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Background: Improving outcomes for lung cancer patients with early stage disease is an unmet medical need, and model systems offer promise in this area. Model systems provide the ability to test and probe individual tumor samples with a wide array of discrete therapeutic agents, as well as novel combination strategies. Carefully engineered 3D model systems can run biological assays with animal model-like complexities, but with the speed, simplicity and affordability of traditional cell culture. A model validation step further informs assay fidelity and predictability. Upon human tumor recapitulation in a mouse, how do we know if this model is good? To what extent does the mouse-derived tumor reflect the human tumor? A clinical trial is underway at UAMS. Patients with early NSCLC have surgery for curative intent, and model systems are developed for insight towards therapeutic strategies upon recurrence. **Method:** All human tumor samples were obtained with patients' consent and IRB approval. Following surgical resection, human NSCLC tumors were grown in PDX models (JAX NSG). Tumor 3D spheroid cultures are performed on primary tumor material as well as PDX derived tumor material. All tumor material undergoes extensive modalities of NGS (ie, DNA, RNA) following best practices from the Broad Institute, and therapeutic targets are assessed. **Result:** Multiple methods and modalities are used for model system analysis and validation. Standard histopathology and multi-omic techniques are employed to examine and contrast the human tumor along with the associated PDX recapitulation through three or more passages. Specifically, the analyses include: i) copy number variation, ii) disease specific mutations via a high coverage DNA panel, iii) expressed mutations, and iv) gene and isoform expression. This is done for initial model validation and also following experiments employing specific therapeutic agents. Model systems will be compared and contrasted from PDX proper, as well as 3D tumor spheroid assays from the primary tumor and a variety of PDX passages. **Conclusion:** As model systems improve, so will the clinical outcomes for cancer patients. To improve model systems, robust bioinformatics approaches are needed for initial model assessment and validation, as well as to aid in the complex analyses associated with drug-based individualized therapy programs. Improved model systems offer the promise of enhanced scientific insights and clinical advances for cancer patients. Limitations in preclinical models are a major weakness in cancer research and is directly associated with the low success rates for translating discoveries to clinical care.

Keywords: Lung cancer, sequencing

P1.03-41 CHRONIC NICOTINE EXPOSURE AFFECTS PD-L1 EXPRESSION AND SENSITIVITY TO EGFR-TKI IN LUNG CANCER

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Background: Smoking histories are independently associated with poor response to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. The aim of the present study was to determine the effect of nicotine exposure on programmed death-ligand 1 (PD-L1) expression in EGFR mutant lung cancer cells. **Method:** Human lung adenocarcinoma PC9 cells were exposed to 1 μM nicotine for 3 months designated as PC9/N, and cells were stimulated with gefitinib (0, 0.1, or 1 μM) for 48 hrs. Cell viability by the MTT assay and morphological changes by immunofluorescence staining were assessed. The protein expression of EGFR, mTOR, AKT, α1-nicotine acetylcholine receptor (nAchR) and PD-L1 were measured by Western blot. Gene expression of α1-nAchR and PD-L1 were examined by RT-PCR. Intratumoral levels of PD-L1 expression were compared according to the burden of smoking dosage in EGFR mutant lung cancer patients. **Result:** Cellular growth was inhibited by treatment with gefitinib, and PC9 cells were significantly more sensitive to gefitinib than PC9/N cells. Pleomorphic appearance with atypical nuclei and to be detached and shrunken with condensed nuclei in PC9 than PC9/N cells. The gene expression level of α1-nAchR and PD-L1 gene were higher in PC9/N cells compared to those in PC9 cells after treatment with gefitinib. Phosphorylation levels of EGFR, mTOR, AKT and PD-L1 level were decreased by gefitinib in PC9/N cells, which was to a lesser extent than that in PC9 cells. In tumors, heavy smokers (≥ 30 PY) showed 28.5% of ≥ 50% PD-L1 tumor proportion score (TPS) while light smoker and never smokers had 12.5% and 9.7% of ≥ 50% PD-L1 TPS, respectively. **Conclusion:** Chronic nicotine exposure could increase PD-L1 expression related to intrinsic resistance to EGFR-TKI in NSCLC patients harboring activating EGFR mutation. Considering the clinical importance of inevitable EGFR resistance, further studies regarding the role of anti-PD-1/PD-L1 treatment are needed, especially in EGFR mutant smokers.

Keyword: Nicotine, PD-L1, EGFR mutation

P1.03-42 ANGIOTENSIN SYSTEM INHIBITORS IMPROVE SURVIVAL IN STAGE IIIA NSCLC AND SHOW ANTI-TUMOR EFFECT IN COMBINATION WITH CHEMOTHERAPY IN A MODEL OF NSCLC

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Background: There is increasing interest in the renin-angiotensin system and its influence on tumor microenvironment. This study investigates the anti-tumor effect of angiotensin system inhibitors (ASI) on the multi-modality treatment of stage IIIA NSCLC and examines a potential mechanism in a murine model of lung cancer. **Method:** We retrospectively reviewed the medical records of 125 patients at a single institution diagnosed with clinical stage IIIA NSCLC who underwent induction chemo-radiotherapy followed by surgery between 2009-2015. Overall survival was compared in patients on or off ASI's. To assess the antitumor efficacy and mechanism of ASI's, cell culture models of lung cancer were treated with losartan or combination losartan+cisplatin and assessed cell survival. Mechanism was investigated with markers of epithelial-mesenchymal transition or surrogates of other signaling pathways (AKT, Stat3, PD-L1). Losartan was then tested in a murine model of lung cancer. **Result:** ASI was associated with improved overall survival on multi-variate analysis of patients treated with multi-modality therapy for stage IIIA NSLC (p =0.047) [Figure 1A]. Losartan(≥0.5μM) significantly *inhibited proliferation and migration of multiple human lung cancer cells, (H441, H358, H1299, SW1573) and a murine lung cancer adenocarcinoma, TC-1. The combination of Losartan and cisplatin significantly improved the cytotoxic effect of cisplatin in lung cancer cells in vitro (*SW1573 p =0.020, TC-1 p =0.012) and reduced the tumor volume of (SW1573$^{\text{-Nude mice}}$, p =0.045 [Figure 1B]; TC-1$^{\text{-C57BL/6 mice}}$, G, p =0.001) in a murine flank tumor model as compared to single drug treatment. Combination

treatment also significantly inhibited epithelial to mesenchymal transition and down-regulated the expression of AKT, Stat3, and PD-L1. **Conclusion:** ASI treatment influences survival in stage IIIA NSCLC. Losartan improves the anti-tumor effect of cytotoxic chemotherapy in lung cancer invitro and significantly reduces tumor burden in a murine lung cancer model. This study suggests a role for ASI therapy in the treatment of lung cancer.

Keywords: NSCLC, Angiotensin system inhibitors, Chemotherapy

P1.03-43 PREOPERATIVE PROGNOSTIC VALUE OF IMMUNE-INFLAMMATION INDEX IN PATIENTS WITH OPERABLE NON-SMALL CELL LUNG CANCER

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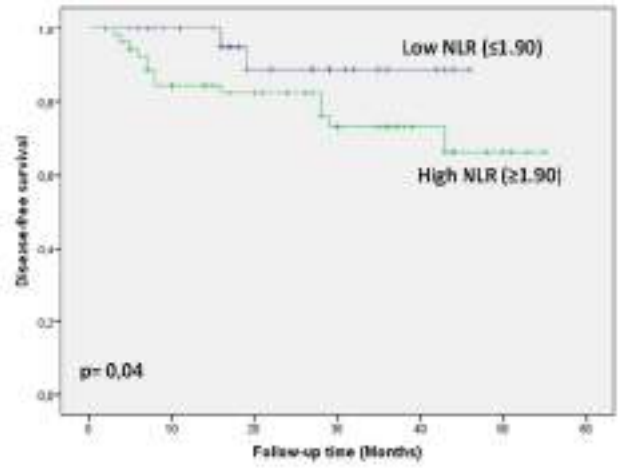
Background: There is increasing evidence that the systemic immune-inflammation response is correlated with clinical outcomes in diverse solid tumors. The aim of the study was to determine preoperative values of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR), and to analyze their impact on histologic outcomes and prognosis in patients with operable non-small cell lung cancer (NSCLC). **Method:** Retrospective study of patients diagnosed of stage I-IIIA NSCLC (7th edition TNM) between May 2014 and October 2018. Exclusion criteria included neoadyuvant therapy, R1-R2 resection, previous autoimmune or hematological disorders, active pre- or postoperative infection, steroid therapy, perioperative blood transfusion and previous history of malignancy other than NSCLC. The NRL, PLR and LMR were calculated by means of a peripherical blood sample 4 weeks prior to surgery. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-off values for above mentioned ratios. The association between NRL, PLR and LMR, and histological outcomes, recurrence, disease free interval (DFI) and overall survival were analyzed. **Result:** Eighty-six patients who underwent surgery for NSCLC were included in this retrospective analysis (51% males, median age 69,5 years). Mean follow-up was 45,7 months. Median overall survival and DFI were 27 and 24 months respectively. There was no statistically significant association between PLR, MLR, and histological variables, DFI or overall survival. The optimal cut-off value was 1.90 for NLR. In our series, INR values superior to 1.90 showed a significantly higher recurrence rate (23.6% vs. 5.5%, p=0.04) (Fig. 1) and a decreased overall survival (90% vs. 97%, p=0.031).



Conclusion: This study demonstrated that NLR is an independent poor outcome marker for patients with I-IIIA NSCLC who underwent surgery. In our series NLR (cut off value >1.90) could be used preoperatively as a valuable prognostic marker for disease free interval and overall survival.

Keywords: lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

P1.03-44 ROLE OF SERUM PROCALCITONIN AS DIAGNOSTIC BIOMARKER OF PNEUMONIA IN LUNG CANCER PATIENT

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Universitas Indonesia, Jakarta/Indonesia

Background: Pneumonia accounts for higher morbidity and mortality than any other infections in lung cancer patients. Procalcitonin (PCT) is a clinical biomarker that widely used to diagnose infection including pneumonia. The cut off level of serum procalcitonin to diagnose pneumonia in lung cancer patient still unclear. The current study aimed to determine the role of PCT in diagnosing pneumonia in lung cancer patients. **Method:** Diagnostic test with cross sectional design was conducted in lung cancer patients with suspected pneumonia admitted to emergency and pulmonary ward of Persahabatan Hospital Jakarta, Indonesia between August – October 2018. Pneumonia was defined as the presence of new or progressive infiltrate or air bronchograms on chest radiograph with minimal 2 acute signs and symptoms of lower respiratory tract infection. Serum PCT level (sPCT), leucocyte count, and absolute neutrophil count between lung cancer patients with and without pneumonia was measured followed by statistical analysis. The optimal sPCT cut off point to diagnose pneumonia in lung cancer was determined using ROC curve. **Result:** A total of 60 subjects enrolled in this study. Lung cancer patients presented with pneumonia was found in 31 patients (51.7%) with mean age 54.68±10.59 yo, which 77.4% were males, 51.6% were adenocarcinomas, 83.9% were stage IV cases, 45.2% were patients with ECOG performance status of 3, 45.2% were underweight and 54.8% were ex-smokers. The sPCT were significantly higher in lung cancer patients with pneumonia compared to those without pneumonia [1.81 (0.08-200) µg/L vversus 0.30 (0.05-3.67) µg/L; p<0.001]. In both group showed an elevation of leucocyte count (17.340 cells/µL versus 13.660 cells/µL) and absolute neutrophil count (14.955 cells/µL versus 11.872 cells/µL) with no significant differences (p=0.297 and p=0.290, respectively). The sPCT showed a good accuracy to diagnose pneumonia in lung cancer with AUC 0.829 (CI 95% 0.722-0.935). The optimal cut off point of sPCT to diagnose pneumonia in lung cancer was 0.65 µg/L with 77.4% sensitivity and 79,3% specificity. **Conclusion:** The sPCT was significantly higher in lung cancer patients with pneumonia than those without pneumonia and showed a better performance in differentiating pneumonia in lung cancer patients compared to leucocyte count and absolute neutrophil count. The optimal cut off level of sPCT to diagnose pneumonia in lung cancer was 0.65 µg/L.

Keywords: Lung cancer, procalcitonin, pneumonia

P1.03-45 CIRCULATING TUMOR CELLS' CLEARANCE IN BLOOD SAMPLES AFTER CHEMOTHERAPY: A GOOD PROGNOSTIC FACTOR FOR OS IN ADVANCED NSCLC

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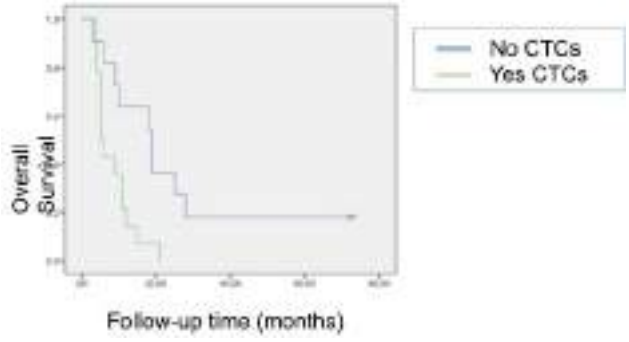
Background: The poor prognosis of patients diagnosed with non-small cell lung cancer (NSCLC) patients in advanced stages requires a close monitoring of treatment´s response in order to plan early changes when necessary. The presence of circulating tumor cells (CTC) in periferic blood samples has showed worse prognosis in different tumors. The aim of the study is analyzing the relationship between the presence of CTCs in periferic blood samples and overall survival (OS) and progression-free interval (PFS) in advanced stages of NSCLC patients. **Method:** Periferic blood samples were obtained from 25 patients diagnosed with NSCLC in advanced stages from April of 2010 to January of 2013 suitable for chemotherapy treatments. One blood sample was taken before treatment (S1) and the other one, after one cycle of chemotherapy (S2). Blood samples were analyzed by CellSearch method. Probability of survival was calculated following the Kaplan-Meier method; differences in survival were examined by the Long-Rank test. **Result:** Median OS and PFS were 10 months and 6 months respectively. OS was 6 months in patients with isolation of CTC in S1 vs 11 months in those with no isolation of CTC; no statistical differences (p=0.978). OS was longer in those patients in whom there was no isolation of CTC in

S2 compared to those in whom CTC were isolated (19 months vs 5 months; p=0.006). Contrary to this, no difference was observed considering PFS with a median of 6.5 months in patients without CTCs in their S2 and 6 months with CTCs present.



Conclusion: In our study, patients with CTC´s isolation in S2 had a worse prognostic, median of 14 months OS, compared to those in whom there were no CTC isolation.

Keywords: circulating tumour cells, advance stage

P1.03-46 LNCRNA H19 DOWNREGULATION PROMOTED RESISTANCE TO EGFR-TKIS THROUGH REGULATING AKT AND SRC ACTIVATING IN NSCLC CELLS

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Background: Most NSCLC patients with EGFR activating mutations initially respond to EGFR-TKI treatment. However, acquired resistance to EGFR-TKIs inevitably occurs after treatment for several months. There are evidences that suggest lncRNAs could play important roles in EGFR-TKI resistance, but limited data is available now. In previous study, we found that LncRNA H19 was downregulated in EGFR-TKI-resistant cells. **Method:** We established two erlotinib-resistant cell lines HCC827-ER and PC9-ER. Real-time quantitative PCR (qPCR) was used to detect H19 levels. We detected gene mutations in the ER cell lines through whole-exome sequencing. We used H19 and H19 shRNA lentiviral expression vector to overexpress or knockdown its expression. MTT cytotoxic and clone formation experiments were performed to assess cell growth inhibition. The apoptosis analysis was evaluated by PARP and caspase-3 degradation. Protein levels in AKT and SRC were examined by western blotting. **Result:** H19 expression was lower in HCC827-ER and PC9-ER cells than in their parental sensitive (PS) cells. We did not detect mutations in EGFR T790M, PI3KCA, or KRAS by whole-exome sequencing of ER cell lines. MTT and clone formation assays showed H19 knockdown caused resistance to erlotinib in PS cells, whereas H19 overexpression not only enhanced erlotinib sensitivity in PS cells but also recapitulated erlotinib sensitivity in HCC827-ER and PC9-ER cells. Treatment with erlotinib increased PARP and caspase-3 cleavage in H19-ovexpressing ER and PS cells. We also found erlotinib treatment decreased levels of phosphorylated AKT and SRC in PS cells, and further lowered their levels in H19-overexpressing PS cells. On the contrast, erlotinib treatment had no effect on levels of phosphorylated AKT and SRC in H19-knockdown PS cells. Finally, we measured the expression of H19 using qPCR in 20 fresh frozen EGFR-mutant NSCLC specimens. Lower expression of H19 was observed in EGFR-TKI-resistant tissue samples. **Conclusion:** H19 was downregulated in erlotinib-resistant NSCLC cells. H19 inhibited AKT and SRC activating to restore sensitivity to erlotinib, which could provide new insight into resistance mechanisms to EGFR-TKIs.

Keywords: LncRNA H19, EGFR-TKIs, NSCLC

P1.03-47 KEAP1 MUTATIONS IN EAST ASIAN PATIENTS WITH NSCLC: AN INVESTIGATION OF PREVALENCE, CLINICOPATHOLOGIC CHARACTERISTICS AND PROGNOSIS

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Background: The KEAP1/NRF2 pathway is a master regulator of the cellular redox state through the induction of several antioxidant defence genes implicated in chemotherapeutic drugs resistance of tumor cells. Because of the rarity of those mutations, associated clinical features and prognostic significance have not been thoroughly described so far. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *KEAP1* mutations. **Method:** A total of 317 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *KEAP1* mutations and other genes were detected by next generation sequencing. **Result:** *KEAP1* gene mutation rate was 10.09% (32/317) in non-small cell lung cancer, including D618Tfs*54 (2 patients), W252L (1 patient), G158C (1 patient), D618Tfs*54 (1 patient), L237Q (1 patient), R415C (1 patient), K97N (1 patient), C368F (1 patient), A95T (1 patient), C273F (1 patient), S243F (1 patient), E149K (1 patient), H96L (1 patient), L70Q (1 patient), G558W (1 patient), E493K (1 patient), A40P (1 patient), E343V (1 patient), E219* (1 patient), G158C (1 patient), D235Tfs*3 (1 patient), I125T (1 patient), R320L (1 patient), R470H (1 patient), E244* (1 patient), G158V (1 patient), C368F (1 patient), I185F (1 patient), N157_M161del (1 patient), R336* (1 patient) and E219Q plus D526N (1 patient), and median overall survival (OS) for these patients was 13.5 months. Among them, all patients were *KEAP1* gene with co-occurring mutations. Briefly, patients with (n=20) or without (n=12) co-occurring *TP53* mutations had a median OS of 14.5 months and 13.5 months respectively (P=0.71); patients with (n=15) or without (n=17) co-occurring *KRAS* mutations had a median OS of 15.0 months and 12.0 months respectively (P=0.79); patients with (n=16) or without (n=16) co-occurring *STK11* mutations had a median OS of 13.5 months and 18.0 months respectively (P=0.60); patients with (n=4) or without (n=28) co-occurring *PIK3CA* mutations had a median OS of not up to now and 12.0 months respectively (P=0.16). **Conclusion:** *KEAP1* gene mutation coexists with other gene mutation in NSCLC. *TP53*, *KRAS*, *STK11* and *PIK3CA* gene accompanied may have less correlation with *KEAP1* mutation in NSCLC patients. Analysis of *KEAP1* mutations shows promise as a way to refine individual patients with NSCLC, and provides more insight into effective treatment strategies for patients with *KEAP1* mutations.

Keywords: prognosis, non-small-cell lung cancer, KEAP1 mutation

P1.03-48 VASOHIBIN 2 PROMOTES ANGIOGENESIS AND LYMPHANGIOGENESIS OF LUNG SQUAMOUS CELL CARCINOMA THROUGH SNAIL-DEPENDENT VEGF-D SIGNALING PATHWAY

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Background: Tumor metastasis is a process in which tumor cells spread to the secondary sites via the lymphatic and blood vessels. In lung squamous cell carcinoma (LUSC), the molecular mechanisms involved in lymphangiogenesis and lymphatic metastasis remain unclear. **Method:** We analyzed mRNA expression profiles of 535 primary LUSC samples from TCGA to screen the most differentially expressed genes related to the poor prognosis of LUSC patients and validated in an independent Chinese LUSC cohort. We focused on *Vasohibin 2* (VASH2) and investigated its biological functions in LUSC proliferation, apoptosis, migration, invasion, as well as lymphangiogenesis by forced over-expressing VASH2 in LUSC cell line H520 *in vitro*. We also investigated the anti-tumor efficacy of VASH2 target treatment in LUSC xenograft-bearing mice models. **Result:** We identified 12 genes closely related to poor prognosis of LUSC patients, among which VASH2 was validated in an independent Chinese LUSC cohort and displayed high potential of lymphatic metastasis. Forced over-expression of VASH2 promoted the proliferation and invasion of LUSC cells via up-regulating

specific transfer factor snail. Furthermore, VASH2 facilitated lymphangiogenesis and angiogenesis via up-regulation of snail-dependent vascular endothelial growth factor-D (VEGF-D) in LUSC cells *in vitro and vivo*. Importantly, specific VASH2 blocking antibody dramatically inhibited tumor development and progression in LUSC xenograft-bearing mouse models by interfering tumor proliferation and lymphangiogenesis *in situ*. **Conclusion:** In conclusion, VASH2 might serve as a novel predictive biomarker and a potential therapeutic target for LUSC via inhibiting tumor growth and local lymphangiogenesis.

Keywords: Vasohibin 2, Lymphangiogenesis, LUSC

P1.03-49 SYSTEMATIC DYSREGULATION OF CELL CYCLE BY LNCRNAS IN LUNG ADENOCARCINOMA

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Background: LncRNAs are associated with tumor progression, immune escape, and survival, but how do lncRNAs systematically change the tumor microenvironment and what biological function is dysregulated are less reported. **Method:** In our previous report, lung adenocarcinoma (LUAD) RNA sequencing data were downloaded from The Cancer Genome Atlas (TCGA). Differential analysis and lncRNA- protein-coding-gene co-expression analysis was performed; the signal pathways of expressed genes are clustered and enriched. **Result:** AC109642.1, RP11-582J16.4, RP11-378A13.1, TBX5-AS1, AC090616.2, AC079630.4, SFTA1P, FENDRR, RP11-736K20.4, RP11-389C8.2 and MIR22HG are low expressed in cancer tissue compared to tumor-matched normal tissue, while the EEF1A1P6, MBNL1-AS1, ADAMTS9-AS1, LINC00987, LINC01197, EP300-AS1, PCAT19, OR7E47P, AC093110.3, RP11-366L5.1, LINC00968, CTD-2562J17.6, RP11-203P23.2, AF131215.2, RP11-434D9, LINC00702, RP11-1024P17.1 and MAGI2-AS3 are high expressed. These lncRNAs regulated coding proteins are clustered into seven categories and systematically mediated cell cycle dysfunction in LUAD.

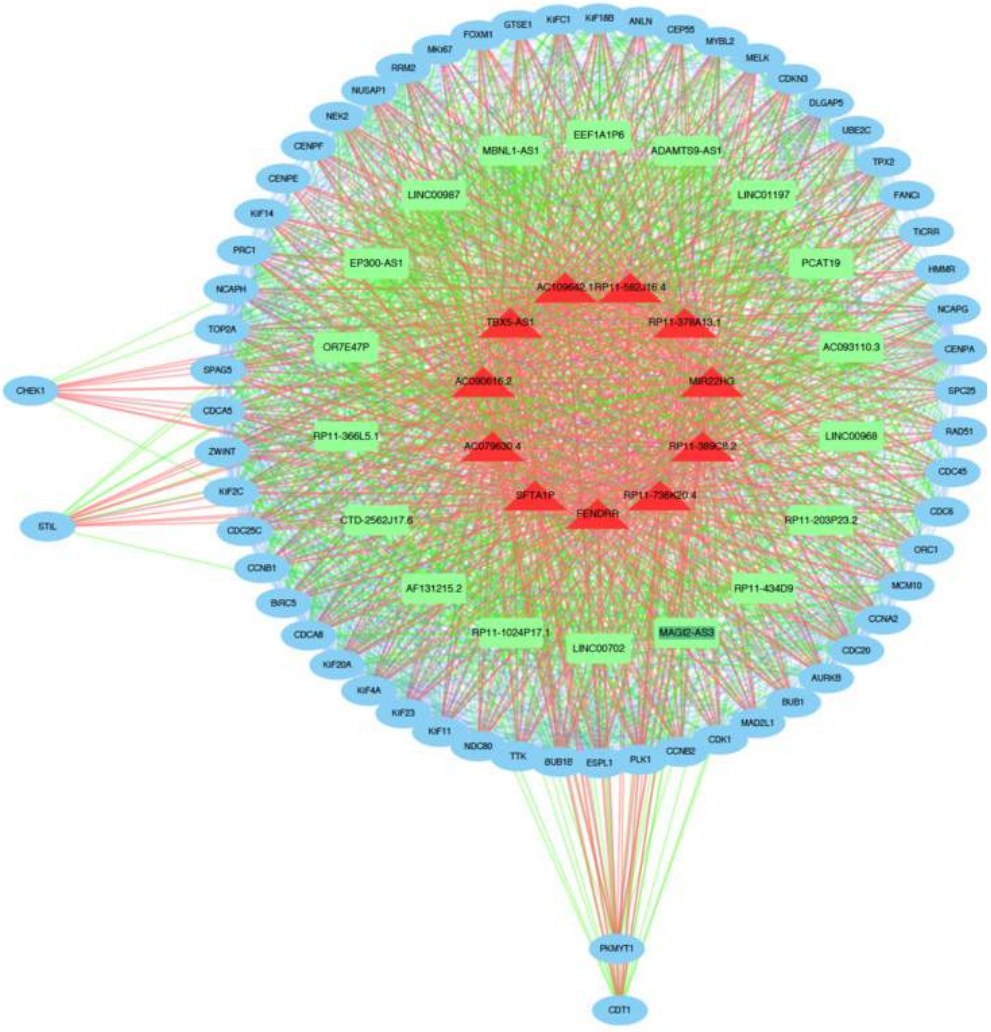

Figure 1 The network of lncRNAs regulated protein-coding genes. The red triangles indicate low expressed lncRNAs in tumor tissue; the green rectangular indicate high expressed lncRNAs in tumor tissue and the blue ovals indicate regulated coding genes. **Conclusion:** This is the first time to reveal that the dysregulated lncRNAs systemically affect the cell cycle in LUAD tissue. The dynamic change of lncRNAs and the associated protein-coding genes network could give us a better epigenetic understanding and future direction of targeting uncontrollable LUAD growth.

Keywords: cell cycle, lncRNAs, lung adenocarcinoma

POSTERS

P1.03-50 TYPE- AND STAGE-SPECIFIC GENOMIC PROFILES IN EAST ASIAN LUNG CANCER PATIENTS WITH NO TKI-RELATED DRIVER GENE MUTATIONS

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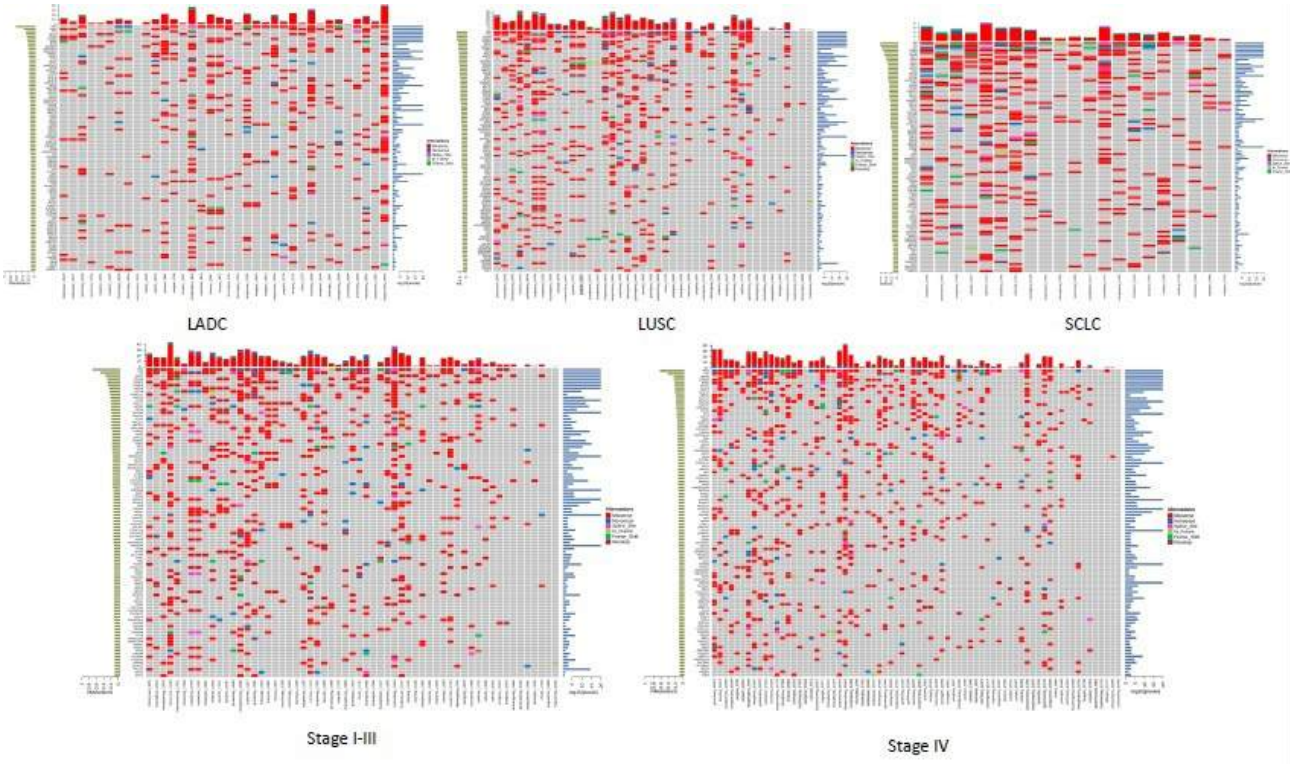
Background: It is widely accepted that the development of advanced lung cancer or distant metastases rely on driver gene mutations, but the carcinogenesis of lung cancers without key driver gene mutations has not been fully understood. The genomic landscape of lung adenocarcinoma (LADC), lung squamous cell carcinoma (LUSC) and small cell lung cancer (SCLC) without TKI-related driver gene mutations in East Asian has not been well investigated. Systematic study of these subtypes may identify biomarkers to distinguish different types and find novel tractable targets for therapy. We have therefore studied the genomic profiles of these types of lung cancers to identify type-specific and stage-specific gene mutations. **Method:** 32 LADC patients, 43 LUSC patients and 26 SCLC patients with no TKI-related driver gene (EGFR, ALK, ROS1, RET, BRAF, C-MET, HER2) mutations were included in this study. Genomic profiles were determined with lung cancer tissue by whole-exome sequencing (WES). Sequencing data were analyzed with R packages and statistics was performed with SPSS 20. **Result:** In 101 patients enrolled, TP53, TTN, MUC4, ZFHX4 and CSMD3 mutations were commonly detected in all 3 types of lung cancer, and TP53 was the commonest mutated gene. Markedly, KRAS mutations were found only in LADC, and CSMD1 mutations were more frequent in LUSC, whereas RB1 mutations were observed exclusively in SCLC. LRP1B and RYR2 mutations were found more frequently at late stages. Copy number variations (CNV) in TERT, RICTOR and FGFR1 were seen in all 3 subtypes. The PIK3CA copy number gain was commonly seen in LUSC and SCLC other than that in LADC. In contrast, the CDKN2A copy-number loss was found in LADC and LUSC, but not in SCLC. The PTEN copy number loss was only identified in LUSC. No significant differences in TMB were observed among these 3 subtypes of lung cancer. However, statistical significance in TMB was attained between non-small cell lung cancer (NSCLC) and SCLC (P=0.022) in stage IV patients when the cut-off of TMB was set to 4.5 muts/MB.



Conclusion: Results from this genomic study confirmed the mutual and exclusive gene variations (including gene mutations and copy number variations) in 3 subtypes of lung cancer. It showed that gene variations were associated with lung cancer subtypes in patients with no TKI-related driver gene mutations. These findings might detecte subtype-specific biomarkers to assist histological-based diagnosis, and help to identify potential type-specific targets for lung cancer therapy.

Keywords: Lung cancer, WES, gene mutations

P1.04-01 BODY MASS INDEX AND AGE DO NOT INFLUENCE SURVIVAL IN PATIENTS WITH LUNG CANCERS TREATED WITH PD1/PDL1 IMMUNE CHECKPOINT INHIBITORS

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Background: Age and body mass index (BMI) are important factors in patients treated with chemotherapy. However, in the era of immune checkpoint inhibitors (ICI), the importance of these baseline characteristics is unclear. For example, pooled analysis of age did not influence the clinical response to ICI, whereas patients with BMI >35 had better outcomes in melanoma and renal cell carcinoma. More data are needed to clarify the role of these two characteristics in non-small cell lung cancer (NSCLC) patients amenable ICI. **Method:** We conducted a retrospective analysis of patients treated with anti-PD1 ICI for advanced NSCLC at the Dijon Cancer Center (n=177), University of Montreal University Hospital (n=106) and Quebec Heart and Lung Institute (n=98). BMI and age were considered as continuous or categorical variables. Patients' baseline characteristics were compared using the Chi-squared test. Survival curves were estimated by the Kaplan-Meier method and compared with the Log-rank test in a univariate analysis. Multivariate cox regression model was used to determine hazard ratios and 95% confidence intervals for progression-free survival (PFS) and overall survival (OS) between the groups, adjusting for other clinicopathologic features. **Result:** Among 381 patients included, the median BMI was 24.5 (range 16.2-43.4) and 32.7% and 13.6% were classified as overweight or obese respectively. The median age was 66 (range 37-89) and 29% were older than 70 years-of-age. Considering BMI and age as continuous or categorical variables, they were not associated with PFS or OS, with the exception of BMI in the Dijon cohort (continuous: HR=0.95, 95%CI[0.91-0.99]; < 25 vs > 25: HR=0.68, 95%CI[0.47-0.99]). Subgroup analysis and multivariate cox regression did not reveal significant interaction of these two factors with outcomes. There was no difference in toxicity between the groups. ECOG performance status was the only significant factor in the three cohorts. **Conclusion:** Unlike previously described in the era of chemotherapy, obesity and age were not associated with outcomes in NSCLC patients treated with ICI.

Keywords: Immune Checkpoint Inhibitors, NSCLC, BMI / age

P1.04-02 EFFICACY AND SAFETY OF SINTILIMAB WITH ANLOTINIB AS FIRST-LINE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Given the synergy effect of immunotherapy and anti-angiogenic therapy in advanced NSCLC, FDA approved atezolizumab plus bevacizumab and chemotherapy as first-line treatment. However, chemo-free first-line strategy of PD-1/PD-L1 inhibitor combining angiogenesis modulator remains to be explored. This is the first trial evaluating sintilimab (anti-PD-1) plus anlotinib (multi-target TKI against tumor angiogenesis and proliferation) in treatment-naive advanced NSCLC patients and is also one arm from phase I anlotinib-based trial (NCT03628521). **Method:** Treatment-naive, stage IIIB/IV NSCLC patients aged 18-75 with ECOG PS 0-1 were eligible. Patients with EGFR, ALK or ROS1 mutations were excluded. Participants were given intravenous sintilimab (200mg q3w) and oral anlotinib (12mg/d 2 weeks on/1 week off) until progression or unacceptable toxicity. The primary endpoints were ORR and safety. The secondary endpoints included DCR, PFS and OS. AEs were graded according to CTCAE v4.0. **Result:** From Septembe-2018 to February-2019, 22 patients were enrolled. Most were male (95.5%), former/current smokers (63.6%) and squamous cell histology (54.5%). 4 had baseline brain metastases. All patients have received at least one tumor assessment as of Jul-3th-2019. Among all, 17 achieved confirmed PR, 5 achieved SD, ORR was 77.3% and DCR was 100%. 6m-PFS rate was 93.8% (95%CI: 63.23%, 99.10%). Overall, sintilimab and anlotinib was well tolerated. 7 (31.8%) had grade 3 and above treatment related adverse event (TRAE). The most common TRAE were hematuria, hyperuricemia, hypertension, increased ALT and rash, etc. 21 patients had baseline PD-L1-evaluated and 17 patients got TMB status (details in table). Notably, 2 of 5 SD patients developed cavities inside, suggesting a sign of synergetic anti-tumor effect from combination regimen. **Conclusion:** In this interim analysis, sintilimab plus anlotinib showed high ORR (77.3%) and DCR (100%) with tolerable safety profile, supporting worthy of further development from this convenient chemo-free regimen in first line setting.

Table 1. Response rates

Best Overall Response	Overall (n=22)	PD-L1 + (n=13)	PD-L1 - (n=6)	TMB ≥ 10 (n=6)	TMB <10 (n=11)
CR, n (%)	0	0	0	0	0
PR, n (%)	17 (77.3%)	9 (69.2%)	7 (87.5%)	5 (83.3%)	8 (72.7%)
SD, n (%)	5 (22.7%)	4 (30.8%)	1 (12.5%)	1 (16.7%)	3 (27.3%)
PD, n (%)	0	0	0	0	0
ORR, n (%)	17 (77.3%)	9 (69.2%)	7 (87.5%)	5 (83.3%)	8 (72.7%)
DCR, n (%)	22 (100%)	13 (100%)	6 (100%)	6 (100%)	11 (100%)

Keywords: advanced NSCLC, PD-1 inhibitor, multi-target angiogenesis agent

P1.04-03 HLA AFFINITY FOR MUTANT EGFR DERIVED PEPTIDES IDENTIFIES A GROUP OF PATIENTS WITH EGFR DRIVEN NSCLC AND FAVORABLE PROGNOSIS

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Background: Tumor mutations generate neopeptides with the potential to elicit T cell responses. Most commonly, passenger mutations are involved in this process, whereas driver mutations are restricted by the HLA genotype. Here, we hypothesized that peptides derived from mutant EGFR with ability to be presented by the host HLA molecules might elicit T cell responses against EGFR mutation positive tumors. **Method:** We used the NETMHCpan platform to predict HLA A, B and C alleles that bind to peptides derived from EGFR p.L858R and EGFR p.E746_A750del but not to the closest wild type peptides. We termed the identified alleles as "protective alleles" based on their potential to elicit T cell responses against mutant EGFR. Further, we classified patients with EGFR mutation positive lung adenocarcinoma in the TCGA database with known HLA genotype into having at least one protective allele ("protected" group) or having none of these alleles ("non-protected" group). **Result:** We identified HLA alleles A*31:01, A*33:01, A*68:01 and B*08:01 as protective for EGFR p.L858R and alleles A*03:01 and A*11:01 as protective for EGFR p.E746_A750del. These alleles with the exception of A*11:01 are found more common in European compared to Asian populations. In the TCGA population, we identified 20 patients with EGFR p.L858R and 14 patients with EGFR p.E746_A750del positive lung adenocarcinoma and complete follow up and HLA data. Among them, 11 classified in the "protected" and 23 in the "non-protected" group. There were no significant differences in the two groups with respect to gender, age or stage at diagnosis. Patients in the "protected" group had longer overall survival (p value=0.0011) and disease-free survival (p value=0.0047) compared to the "non-protected" group. Presence of the same alleles did not affect prognosis in patients from the TCGA with KRAS mutation positive adenocarcinoma. Difference in overall survival remained significant after controlling for stage, gender and age at diagnosis in a Cox proportional hazards model (risk ratio 0.01, 95% CI 0.001-0.34). **Conclusion:** Here, we present a methodology to identify HLA alleles with the potential to elicit EGFR directed T cell responses against mutant EGFR. Interestingly, the identified alleles are more common in European populations, known to carry less risk for EGFR mutations compared to Asian populations. Presence of such alleles

predicts better prognosis in an early stage EGFR mutation positive lung cancer population, consistent with our hypothesis that they might drive adaptive immunity against mutant EGFR.

Keywords: HLA, EGFR, adaptive immunity

P1.04-04 DNA DAMAGE RESPONSE GENE ALTERATIONS ARE ASSOCIATED WITH HIGH TUMOR MUTATIONAL BURDEN AND CLINICAL BENEFIT FROM PD-1 AXIS INHIBITION IN NSCLC

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Background: DNA damage response (DDR) gene alterations are associated with increased tumor infiltrating lymphocytes, higher genomic instability, and higher tumor mutational burden (TMB) in cancer. Whether DDR alterations are associated with benefit from immune-checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC) is unknown. **Method:** Clinicopathologic and genomic data were collected from patients (pts) with advanced NSCLC at the Dana-Farber Cancer Institute treated with PD-(L)1 inhibitors. Targeted next-generation sequencing (NGS) by OncoPanel was used to determine DDR gene mutation status and TMB. All loss-of-function alterations in DDR genes (including nonsense, frameshift, or splice site) were classified as pathogenic. Missense mutations were manually evaluated and classified as pathogenic if considered to be deleterious in the Catalogue of Somatic Mutations in Cancer (COSMIC) and ClinVar databases, as well as the PolyPhen-2 (Polymorphism Phenotyping v2) functional prediction tool. **Result:** Of 223 pts with successful NGS who received ICIs, 116 (52.0%) were identified as having pathogenic DDR mutations (DDRpos) with alterations in the following genes: FANC genes (20%) ATM (13.9%), POL genes (11%), ERCC genes (8%), BRCA1/2 (8%), MLH1/MSH2/MSH6 (7%), CHEK1/2 (7%), RAD genes (6%), ATR (5%), BRIP1 (3%), XRCC genes (3%), BARD1 (2%), PMS (2%), NEIL (2%), BAP1 (1%), PALB2 (1%). DDRpos and DDR negative (DDRneg) groups were well balanced in terms of age, gender, histology, performance status (PS), smoking status, baseline presence of brain metastasis. The median TMB was significantly higher in the DDRpos group compared to the DDRneg group (12.9 vs 8.3 mutations/megabase [mut/Mb], P < 0.001), including among never smokers (11.0 vs 6.8 mut/Mb, P = 0.02). No difference in median PD-L1 expression was observed between groups (50% vs 50%, P = 0.52). Compared to DDRneg pts (N=107), DDRpos pts had a significantly higher objective response rate (30.4% vs 16.8%, P = 0.001), longer median progression-free survival (4.3 vs 2.3 months, HR: 0.64 [95%CI: 0.48-0.86], P = 0.003) and median overall survival (16.5 vs 11.2 months, HR: 0.62 [95%CI: 0.44-0.88], P = 0.008) with PD-(L)1 therapy. After adjusting for ECOG PS, smoking status, baseline brain metastasis, and line of therapy, DDRpos status was associated with significantly longer PFS (HR: 0.64 [0.48-0.86], P < 0.01) and OS (HR: 0.58 [95%CI: 0.41-0.83], P < 0.01) in multivariate analysis. **Conclusion:** Pathogenic DDR alterations are frequent in NSCLC and are associated with higher TMB and improved clinical outcomes among NSCLC pts treated with PD-1 axis inhibition.

Keywords: DNA damage response genes, Immunotherapy, Non-Small Cell Lung Cancer

P1.04-05 PD-L1 EXPRESSION (SP263) IN LUNG CANCER AND PAIRED BRAIN METASTASES – A SINGLE CENTER STUDY IN 211 PATIENTS

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Background: Lung cancer presents with brain metastases (BM) in a significant number of cases and resected BM are often the only tissue available for analysis of predictive biomarkers. Studies have shown some molecular divergence between BM and primary lung tumor, but data on paired samples is rare. Here we analyzed the expression of the predictive biomarker programmed cell death ligand 1 (PD-L1) in BM and paired primary tumors. **Method:** In a single-center retrospective study, we assembled a cohort of consecutive BM resected and diagnosed at our University hospital between 2000 and 2015. We analyzed PD-L1 expression (Ventana SP263 kit) on full slides of lung cancer BM (N=211) and available paired primary tumors (N=87), using the increments <1%, 1-49% and ≥50%. **Result:** Our BM cohort comprised 145 (68.7%) adenocarcinomas, 24 (11.4%) squamous cell carcinomas, 34 (16.1%) small cell carcinomas and large cell neuroendocrine carcinomas and 8 (3.8%) others. PD-L1 staining was evaluable in 193 BM and 87 paired primary tumors. There was no tumoral PD-L1 expression in the high-grade neuroendocrine carcinomas. Among the non-neuroendocrine cancer BM, 86/165 (52.1%) expressed <1% PD-L1, 36/165 (21.8%) 1-49%, and 43/165 (26.1%) ≥50%. PD-L1 scores significantly correlated between BM and primary tumors (p<0.001), with a complete congruence in 62/77 cases (80.5%). Clinically significant discrepancies (cut-off 50%) were present in 9/77 (11.7%) cases: 6 cases were primary tumor-positive/BM-negative, and 3 cases BM-positive/primary tumor-negative. Only 4/9 patients with discrepant PD-L1 scores received chemotherapy in between tissue acquisition of BM and primary tumor, failing to serve as an explanation. Tissue from at least 2 separate brain metastases was available in 12 patients, with discrepant PD-L1 scores regarding the 50% cut-off in only 1 patient (8.3%), and regarding the 1% cut-off in 2 patients (16.7%). There was no association between PD-L1 expression in the BM and overall survival (p=0.95). **Conclusion:** In conclusion, we show that PD-L1 scores are concordant in most of paired BM and primary tumors. The discordant cases could not be explained by longer time lapses or chemotherapy or radiotherapy in between tissue acquisition, nor by scarce tissue availability of the primary tumor, e.g. due to biopsies only, and may be due to tumor heterogeneity.

Keywords: Lung cancer, brain metastasis, PD-L1

P1.04-06 TUMOR MICROENVIRONMENT LANDSCAPE IN LUNG ADENOCARCINOMA BY SINGLE-CELL SEQUENCING

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Background: Lung cancer is the leading cause of cancer cell death in worldwide. Failure of early detection, high recurrence rate and metastasis all contribute to the low survival rate in this detrimental disease. In particular, frequent brain metastasis confers an imperative challenge in the management of lung cancer. Single-cell RNA sequencing provides specific profiling of cell populations at the single-cell level. Interpretation of single-cell transcriptome data for the discovery of therapeutic targets and prognostic biomarkers is an ongoing challenge in precision cancer medicine. Especially, the influence of immune microenvironment in tumor has been accepted as a key factor for determining the therapeutic outcome. Despite the diversity of immune infiltrates in lung adenocarcinoma, single-cell RNA sequencing has not yet been applied for a large-scale tumor and immune profiling. **Method:** Samples were obtained from the primary tumor, lymph node or brain metastases, and pleural fluids of 44 patients with lung adenocarcinoma. Following lung tumor resection, normal lung tissues from a distal region as well as normal lymph nodes were collected for comparison. We dissociated the whole tissues into single cell suspension and then performed scRNA-seq using droplet-based 10x Genomics Chromiunm platform. **Result:** After quality filtering, we cataloged a total of 208,506 cells into 9 distinct cell lineages annotated by expression of known marker genes. We identified epithelial cells including cancer cells, stromal cells (fibroblasts and endothelial cells), immune cells (T, NK, B, myeloid, and MAST cells) as common cell types, and oligodendrocytes uniquely from brain metastases. The most abundant immune cell populations at the lung tumor site were T lymphocytes and myeloid cells. Notably, primary tumor and lymph node metastases showed substantial differences in the immune cell composition. These differences reflected the original tissue microenvironment, grossly altered by tumor progression and invasion. Therefore, our lung adenocarcinoma atlas illustrates the dynamic cellular landscape during cancer progression which may reveal progression associated changes for each cellular component in unprecedented

scale and manner. **Conclusion:** These results provide specific tumor microenvironmental patterns in lung adenocarcinoma. Thus, single cell-level transcriptome profiles provide clues to expand therapeutic windows into the combination therapy with immune and anti-cancer reagents.

Keywords: lung adenocarcinoma, Single-cell RNA sequencing, tumor microenvironment

P1.04-07 IMMUNE SUPPRESSIVE MICROENVIRONMENT AND HIGHLY CLONAL CONCORDANCE OF TCR REPERTOIRE IN BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER

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Background: The tumor immune microenvironment (TIME) of lung cancer brain metastasis is largely unexplored. We performed immune profiling and sequencing analysis of paired resected primary tumors and brain metastases of non-small cell lung carcinoma (NSCLC). **Method:** TIME profiling of archival formalin-fixed and paraffin embedded specimens of paired primary tumors and brain metastasis from 39 patients with surgically resected NSCLCs was performed using a 770 immune gene expression panel (NanoString Technologies, Seattle, WA) and by T cell receptor beta repertoire (TCRß) sequencing (Adaptive Biotechnologies, Seattle, WA). Immunohistochemistry was performed for validation. Targeted sequencing was performed to catalog hot spot mutations in cancer genes (ThermoFisher Scientific, Waltham, MA). **Result:** Somatic hot spot mutations were mostly shared between both tumor sites (28/39 patients; 71%). We identified 161 differentially expressed genes, indicating inhibition of dendritic cell maturation, Th1, and leukocyte extravasation signaling pathways, in brain metastases compared to primary tumors ($p < 0.01$). The proinflammatory cell adhesion molecule vascular cell adhesion protein 1 was significantly suppressed in brain metastases compared to primary tumors. Brain metastases exhibited lower T cell and elevated macrophage infiltration compared with primary tumors ($p < 0.001$). T cell clones were expanded in 64% of brain metastases compared with their corresponding primary tumors. Further, while TCR repertoires were largely shared between paired brain metastases and primary tumors, T cell densities were sparse in the metastases. **Conclusion:** We present findings that the TIME in brain metastases is immunosuppressed when compared to matched primary tumors in NSCLC patients, and that thus may help guide immunotherapeutic strategies for NSCLC brain metastases.

Keywords: immune microenvironment, brain metastasis, Non-Small Cell Lung Cancer

P1.04-08 RANDOMIZED CONTROLLED PHASE III TRIAL OF ADJUVANT CHEMOIMMUNOTHERAPY TO LUNG CANCER PATIENTS: RESULTS OF MALIGNANT EFFUSIONS

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Background: Elucidation of cancer immunoediting from immune surveillance to immune escape and approval of immune check point inhibitors by FDA prompted immunotherapy became a forth modality next to surgery, chemotherapy and radiotherapy. We have recruited advanced lung cancer patients with poor prognosis who had undergone surgery to improve prognosis by immunotherapy. **Method:** Objective and methods: Post-surgical lung cancer patients were randomly designated to receive either chemoimmunotherapy (4 courses of chemotherapy with 10-14 courses of cellular immunotherapy: group A) or chemotherapy (4 courses of chemotherapy: group B). Immunotherapy comprised adoptive intravenous transfer of autologous activated killer T cells and dendritic cells (AKT-DC) obtained from the regional lymph nodes of lung cancer patients. The study inclusion criteria were: <76 years; PS 0 or 1; non-small cell lung cancer; pathological stage, IB-IV. Patients whose surgery was palliative or in whom macroscopic residual tumors remained after surgery were excluded but those with microscopic residual tumors detected after a cytopathological examination were included in the study. Patients with pleural dissemination were excluded but those with malignant pleural effusion were included and received intra-thoracic chemotherapy with 20mg CDDP 4 times (group B) or chemotherapy with 4 to 8 courses of AKT-DC immunotherapy (group A) through a subcutaneous port with intrathoracic catheter installed in the thoracic cavity after resection of the primary tumors. A patient who had a recurrence of malignant ascites in group A received peritoneal infusion of AKT-DC after cell-free concentrated ascites reinfusion therapy (CART). **Result:** A hundred-and three patients were selected for randomization. The 2-, 5-, and 7-year overall survival rates were 96.0% 69.4%, and 55.1 in group A (n=51) and 64.7%, 45.1%, and 38.1% in group B (n=52), respectively. The Hazard ratio was 0.439 in favor of group A by multivariate analysis. There were 11 group A and 9 group B patients with malignant pleural effusion. One patient in group A and 6 patients in group B had recurrence and 3 died within 2 years in group B. The difference was also significant in favor of group A. A patient with malignant ascites(received 5 times AKT-DC therapy with 7 courses of CART in 2 months. Complete elimination of tumor cells accompanied with ascites eradication resulted in 9 months prolongation of survival after recurrence. **Conclusion:** Patients with lung cancer benefited from adoptive cellular immunotherapy as an adjuvant to surgery. Intrathoracic and peritoneal cellular immunotherapy with AKT-DC are effective to patients with malignant effusions.

Keywords: adoptive immunotherapy, malignant effusion, randomized controlled phase III study

P1.04-09 PREDICTIVE CLINICAL AND MOLECULAR FEATURES OF LONG-TERM SURVIVORS RECEIVING IMMUNE CHECKPOINT INHIBITORS FOR STAGE 4 NON-SMALL CELL LUNG CANCER

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Background: We hypothesized that clinical features could predict for durable response in patients treated immune checkpoint inhibitors (ICI). We performed an exploratory retrospective analysis with the primary endpoint of determining features associated with long-term survival. **Method:** We identified 212 consecutive patients with stage 4 NSCLC who received PD-1-ICI on clinical trials between 2011-2015. Overall survival (OS) was estimated by Kaplan–Meier; multivariate analyses were performed using Cox regression. **Result:** Baseline Characteristics: median age 67, 52% male, 69% non-squamous, median 31 pack-years-smoking, 63% chemotherapy-naïve, 31% *KRAS*-mutant, 11% *PIK3CA*-mutant. At a 57-month minimum follow-up, median OS was 12.2 mo (95%CI 10.2-14.2). Attaining PR/CR was associated with long-term survival (HR 0.21, $p < 0.001$). Long-term (>4-yr) survivors were more likely non-squamous histology, *PIK3CA*-wild-type, and low baseline neutrophil-to-lymphocyte proportion (Figure_1). Patients who received dual PD-1/CTLA-4-ICI (39%) had improvements in ORR (43% vs. 23%), time-to-progression (TTP, $p = 0.001$) and OS (HR 0.63, $p = 0.006$) versus PD-1 alone.

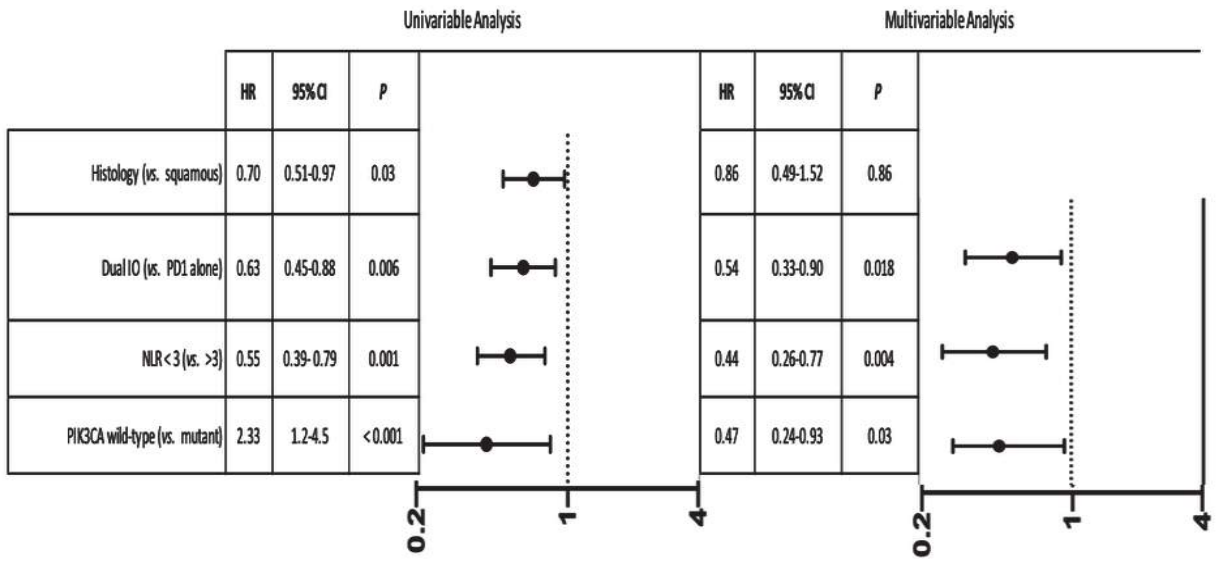

Figure 2. Treatment and outcomes of >4-year survivors (N = 38).

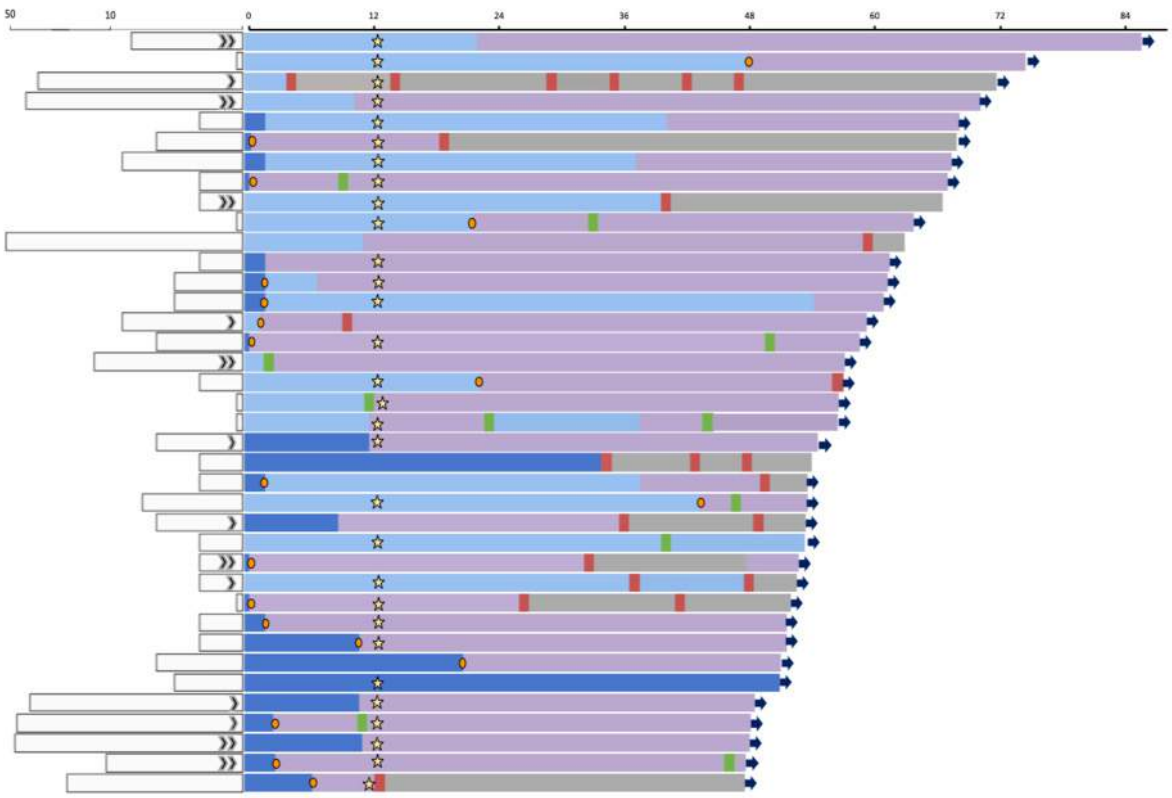

Figure Legend: OS, overall survival; CR, complete response; PR, partial response; NED, no evidence of disease; Dual ICI, anti-PD-1/CTLA-4 agents; TTD, time to treatment discontinuation

Conclusion: Objective responses to ICI with subsequent oligoprogression may be effectively salvaged with local ablative therapy in select cases. Prospective validation of surrogate biomarkers of immune response remain of paramount importance. Furthermore, durable responses exceeding 5 years may be attained despite early cessation of ICI. The role and clinical significance of *PIK3CA* mutations and ICI-resistance requires further investigation.

Keywords: Checkpoint inhibitors, Non-Small Cell Lung Cancer, Immunotherapy

P1.04-10 IDENTIFICATION OF IMMUNOTHERAPY TARGETS IN STK11 MUTANT NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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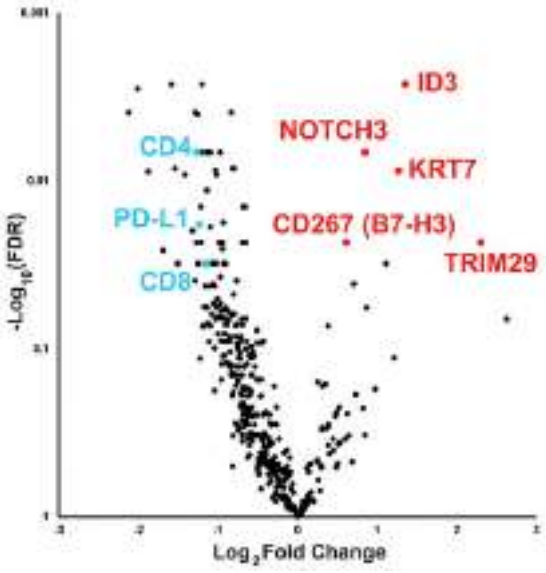
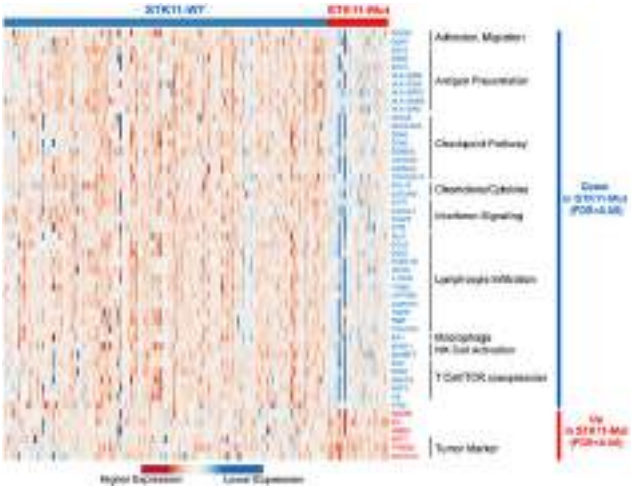
Background: The use of PD-1/PD-L1 checkpoint inhibitors (CPI) has dramatically altered the treatment of advanced Non-Small Cell Lung Cancer (NSCLC). However, a large proportion of patients with NSCLC do not derive clinical benefit from CPI treatment. Recent studies have identified STK11 mutations leading to loss of LKB1 in non-squamous NSCLC as drivers of primary resistance to CPI treatment. Using a clinical cohort of patients whose tumors underwent comprehensive genomic and immune transcriptomic analysis, we characterized the immune gene expression profile of STK11 mutant non-squamous NSCLC tumors and identified potential novel immunotherapy targets in STK11 mutant non-squamous NSCLC. **Method:** We performed comprehensive analysis of the genomic and immunological landscape of 204 formalin-fixed, paraffin-embedded tumor samples (obtained prior to CPI treatment) from advanced stage non-squamous NSCLC patients treated at Roswell Park Comprehensive Cancer Center using a CLIA-certified laboratory test that included targeted NGS genomic sequencing, gene fusion analysi,s and RNA-seq of 394 immune transcripts. Differential gene expression analysis was performed using R/Bioconductor package limma with Benjamini-Hochberg adjusted p-values reported . This study was approved by Roswell Park internal review board review (protocol BDR 091817) according to institutional policy for nonhuman subjects research. **Result:** Among the cohort of 204 cases, 30 contained truncating STK11 mutations. STK11 mutant cases showed an immunosuppressive environment with decreased PD-L1 mRNA expression (p=0.01) and decreased T-cell inflammation gene expression signature (p=0.0029). Analysis of differentially expressed immune genes signatures showed significant decreases in antigen presentation (p=0.015) and processing (p=0.044), NK cell activation (p=0.039), chemokine and cytokine signaling (p=0.044), immune checkpoint pathways (p=0.015), and Interferon gamma signaling (p=0.039). The top upregulated gene was TRIM29 (p=0.024). Other overexpressed targets included CD276 (p=0.024) also known as B7-H3, ID3 (p=0.002), KRT7 (p=0.008), and NOTCH3 (p=0.006). Interrogation of the TCGA LUAD dataset also demonstrated elevated TRIM29 expression (p=0.006) in KRAS/STK11-mutant (KL) compared to KRAS/STK11-wild-type samples. We also confirmed elevated TRIM29 expression in a panel of KL human cell lines. TRIM29 is an E3 ubiquitin ligase known to play a role in innate immune responses to DNA viral infections through targeting STING for degradation. Given recent studies implicating decreased STING expression in STK11 mutant cell line panels, TRIM29 represents a potential novel therapeutic candidate in this cohort of patients resistant to CPI treatment.





Conclusion: Using a large clinical cohort of non-squamous NSCLC patients we characterized the immunsuppressive environment of STK11 mutant tumors and identified the E3 ubiquitin ligase TRIM29 as a potential therapeutic target.

Keywords: immune microenvironment, stk11, Checkpoint Inhibitor Resistance

P1.04-11 DEPICTING THE INTRA-TUMORAL VIRAL AND MICROBIAL LANDSCAPE OF LOCALIZED NSCLC USING STANDARD NEXT GENERATION SEQUENCING DATA

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Background: Studies from our group and others have shown that bacteria and viruses present in the tumor may impact therapeutic responses. In the specific context of non-small cell lung cancer (NSCLC), intra-tumoral viral DNA and bacteria have been reported previously to be linked to therapeutic outcomes. However, the interplay between intra-tumoral microorganisms and the host immune response in NSCLC remains unknown. Moreover, the prognostic and predictive therapeutic value of localized NSCLC-specific microbial composition has yet to be defined. **Method:** RNA-sequencing (RNA-seq) (n=82) and whole exome sequencing

(WES) (n=80) was performed on surgically resected (pTNM I-III) tumors from lung cancer patients enrolled in the ImmunogenomiC prOfiling of NSCLC (ICON) project. Intra-tumoral bacteria, viruses and fungi were queried with MetaPhlAn2, a bioinformatical analysis pipeline which employs unique clade-specific marker genes, using reads from RNA-seq and WES that did not map to the human genome/transcriptome. Generated data were correlated to patients' clinicopathologic parameters as well as immune profiling using previously validated multiplex IHC panels based on Vectra 3.0™ multispectral microscopy IHC panels and image analysis (InForm™ 2.2.1 software). **Result:** Our analyses revealed that 18.29% (n=15/82) of tumors contained bacterial signatures. The most frequent bacterial signature was related to *Escherichia* (n=9/15). Moreover, 6.49% (n= 5/77) of tumors had evidence of human viral signatures, including the Epstein-Barr virus (n=1/5). No tumors contained fungal signatures. Preliminary clinicopathologic analyses suggested that patients whose tumors harbor bacterial signatures had a trend towards decreased overall survival (p=0.12). Tumors from former smokers were also more likely to contain bacterial signatures (p=0.11). Preliminary multiplex immune cell IHC analyses did not highlight statistically significant associations with the presence of intra-tumoral bacteria. **Conclusion:** Our results suggest that a significant proportion of localized NSCLC tumors may harbor components of the human microbiome. Further studies using larger cohorts and dedicated intra-tumoral microbiome and virome methodologies will be needed to better define these findings and to delineate associations with the local immune infiltrate.

Keywords: Microbiome, Virome, early-stage NSCLC

P1.04-12 TUMOR UPTAKE AND BIODISTRIBUTION OF 89ZR-LABELED PEMBROLIZUMAB IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

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Background: Pembrolizumab, a monoclonal antibody targeting PD-1, is approved as monotherapy for the treatment of advanced NSCLC, depending on tumor PD-L1 (T-PD-L1) expression level. However, T-PD-L1 expression correlates moderately with response to pembrolizumab treatment. Therefore, there is need for biomarkers that accurately discriminate between responders and non-responders. Whole body ^{89}Zr-pembrolizumab PET/CT allows to quantify pembrolizumab uptake in tumor lesions and to study pembrolizumab biodistribution in non-malignant tissues. **Method:** Patients with advanced stage NSCLC and eligible for pembrolizumab monotherapy were enrolled. Following tracer injection (standard dose: 2mg ^{89}Zr-pembrolizumab, 37 MBq), the first 3 patients received whole body PET/CT-scans at 1h, 72h, 120h and 168h post-injection. Subsequent 10 patients were scanned at 72h and 144h post-injection. Biodistribution and tumor uptake were assessed visually by an experienced nuclear physician. Quantitative uptake was calculated as SUV_{peak} for delineable lesions and correlated to T-PD-L1/PD-1 IHC and response. A tumor biopsy after the last line of prior treatment was required to assess T-PD-L1/PD-1 IHC status (22C3 assay). Response was defined as partial or complete, after 6 months, according to RECIST criteria. **Result:** Thirteen patients (5 ≥50%, 4 1-49%, 4 negative by PD-L1 IHC) were enrolled (6 first line, 7 second/third line treatment). One patient experienced grade 3 myalgia after tracer injection. ^{89}Zr-pembrolizumab biodistribution was comparable to ^{89}Zr-nivolumab biodistribution with relatively high uptake in the spleen, likely due to binding to PD-1 receptors on lymphocytes/dendritic cells, and in the liver likely due to catabolism of the tracer. Imaging revealed tumor uptake in all patients, but not in all lesions. Visual assessment confirmed 70 lesions (including non-malignant lymph nodes) at 72h post-injection (SUV_{peak} range 1.7-13.0). Not all tumor lesions showed tracer uptake and uptake was heterogeneous within and between patients. In 3 patients response was observed. Pretreatment T-PD-L1≥50% was predictive for response (p=0.023). SUV_{peak} was higher in responding patients than in non-responding patients (median $SUV_{peak\ of\ all\ visible\ lesions}$ 8.0 vs 5.5, p=0.033). In line with these results, responding lesions (n=10) had a higher SUV_{peak} compared to non-responding lesions (n=24, median 8.1 vs 5.5, p=0.025). Tumor tracer uptake did not correlate with PD-1 expression (low PD-1 expression SUV_{peak} 6.0 vs high PD-1 expression SUV_{peak} 7.7, p=0.3). **Conclusion:** ^{89}Zr-pembrolizumab injection was safe with only one grade 3 possibly related adverse event. Tumor ^{89}Zr-pembrolizumab uptake correlated with response to pembrolizumab treatment. Further research is needed to study the value of this biomarker as standalone biomarker or as added information to T-PD-L1 expression by immunohistochemistry.

Keywords: advanced NSCLC, 89Zr-pembrolizumab, Immuno-PET

P1.04-13 DELINEATING SPATIAL HETEROGENEITY OF TUMOR MUTATIONAL BURDEN (TMB) COUNTS IN PULMONARY ADENOCARCINOMA

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Background: Tumor mutational burden (TMB) is an emerging biomarker to identify patients more likely to benefit from immuno-oncologic therapy. Therefore, academia- and industry-driven endeavors are underway to establish mostly panel-based sequencing solutions. Aside from various unsettled technical aspects, tumor biology itself might play an important role in determining a tumor's TMB. Intratumor heterogeneity (ITH) is frequent in pulmonary adenocarcinoma (ADC) and seems to be a key factor regarding response failure and resistance development during therapy. In addition, ITH might contribute to inconsistent distribution of a biomarker and therefore an assay's readout might depend on the region of tumor which is submitted for testing. Therefore, the assessment of ITH is an essential step in the evaluation of new diagnostic applications. **Method:** All ADC specimens used for this study were obtained from surgical procedures at the Thoraxklinik at Heidelberg University and diagnosed according to the criteria of the 2015 WHO Classification of lung tumors at the Institute of Pathology at Heidelberg University. Formalin-Fixed Paraffin-Embedded tissue sections were supplied by the tissue bank of the National Center for Tumor Diseases. To evaluate the significance of ITH on TMB estimation, 2-4 intratumoral regions (total 69) and up to 2 locoregional lymph node metastases (total 23) derived from 24 patients were analyzed. Following DNA extraction, all samples were sequenced using the 1.7 Mbp sized TruSightTM Oncology 500 panel, on a NextSeq 500 sequencing system (both Illumina Inc., San Diego, CA, USA). Procession of sequencing data and mutation calling was carried out using the TruSightTM Oncology 500 Local App (pipeline version 1.3.0.39). **Result:** TMB counts of the multiregional tumor samples and locoregional lymph node metastases ranged from 0 - 52.55 mut/Mbp and had a median value of 7.04 mut/Mbp. TMB status of tumor segments, lymph node metastasis or a case specific aggregate TMB were determined applying a cut-point of 10 mut/Mbp. 71% of the analyzed tumors had consistent TMB values when considering all associated estimates. Three cases were TMB-high except for at least one lymph node metastasis. Another three cases had inconsistent TMB approximations between different tumor regions. In one case only the aggregate TMB value would justify a TMB-high classification, whereas the individual analysis of each tumor segment resulted a TMB-low status. In a paired analysis of the average TMB values lymph nodes hada significantly (p = 0.016) lower TMB values compared to corresponding tumor segments. **Conclusion:** Our data demonstrate that panel-based TMB estimation applying the TSO500™ panel correlates strongly and significantly with WES-based TMB determination. The multiregional analysis showed that TMB measurement can be subject to intratumor heterogeneity in pulmonary ADC, which can impact clinical decision making and therapy. However, spatial genetic heterogeneity reflecting tumor biology needs to be carefully dissected from technical conditions resulting in pseudo-heterogeneity, especially a valid tumor cell content estimation and the correct identification of polymorphisms / germ line mutation seem to be crucial points in this consideration. Further, lymph node metastases had significantly lower TMB values compared to corresponding tumor tissue, questioning the applicability of these samples for TMB estimation in a clinical setting.

Keywords: Intra tumor heterogeneity, lung adenocarcinoma, tumor mutational burden (TMB)

P1.04-14 EARLY CHANGES IN PLASMA CXCL2 AND MMP2 LEVELS PREDICTS THE RESPONSE TO ANTI-PD-1 THERAPY IN NON-SMALL-CELL LUNG CANCER

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Background: Previously we reported that changes in the plasma levels of CXCL2 and MMP2, measured by a bead-based multiplex assay: Bio-Plex 200 system, were significantly associated with the clinical outcomes of anti-PD-1 therapy (Matsuo, et al. *IJC*. 2018). Here we attempted to validate CXCL2 and MMP2, measured by ELISA, as a marker of the effectiveness of anti-PD-1 therapy in expanded patient cohort. **Method:** Peripheral blood samples were taken from 97 patients with non-small cell lung cancer before nivolumab or pembrolizumab treatment and after 4-10 weeks from the patients who continued these drugs. The levels of CXCL2 and MMP2 were examined before and after anti-PD-1 therapy. We employed Cox regression analysis for CXCL2 and MMP2 as a single explanatory carriable. In comparing the fitness of CXCL2 and MMP2 Cox models, discrimination was assessed by the Harrell's C-statistic for survival data. Bootstrap methods with 10000 resamplings were used to assess the stability of the regression analysis predictors. The optimal cutoff point was determined as the point at which the Youden index was maximized by ROC curve. Survival curves were generated using the Kaplan–Meier method and comparisons made using the log-rank test. **Result:** The changes in the plasma levels of CXCL2 after treatment were significantly correlated with PFS (HR 1.003, 95%CI: 1-1.005, *P*=0.026) and OS (HR 1.004, 95%CI: 1.001-1.007, *P*=0.003). The C-statistic of the CXCL2 model for PFS and OS were 0.652 (95% CI: 0.437-0.727) and 0.626 (95% CI: 0.528-0.722), respectively. The decreasing revels of CXCL2 tended to be related to better DCR (*P*=0.134). The changes in the plasma levels of CXCL2 < 29.1 pg/ml was associated with better PFS (HR 2.872, 95%CI: 1.785-4.618, *P*<0.001) and OS (HR 2.800, 95%CI: 1.633-4.801, *P*<0.001). The changes in the plasma levels of MMP2 after treatment were also significantly correlated with PFS (HR 0.998, 95%CI: 0.996-0.999, *P*=0.003) and OS (HR 0.998, 95%CI: 0.996-0.999, *P*=0.001). The C-statistic of the MMP2 model for PFS and OS were 0.599 (95% CI: 0.515-0.673) and 0.614 (95% CI: 0.523-0.703). The increasing revels of MMP2 was significantly related to better DCR (*P*=0.020). The changes in the plasma levels of MMP2 > 0.847 ng/ml was associated with better PFS (HR 0.614, 95%CI: 0.388-0.971, *P*=0.037) and OS (HR 0.501, 95%CI: 0.295-0.852, *P*=0.011). **Conclusion:** The early change of CXCL2 and MMP2 were significantly associated with the clinical outcomes of anti-PD-1 therapy. Since these factors in plasma can be easily measured by minimally invasive method, they could be clinically applicable as biomarkers for predicting the clinical benefit of anti-PD-1 therapy for NSCLC patients.

Keywords: CXCL2, MMP2, pd-1

P1.04-15 SMOKING STATUS IS NOT A REPLACEMENT BIOMARKER FOR TUMOR MUTATION BURDEN IN NON-SMALL LUNG CANCER

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Background: Recent clinical studies suggest tumor mutation burden (TMB) as a promising therapeutic biomarker of anti-tumor immune checkpoint blockade (ICB). Given the causal link between cancer-causing mutations and tobacco smoking, patients with a significant smoking history may respond better to ICB. However, it is not clear if smoking history is an adequate surrogate biomarker for TMB. Here, we sought assess the clinical utility of smoking history in predicting tumor mutation burden. **Method:** Publicly available smoking history and DNA somatic alteration data from NSCLC were downloaded from The Cancer Genome Atlas and a large dataset of lung adenocarcinoma tumors published by Imielinski, et al (*Cell*, 2012) Tumor mutation burden was calculated as the sum of all somatic mutations divided by the exome sequencing coverage. Smoking history was analyzed both as categorical (ever, never, former) and semi-continous variables (pack years). Hypermutancy was defined as greater than or equal to 10 mutations per megabase. **Result:** A total of 395 LUAD and 419 LUSC patients were included in this analysis. Smokers had significantly higher tumor mutation burdens than non-smokers; however, in both LUAD and LUSC, there were smokers with low TMB and non-smokers with high TMB. Smoking pack year history (SPY) was weakly positively correlated (Spearman $\rho = 0.20$, $p = 2.5 \times 10^{-4}$) in LUAD but uncorrelated (Spearman $\rho = -0.026$, $p = 0.61$) in LUSC. Non-smokers and patients without a recorded SPY were excluded from the SPY analysis. We calculated AUCs for predicting hypermutancy in tumors, using variable thresholds of SPY. In LUAD and LUSC, SPY had an AUC of 0.38 and 0.47 in predicting TMB, showing that SPY was not better than random prediction. We also sought to predict TMB from smoking as a binary variable. In LUSC, 8/18 (44%) non-smokers and 253/447 (57%) smokers were hypermutant. In LUAD, 9/61 (15%) non-smokers and 219/391 (56%) smokers were hypermutant. Additionally, we repeated this analysis on matched smoking history and TMB from an independent cohort of 162 LUAD tumors published by Imielinski, et al. Similarly, we found that 1/27 (4%) of nonsmokers and 66/135 (49%) of smokers were hypermutant. In this cohort, the AUC in predicting TMB with SPY was 0·21. **Conclusion:** In this study, we investigated the relationship between tobacco smoking and TMB. While the average lung cancer patient with a history of tobacco smoking has a higher TMB than the average never-smoker, there is not a clear relationship between the extent of exposure in pack years and TMB. In general, smoking is not an informative biomarker for TMB, however, non-smokers who develop LUAD are unlikely to have high TMB. This study highlights the value of next generation sequencing for TMB in predicting therapeutic response to ICB.

Keywords: Tumor Mutation Burden, Non-Small Cell Lung Cancer, Immunotherapy

P1.04-16 EARLY ANTIBIOTIC USE AFFECTS THE EFFICACY OF FIRST LINE IMMUNOTHERAPY IN LUNG CANCER PATIENTS BUT ROUTE OF ADMINISTRATION SEEMS TO BE DECISIVE

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Background: Several studies found that cancer patients treated with PD-1 immune checkpoint inhibitors (CKIs) who receive antibiotics (ATX) had worse efficacy outcomes because ATX can dysregulate gut microbiota. There are some data in pretreated non-small-cell lung cancer (NSCLC) and few data about the route of ATX administration, but it`s unkown whether ATX administration can also affect efficacy of CKIs in first line setting in patients treated with pembrolizumab monotherapy. **Method:** This is a multicenter retrospective study. We included consecutive patients with advanced NSCLC with high PD-L1 expression (50%) treated with pembrolizumab monotherapy in first line, between September 2016 and March 2019, from 12 hospitals in Spain. The aim of the study was to evaluate if patients taking ATX 2 months before or within the first month after starting CKIs had worse OS, and if OS was affected by the route of administration and type of prescribed ATX. **Result:** 121 patients were evaluated. Median age was 68 years (38-88). 90 (74,4%) were male and 90 (74,4%) had PS1. Predominant histologies were adenocarcinoma (68,6%) and squamous-cell carcinoma (23,1%). Median number of cycles was 7 (1-33). Median follow-up: 6,5 months. Most were current or former smokers (95,9%). Only 1 patient had driver mutation (ALK rearrangement). 66,9% had 2 or more metastatic locations, 18,2% had central nervous system (CNS) disease, 17,4% liver metastasis, and 41,3% bone metastasis. 45,5% received ATX,

65,5% of them intravenously and 34,5% orally. Most prescribed ABX were quinolones (40,7%) and penicillin or derivatives (35,2%). 21,5% received subsequent chemotherapy. Response rate was 40,4% according to RECISTv1.1 criteria. 11% had hyperprogression and 7,2% pseudoprogression. Estimated 12-month-OS was 62% (95%CI: 49.1%-72.5%) and estimated 12-month-PFS was 44.2% (95%CI: 31.1%-56.5%) Patients who received ABX had more risk of disease progression as best response (52,2% vs 24,5%,RR: 2.1, 95%CI: 1.2-3.7, p=0.007). Patients who received ATX had shorter OS (HR:1.9, 95%CI: 1.1-3.7, p=0.047) and shorter PFS (HR:2.6, 95%CI: 1.4-4.8, p=0.002). Patients who received ATX intravenously had shorter OS than those not treated (HR:2.8, 95%CI: 1.4-5.6) and than those who received ABX orally (HR:3.5, 95%CI: 1.2-10.3, p=.025)). Patients treated with ABX also had shorter PFS than those not treated (HR: 3.5, 95%CI:1.8-6.8, p<0.001) and than those who received ABX orally (HR: 2.2, 95%CI:1-4.8, p=0.05). Similar HR were estimated adjusting by age, gender, stage, and hepatic and bone metastasis presence. There were no OS and PFS differences between patients who received ABX orally and those who did not received them. There were no survival differences according to type of ABX. **Conclusion:** Our results suggest that use of intravenous ABX has a negative impact on disease control rate and survival outcomes (PFS and OS) in patients with naïve advanced NSCLC and high PD-L1 expression treated with pembrolizumab monotherapy in first line setting. Patients who received oral ABX had similar efficacy than those not treated with ABX. To our knowledge, this is the first retrospective study evaluating the impact of ATX on the efficacy of CKIs in first-line treatment setting of NSCLC patients.

Keyword: antibiotics, NSCLC, pembrolizumab, immunotherapy, first line

P1.04-17 PHASE I/II STUDY OF NIVOLUMAB AND VOROLANIB IN PATIENTS WITH REFRACTORY THORACIC TUMORS

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Background: Single-agent nivolumab has limited efficacy in thoracic tumors. The antitumor activity of VEGF TKIs is typically attributed to their effect on angiogenesis; however, emerging data suggest these agents can modulate the immune system, especially in the immune suppressive microenvironment. Preliminary results in multiple solid tumors demonstrated clinical benefit when nivolumab was added to anti-angiogenic agents albeit with increased toxicities. Vorolanib was designed to improve the safety profile without compromising efficacy. No dose-limiting toxicities (DLTs) from vorolanib were reported in multiple single-agent phase I trials. **Method:** NCT03583086 is an ongoing multi-institutional, phase I/II study of nivolumab and vorolanib in patients with thoracic tumors who have failed at least one prior line of therapy. A standard 3+3 dose escalation design was planned with three doses of vorolanib (200, 300, and 400 mg once-daily) and 240 mg nivolumab every two weeks to determine the maximum tolerated dose. Phase II will evaluate the response rate in five cohorts: PD-1/PD-L1 naïve non-small cell lung cancer (NSCLC), PD-1/PD-L1 primary refractory (defined as progression on PD-1/PD-L1 therapy within 12 weeks), NSCLC patients with acquired resistance (achieved at least stable disease and then progressed) to PD-1/PD-L1, thymic carcinoma, and small cell lung cancer patients who have progressed on prior platinum-based chemotherapy. Exploratory correlatives will assess changes in the innate and adaptive immune responses after treatment. **Result:** Phase I enrolled 10 patients (eight NSCLC and two thymic cancers); one patient was not evaluable for DLT and replaced. No DLTs were observed in three patients at the first dose level of 200 mg. Vorolanib was escalated to 300 mg, and elevated ALT (Grade 3) occurred in two of six patients just beyond the DLT period but deemed clinically significant; thus, 200 mg vorolanib with 240 mg nivolumab is being evaluated in expansion cohorts. The most common adverse events were elevated ALT, AST, and lipase, diarrhea, and fatigue; most were Grade 1/2. Grade 4 hyperglycemia and elevated lipase and Grade 3 elevated serum amylase occurred in one patient each. In seven efficacy-evaluable patients (2 immunotherapy naïve NSCLC; 3 NSCLC with prior immunotherapy; 2 thymic cancer), two partial responses were observed (1 PD-1/PD-L1 naive NSCLC and 1 thymic cancer patient); the NSCLC patient was also PD-L1 negative. Three NSCLC patients with prior PD-1/PD-L1 inhibitors had tumor regression; two of these had acquired resistance and the other was primary refractory to prior immunotherapy. **Conclusion:** The combination of 200 mg vorolanib and 240 mg nivolumab was generally well tolerated. Clinical activity was observed in both PD-1/PD-L1 naïve patients and those treated with prior immunotherapy. Final phase I results and available phase II data will be presented.

Keywords: immunotherapy combination, VEGFR inhibition

P1.04-18 INTERLEUKIN-5 DRIVES THE EXPANSION OF PULMONARY B-1 B CELLS AND RESTRICTS LUNG TUMOR GROWTH

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Background: Therapies that target immune cells to treat lung cancer are becoming commonplace, highlighting the critical role of the immune system in the lung microenvironment. The lungs are host to a variety of immune populations, including B cells, whose primary function is to secrete antibodies that target foreign pathogens. Despite the presence of B cells in solid tumors and their prevalence in the lung, the role of B cells in lung cancer is largely undefined. We have found that transgenic mice which over-express the protein IL-5 (IL5Tg mice) have both an expansion of lung B cells and a decrease in lung tumor burden. IL-5 has previously been shown to induce the proliferation, recruitment, and antibody production of certain B cell subsets. Therefore, we hypothesize that IL-5-responsive B cells may decrease lung tumor growth. **Method:** We used IL5Tg transgenic mice that over-express IL-5 to study the impact of B cells on tumor growth in the lungs. Lewis lung carcinoma (LLC) cells were injected intravenously (IV) to seed the lungs. Circulating serum antibodies were quantified by ELISA. Flow cytometry was used to quantify immune cell subsets in the lungs, as well as antibody binding to tumor cells and tumor cell cytotoxicity. Histological analysis was used to measure tumor burden. **Result:** We found that the increase in lung B cells in IL5Tg mice was due to an increase in B-1 B cells which co-expressed the antibody class immunoglobulin M (IgM). Importantly, IL5Tg mice had a decrease in lung tumor burden compared to WT mice, as well as an increase in the total number of lung-infiltrating B cells compared to naive mice. Circulating IgM was elevated in IL5Tg mice compared to WT, and we found that these IgM antibodies were able to bind to LLC cells. Binding of IgM antibodies to the surface of target cells has previously been shown to induce cell death via the complement pathway, and preliminary data suggests that serum antibodies from IL5Tg mice can induce tumor cell cytotoxicity. **Conclusion:** We have found that excess IL-5 drives the expansion of lung B-1 B cells and decreases lung tumor burden, suggesting that IL-5 may promote anti-tumorigenic immune cell activities in the lungs. Illuminating the specific role of B cells in lung cancer growth will help deconvolute the complex interplay between host immune cells and malignant cells and could reveal new avenues for immunotherapy development.

Keywords: B cells, Antibody, Interleukin-5

P1.04-19 ASSOCIATION BETWEEN EFFICACY AND IRAES IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER RECEIVING IMMUNE-CHECKPOINT INHIBITORS

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Background: Immune-checkpoint inhibitors (ICIs) are a standard treatment in advanced non-small cell lung cancer (NSCLC). They can induce immune-related adverse events (irAEs) that may compromise treatment continuation. We report our experience in advanced NSCLC patients receiving ICIs, the incidence of irAEs and its correlation with efficacy. **Method:** 267 patients with advanced

NSCLC receiving ICIs in two Spanish institutions from March 2013 to August 2018 were analyzed. IrAEs were graded following CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survival (OS) using landmark analysis. **Result:** Median age was 66.1 years [26-85], 70% were male. 86 (32%) patients presented squamous and 181 (68%) non-squamous histology. Most frequent ICIs were nivolumab (44%), pembrolizumab (26%) and atezolizumab (17%), used as monotherapy (78%), in combination with chemotherapy (12%) or with anti-CTLA4 (9%). 30% patients were treated with ICIs in first line and 70% in second line or beyond. Median duration of treatment was 2.8 months [0.1-56.4]. 152 patients (57%) experienced a total of 255 irAEs, and the median number of irAEs/patient was 1 [0-5]. Most frequent irAEs was skin toxicity (34%), followed by diarrhea (16%) and hypothyroidism (11%). 36 patients (14%) presented grade 3-4 irAEs and there were 5 treatment-related deaths: 4 pneumonitis and 1 hepatitis. Patients receiving ICIs in second line or beyond experienced significantly less irAEs (49%) than those treated in first line (74%) (p <0.001). With a median follow-up time of 8.5 months [0.3-56.4], the landmark analysis showed that PFS was significantly longer in patients with irAEs: 12.4 months (95%CI, 1.9-22.9) vs 4.1 months (95%CI, 2.6-5.6) (p < 0.001). Similarly, OS among patients with irAEs was significantly higher: 28.2 months (95%CI, not calculated) vs 12.5 months (95%CI, 10.8-14.2) (p < 0.001). Disease control rate was significantly better in patients with irAEs: 77% vs 39%, odds ratio 0.20 (95%CI, 0.11-0.34) (p < 0.001). Besides, duration of response was significantly longer: 6.1 months [0.5-50] vs 2.6 months [0.2-51.9] (p < 0.001). 44 patients (17%) discontinued treatment due to toxicity. Within this group, 66% patients did not progress after immunotherapy, in contrast to 29% in the rest of the population (p < 0.001). Multivariable analysis revealed that cutaneous, endocrinological and reumathological toxicities were significantly associated with increased OS. **Conclusion:** The presence of irAEs in advanced NSCLC patients treated with ICIs was associated with better outcomes. Patients who discontinued ICIs due to toxicity showed a higher disease control rate.

Keywords: Outcomes, Immune-checkpoint inhibitors, irAEs

P1.04-20 PD-L1 MRNA DERIVED FROM TUMOR-EDUCATED PLATELETS PREDICTS THE CLINICAL OUTCOME OF IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy was promising treatment of advanced non-small cell lung cancer (NSCLC), but only a small part of patients could benefit from the immune checkpoint inhibitors (ICIs). Development of novel biomarkers was of great importance to improve the selection of patients and to avoid unnecessary toxicity. **Method:** We collected data from advanced NSCLC patients who received immunotherapy alone or in combination with chemotherapy as first- or second-line treatment at a single institution. All the patients were wild type of EGFR/ALK and enrolled into clinical trials on ICIs, including nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab and camrelizumab. PD-L1 messenger RNA (mRNA) was detected from tumor-educated platelets before ICIs treatment. Meanwhile, tumoral PD-L1 expression was also determined by immunohistochemistry in archived tissue samples to explore its predictive value and association with TEPs- derived PD-L1 mRNA expression. **Result:** Of 76 patients enrolled into this study, 68 patients (89.5%) received only immunotherapy and 23 patients (30.3%) responded to the treatment, and the median PFS was 3.81 months. There was no correlation between tumoral PD-L1 expression and TEPs-derived mRNA of PD-L1 by Pearson Correlation test (P=0.32). Based on the median of PD-L1 mRNA, 19 patients (44.4%) responded to immunotherapy in high PD-L1 group compared to 5 patients (13.9%) in low PD-L1 group (P<0.01). The median PFS were 2.76 months in low PD-L1 group, compared to 8.28 months in high PD-L1 group (P<0.001), respectively. For the 64 patients who received only immunotherapy, the PFS advantage was persistent in high PD-L1 group (2.76 vs 8.02 months, p=0.002). The median OS was not reached in high PD-L1 group, while it was 13.47 months in low PD-L1 group (P<0.01). **Conclusion:** Tumor-educated platelets derived PD-L1 mRNA could be a surrogate biomarker predicting the PFS and OS of immunotherapy in patients with advanced non-small cell lung cancer.

Keywords: Immunotherapy, Biomarker, tumor-educated platelets

P1.04-21 CELLULAR LANDSCAPE OF NORMAL ADJACENT TO TUMOR MICROENVIRONMENT IN NON-SMALL CELL LUNG CANCER

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Background: Cellular heterogeneity is the dominant ingredient in tumor microenvironment, which plays essential roles in cancer malignancy. Growing evidence have shed light on the important role of tumor-infiltrating immune and stromal cells in cancer progression. **Method:** Here, we portrayed the cellular landscape of a total of 64 cell types in 313 normal lung tissues, 110 adjacent normal tissues and 992 non-small cell lung cancer (NSCLC) tissues using transcriptomic data by integrated bioinformatics analysis. **Result:** In general, adjacent normal tissues presented an intermediate state between normal and tumor tissues, which was that the fraction of immune cells decreased while fraction of stromal cells increased from normal, adjacent to tumor tissues. Moreover, huge difference of tumor-infiltrating cells were detected between lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Interestingly, in LUAD, rather than in LUSC, subtypes of CD4+ and CD8+ T cells were significant higher in tumor tissues compared with adjacent and normal tissues. Stromal cells, such as fibroblast and endothelial cells, also showed great diversity among the normal, adjacent and tumor tissues. Moreover, immune inhibitory receptors (PD1, CTLA4, LAG3 and TIM3) were more commonly co-expressed on certain subtypes of T cells in both LUAD and LUSC compared with adjacent normal tissues. Besides, significant clinical relevance between tumor-infiltrating cells and tumor stages were more prevalence in LUAD, compared with LUSC. Lastly, there were 45 cell types and 27 cell types were significantly correlated with patients overall survival in LUAD and LUSC, respectively. Surprisingly, certain subtypes of T cells were adverse prognosis factors for NSCLC. Taken together, we built powerful prognosis predictors for LUAD and LUSC patient using tumor-infiltrating cells. **Conclusion:** In summary, our analysis provided extensive details of cellular landscape in normal adjacent to tumor tissues in NSCLC and how they were involved in tumor progression. Better understanding of the complex crosstalk between tumor cells and infiltrating cells might provide novel therapeutic targets and biomarker for NSCLC, especially in the immune therapies.

Keywords: Lung cancer, Cellular heterogeneity, Immune

P1.04-22 POTENTIAL DNA REPAIR BIOMARKER FOR RESPONSE TO IMMUNOTHERAPY OF LUNG CANCER PATIENTS

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Background: Because only a fraction of cancer patients responds to immunotherapy, there is an urgent need for methods to predict responders, in addition to the current methods of PD-L1 expression, tumor mutation burden, and mismatch repair deficiency (MSI-H biomarker). With the goal of harnessing DNA repair to fight cancer, we have developed personalized DNA repair blood tests that measure enzymatic activity of OGG1 (8-oxoguanine DNA-glycosylase), MPG (methylpurine DNA-glycosylase) and APE1 (apurinic/apyrimidinic endonuclease-1), which repair primarily oxidative and methylation DNA damage. The three are then combined to yield a personalized DNA repair score (*Cancer Prevention Res.* 7, 398-406:2014; *J. Natl. Cancer Inst.* 104, 1765-1769:2012). The question we posed was whether there is any correlation between the DNA repair score and systemic effects on gene expression. **Method:** The study included 121 non-small cell lung cancer cases and 92 controls. The DNA repair score was determined in PBMC, and gene expression was measured using RNAseq in nasal epithelial cells from all subjects. Gene expression was also measured in bronchial cells from 37 patients. Analysis using DESeq2 software was performed separately on the different tissues (nasal/bronchial) and disease state (cases/controls), with experimental batch, age, gender, smoking status (never, former and current smokers) and cancer histology (in cases) as adjusting factors. Gene Set Enrichment Analysis (GSEA) was used in order to identify whether there is an over-representation of genes belonging

to specific pathways annotated by Gene Ontology. **Result:** With a False Discovery Rate threshold of 0.01, we could find very few genes whose expression correlated with the DNA repair score. However, using GSEA we found that the expression of 185 immune system-related pathways exhibited negative correlation with the DNA repair score, each with q-value<0.001. This correlation was observed in lung cancer patients, but not in control subjects. The dramatic enrichment in the immune response pathways was by far the most pronounced effect, and it was robust against sub-sampling, indicating that it is not a sampling bias. **Conclusion:** Low DNA repair score correlates with broad up-regulation of immune-response pathways in lung cancer patients, but not controls. Low DNA repair might cause more mutations, and increases neoantigens, contributing to the activation of the immune system, similar to tumors with a mismatch-repair deficiency. Since only about 1% of lung cancer cases exhibits a mismatch-repair deficiency, we suggest that a low DNA repair score might serve as a biomarker for response to immunotherapy of these patients, pending additional studies.

Keywords: DNA repair, Blood test, response to immunotherapy

P1.04-23 CHARACTERIZING THE TUMOR IMMUNE MICROENVIRONMENT OF NON-SMALL CELL LUNG CARCINOMA IN PEOPLE LIVING WITH HIV USING IMAGING MASS CYTOMETRY

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Background: Non-AIDS defining cancers (NADCs) have become a leading cause of cancer incidence and mortality in people living with HIV (PLWH). Lung cancer is the most common NADC in this population, with non-small cell lung cancer (NSCLC) as the most common histologic subtype. PLWH develop NSCLC at younger ages, present with later stage of disease, and have worse outcomes. Global immune dysfunction caused by HIV infection, independent of absolute CD4 count, is hypothesized to contribute to this phenomenon. Imaging Mass Cytometry (IMC) provides for multidimensional protein detection using metal-conjugated antibodies and mass spectrometry. Here, we use IMC to investigate the NSCLC tumor microenvironment of HIV+ and HIV- patients, identifying differences in immune function. **Method:** Paraffin-embedded tumor tissue from 18 HIV+ patients and 19 HIV- matched patients were obtained from the Pathology department of Yale-New Haven Hospital. Controls were matched on the basis of age, sex, histology, stage at presentation, and year of cancer diagnosis. An antibody panel consisting of 36 structural, phenotypic, and functional targets was used to characterize these tissues by IMC. Unsupervised clustering with PhenoGraph was used to identify major cell populations. Chi-square test and t-test were used to compare categorical and continuous variables, respectively. **Result:** Between HIV+ and HIV- patients, median age was 53 and 59 years, 61% and 58% presented at stages III/IV, and median overall survival was 8 and 89 months respectively (log rank; $P = 0.006$). Among HIV + patients, 78% were on antiretroviral therapy and 56% had an undetectable viral load at time of cancer diagnosis. No significant difference in overall CD3, CD4, CD8, CD20, or CD68 signal was detected between HIV+ vs HIV- cases. Similarly, no significant difference was seen in expression of inhibitory T-cell receptors (PD1, TIM3, LAG3) on CD4+ or CD8+ cells. CD68 cells from HIV+ cases demonstrated increased PD-L1 expression compared with CD68 cells from HIV- cases (P = 0.006). Three unique subpopulations of epithelial tumor cells were identified by PhenoGraph; these subsets differed in expression of PD-L1, MHC class I and II antigen presentation proteins (HLA-ABC, HLA-DR), and cellular proliferation markers (KI67). Distribution among these three tumor cell subsets varied significantly between HIV+ and HIV- cases (P =0.005). **Conclusion:** In this well-matched cohort of NSCLC, we investigated the tumor microenvironment using highly multiplexed imaging mass cytometry. Despite having similar stages at presentation as HIV- cases, overall survival was markedly decreased among HIV + cases. Though no significant difference in tumor infiltrating immune cells or lymphocyte T cell inhibitory receptor expression was seen, monocytes from HIV+ patients demonstrated increased PD-L1 expression. In addition, distinct subpopulations of tumor cells were identified, with tumors from PLWH having different proportional representation among these subsets. Further genomic and transcriptomic analysis of HIV-associated NSCLC tumors may provide further insight into the effect of HIV infection on tumor phenotype and prognosis.

Keywords: HIV, Tumor-associated immune cell, mass cytometry

P1.04-24 CIRCULATING SUPPRESSIVE IMMUNE CELLS PREDICT THE EFFICACY OF ANTI PD-1 IMMUNOTHERAPY IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The major suppressive immune cells in tumor sites are myeloid derived suppressor cell (MDSC), tumor associated macrophage (TAM), and regulatory T (Treg) cell, and the major roles of these suppressive immune cells include hindering T cell activities and supporting tumor progression and survival. In this study, we analyzed the pattern of various circulating suppressive immune cells in patients with non-small cell lung cancer (NSCLC) to see whether those suppressive immune cells hinder T cell activities leading to poor clinical outcomes. **Method:** Baseline blood samples were collected from stage I to IV NSCLC patients (n=59), and baseline and one week after the therapy paired blood samples from stage IIIB to IV NSCLC patients (n=83) undergoing anti PD-1 immunotherapy either pembrolizumab or nivolumab. The efficacies of peripheral blood suppressive immune cells along with $CD39^+CD8^+$ T cells individually or collectively in anti-PD-1 immunotherapy were evaluated using flow cytometry and T cell suppressive assay. **Result:** G-MDSCs, M-MDSCs, TAMs, Treg cells, and $CD39^+CD8^+$ T cells increased according to NSCLC stage, and MDSCs effectively suppressed T cell activities and induced T cell exhaustion *ex vivo*. Further, the analysis of 83 NSCLC patients treated with anti-PD-1 immunotherapy demonstrated that low G-MDSCs (P_{PFS} = 0.03, Pos = 0.04), M-MDSCs (P_{PFS} = 0.04, Pos = 0.005), TAMs (P_{PFS} = 0.007, Pos = 0.01), and $CD39^+CD8^+$ T cells (P_{PFS} = 0.57, Pos = 0.02) were associated with longer progression-free survival (PFS) and overall survival (OS) compared with high groups. When we performed combined analysis of three suppressive immune cells, G-MDSCs, M-MDSCs, and TAMs collectively, patients who had low frequency of all three suppressive immune cells showed more prominent difference of PFS (6.7 months vs 2 months; P = 0.006), OS (8.5 months vs 4.2 months; P = 0.004), and response rate (94.5% vs 50%) compared to patients with high levels of all three suppressive immune cells. We further sorted patients with all suppressive immune cells plus $CD39^+CD8^+$ T cells low and high. Again, PFS (6.1 months vs 0.8 months; P = 0.006), OS (11 months vs 2.4 months; P = 0.01), and response rate (85.7% vs 16.7%) of all suppressive immune cells low and $CD39^+$ $CD8^+$ T cells low group were significantly increased. **Conclusion:** The analysis of 83 advanced NSCLC patients treated with anti-PD-1 immunotherapy demonstrated that G-MDSC, M-MDSC, TAM and $CD39^+CD8^+$ T cell frequencies in peripheral blood individually and collectively might be useful as potential predictive biomarkers.

Keywords: myeloid-derived suppressor cell, immune checkpoint inhibitor, Non-Small Cell Lung Cancer

P1.04-25 CT BASED VESSEL TORTUOSITY FEATURES ARE PROGNOSTIC OF OVERALL SURVIVAL AND PREDICTIVE OF IMMUNOTHERAPY RESPONSE IN NSCLC PATIENTS

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Background: Recently majority of patients with advanced non-small cell lung cancer (NSCLC) without targetable mutations are treated with immune checkpoint inhibitors (ICI). Since there are currently no validated biomarkers for predicting benefit of immunotherapy (IO), there is an unmet clinical need for development of such biomarkers. The tumor vasculature is a key component of the tumor micro-environment that can influence its behavior and therapeutic refractoriness. We aimed to evaluate the prognostic and predictive potential of quantitative vessel trotuosity (QVT), in the NSCLC patients treated with ICI drugs. Two hypotheses were established: first, the QVT on pre-treatment CT scans of NSCLC patients are associated with overall survival (OS). Second, the prognostic QVT features can lead to identify the patients who will benefit from IO.

Method: This study include 128 patients with advanced NSCLC. All patients underwent a baseline contrast CT imaging. Patients who did not receive IO drugs after 2 cycles due to a lack of response or progression as per RECIST were classified as non-responders. The dataset was splitted into a discovery (N=64) and validation sets (N=64). A set of 74 QVT features pertaining to tortuosity and curvature of tumor vasculature was extracted in CT scans. The initial set of QVT features were reduced to 8 features using least absolute shrinkage and selection operator (LASSO) in conjunction with OS data of the patients. Then, cox proportional hazard model was used to determine the contribution of each feature for categorizing survival groups. The weighted sum of selected 8 features gave a risk score (QRS) per patient. Patients in validation set were stratified based on QRS using the cutoff and feature weights learned in the discovery set. Prognostic features in conjunction with a linear discriminant machine learning model and OS were used to build a model to predict the response to IO. The prognostic features were also used for unsupervised clustering of the patients. **Result:** The QRS risk score was able to stratify patients into two survival groups in validation set (Fig1. a-b) with p-value=0.022, Hazard ratio (HR)=0.47 and concordance index (CI)=0.61. The response prediction model yielded an AUC of 0.64±0.03 (Fig1.c). The agreement between patients with high OS and positive response to therapy was found to be 0.62 on unsupervised clustering method (Fig1. d).

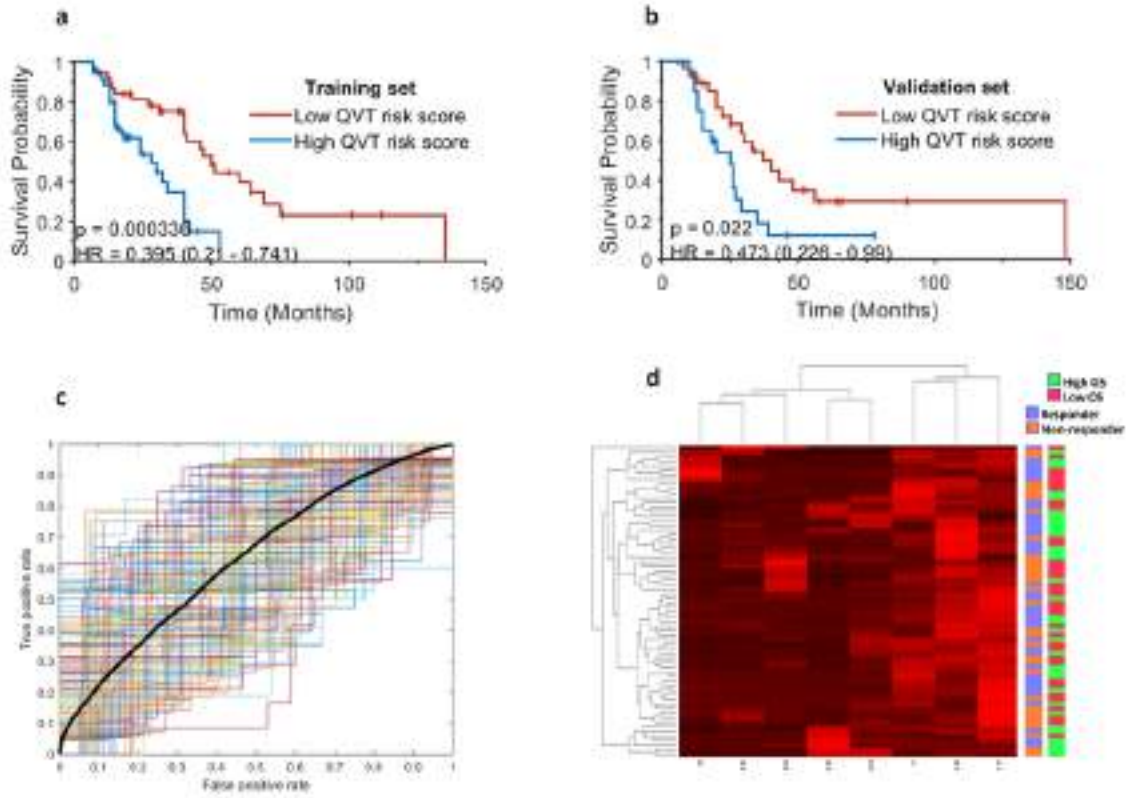

Fig1. a-b) Kaplan-Meier curves of survival estimates for the patient groups with low- and high- QRS scores in training and validation sets. c) The ROC curve of the response prediction model. d) The patients clusters which were created based on prognostic features.

Conclusion: The CT extracted QVT features was found to be prognostic of OS and also showed predictive value that could be used to identify patients who will benefit from IO.

POSTERS

P1.04-26 EMT-ASSOCIATED RESPONSE AND RESISTANCE TO MEK INHIBITOR AND IMMUNE CHECKPOINT BLOCKADE COMBINATIONS IN KRAS-MUTANT NSCLC

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Background: Current work by our group using mutant KRAS and TP53 (KP) mouse models of NSCLC have shown that rationally designed therapies combining PD-L1 immune checkpoint blockade (ICB) with MEK inhibitors (MEKi) significantly decreases tumor growth and metastases compared to either monotherapies in syngeneic KP mice tumors. Despite these encouraging results, therapeutic resistance still occurs. Analyses from these tumors showed an increase in T_{regs} and CTLA-4 immune checkpoint expression. As anti-CTLA-4 ICB is particularly effective in increasing the CD8 / T_{reg} ratio, we hypothesized that the addition of this agent may improve the outcome. **Method:** Using *in vivo* KP syngeneic mouse models, we compared tumor size, tumor weight and lung metastatic nodules between two treatment regimens: the triple combination of selumetinib (MEKi) and anti-PD-L1 with either: 1) anti-CTLA-4 or; 2) IgG2b isotype control. FACS-based immunoprofiling was conducted at the time of response (5 weeks following treatment initiation) and resistance (maximal tumor volume). Whole tumors at the time of response and resistance, as well as *ex vivo* resistant cell lines, were also characterized by qPCR and Western Blotting (WB). Moreover, whole tumors from multiple treatment combinations and KP models were processed for custom codeset *Nanostring* mRNA analyses. **Result:** The addition of anti-CTLA-4 to anti-PD-L1 and MEKi improved survival in the epithelial 393P KP mouse model (HR=3.517; p=0.03). Because FACS immunoprofiling of cytotoxic $CD8^+$ T cells subtypes, NK cells and T_{regs} did not reveal statistically significant changes (p>0.05), we investigated potential tumor-intrinsic mechanisms. All resistant 393P cell lines displayed a mesenchymal morphology. Furthermore, whole tumors from the anti-CTLA-4 group demonstrated significantly less expression of Zeb1 (WB; p=0.05) at the time of response. *Nanostring* analyses comparing anti-PD-1 + anti-CTLA-4 vs anti-PD-L1 monotherapy in 344SQ KP mesenchymal tumors also showed statistically significant downregulation of epithelial-to-mesenchymal (EMT) markers (p=0.001). Finally, *in vivo* experiments using resistant 393P (MEKi + ICB) and mesenchymal 344SQ cells, demonstrated abrogation of the survival benefit initially observed with sensitive epithelial 393P cells upon treatment with combination therapies. **Conclusion:** The combination of a MEKi, anti-PD-L1 and anti-CTLA-4 improves survival in epithelial syngeneic KP pre-clinical models of NSCLC, and this benefit is associated with downregulation of EMT markers. Therefore, further in-depth studies are required to understand the effect of ICB on EMT. In an upcoming single center, Phase I / II clinical trial, two combination schedules of selumetinib, tremelimumab and durvalumab will be compared with historical controls in patients with previously treated, metastatic NSCLC.

Keywords: MEK inhibitor, KRAS-mutant NSCLC, Immune checkpoint blockade

P1.04-27 PROCESSING ESCAPES: NOVEL RESISTANCE MECHANISMS UNDER IMMUNE CHECKPOINT INHIBITION IN NSCLC

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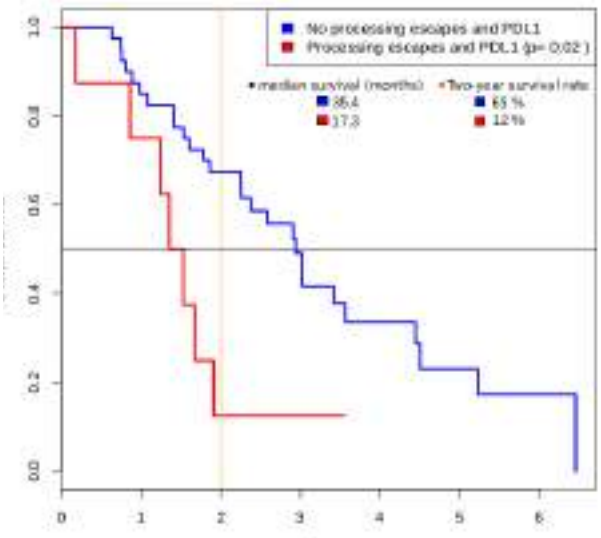
Background: Immune checkpoint inhibition, especially the blocking of PD-1 and PD-L1, has become one of the most thriving therapeutic approaches in modern oncology. Unfortunately, 60-80% of all patients will develop long-term resistances under immunotherapy. We believe immune evasion caused by altered tumour epitope processing may be one possibility to explain therapy resistance. In a previous work, we were able to establish these so-called processing escapes as an intrinsic immune escape mechanism in patients suffering from neuroendocrine lung cancers. In the present study, we aim to demonstrate the effects of processing escapes on immunotherapy outcome in NSCLC-patients. **Method:** Whole exome sequencing data of 400 NSCLC-patients (AdC and SCC) were extracted from the TCGA database serving as a training cohort. The validation cohort was composed of primary tumour probes from 48 NSCLC-patients, who received Nivolumab treatment. Mutational characteristics of these patients were determined by targeted amplicon-based sequencing including hotspots and whole exomes of 22 genes. The effect of mutations on proteasomal processing was evaluated by deep learning methods previously trained on 1260 known MHC-I ligands. Cox-regression modelling was used to determine the influence on overall survival. **Result:** In the training cohort, processing escapes were connected to decreased overall survival (p= 0.025) as well as lowered expression of immune factors including Granzyme K (p= 0.15), CD20 (p=0.05) and CD40L (p= 0.025). In the validation cohort, the group of patients showing high abundances of processing escapes in combination with high levels of PD-L1 (n=9/48) had a significantly decreased overall survival (figure 1). The predictive significance of processing escapes proved to be independent of mutational load or PD-L1 status in multivariate analysis.



Conclusion: Based on our retrospective data, the impact of processing escapes and PD-L1 status as a composite predictive score for checkpoint inhibitor response in NSCLC should be further investigated in prospective studies.

Keyword: Antigen processing, Immune checkpoint inhibition, Deep learning, NSCLC

P1.04-28 COAST: DURVALUMAB ALONE OR WITH NOVEL AGENTS FOR LOCALLY ADVANCED, UNRESECTABLE, STAGE III NON-SMALL CELL LUNG CANCER

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Background: The standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) is platinum-based chemotherapy with concurrent radiotherapy, followed by durvalumab consolidation for 12 months. When administered after completion of concurrent chemoradiotherapy (cCRT) in patients with unresectable NSCLC in the PACIFIC study, durvalumab demonstrated superior clinical outcomes vs placebo in terms of progression-free survival (PFS; hazard ratio [HR] 0.51; 95% CI: 0.41, 0.63) and overall survival (OS; HR 0.68; 99.73% CI 0.47, 0.997; p=0.0025).[1] Comparing durvalumab with placebo, the 24month OS rate (95% CI) was 66.3% (61.7, 70.4) vs 55.6% (48.9, 61.8), median PFS was 17.2 months (13.1, 23.9) vs 5.6 months (4.6, 7.7) and objective response rate was

30.0% (25.8, 34.5) vs 17.8% (13.0, 23.6).[1,2] However, despite cCRT followed by durvalumab, most patients with unresectable stage III NSCLC relapse and eventually die from NSCLC. The COAST study (NCT03822351) is a platform trial that aims to identify potential combinations of durvalumab with novel agents to improve response rates over monotherapy. **Method:** This multidrug, randomized, phase 2 trial is evaluating the clinical activity and safety of durvalumab alone or in combination with the novel agents oleclumab (MEDI9447) and monalizumab (IPH2201) in patients with unresectable, stage III NSCLC who have not progressed following definitive cCRT. New treatment arms evaluating other durvalumab combinations may be added based on emerging preclinical and clinical data. The primary endpoint is objective response per RECIST v1.1 with monotherapy and combination therapy. Secondary endpoints include safety, efficacy (duration of response, disease control, PFS, 12-month PFS rate, OS), pharmacokinetics and immunogenicity. The COAST study is open for accrual with an estimated total target enrollment of up to 60 patients per treatment arm. References [1]Antonia SJ, et al. N Engl J Med 2018;379:2342–50. [2]Antonia SJ, et al. N Engl J Med 2017;377:1919–29. **Result:** Section not applicable **Conclusion:** Section not applicable

Keyword: locally advanced NSCLC, consolidation treatment, checkpoint inhibition

P1.04-29 DYNAMIC CHANGES OF PLASMA PD-L1 MRNA EXPRESSION PREDICT RESPONSE TO ANTI-PD-1/ANTI-PD-L1 TREATMENT IN MALIGNANCIES

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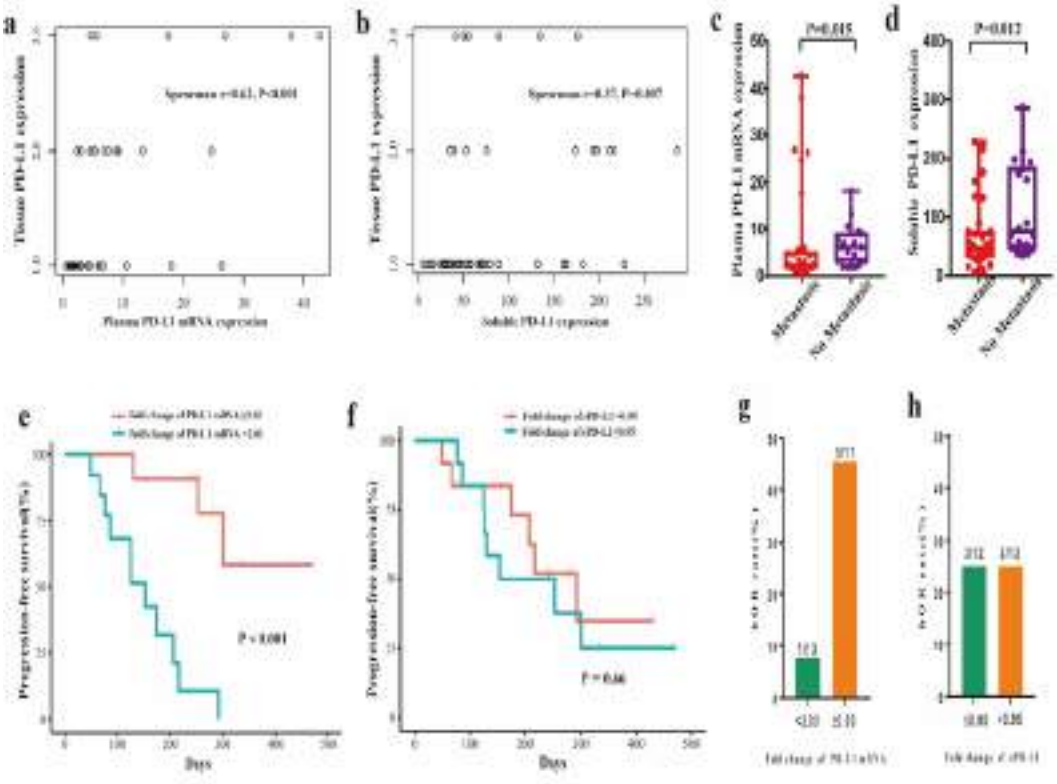
Background: PD-L1 expression in malignant tumor tissues is a rational biomarker to predict the efficacy and prognosis of anti-PD-1/anti-PD-L1 treatment, but few studies focus on the role of blood PD-L1 expression. **Method:** Fifty-one paired tissue samples and blood samples, as well as clinicopathologic features, were collected from patients with diverse malignancies to investigate the correlation among tissue PD-L1 (tPD-L1) expression, plasma PD-L1 mRNA expression, soluble PD-L1 (sPD-L1) expression and clinicopathologic features. Tissue PD-L1 were measured by immunohistochemistry. PD-L1 mRNA and self-designed plasma external reference PLACON were measured by quantitative real-time PCR. Soluble PD-L1 were detected by ELISA kit. Then, dynamic changes of blood PD-L1 expression (at baseline and within 2 months) were measured to evaluate the efficacy of patients with malignancies (n=24) who received anti-PD-1/anti-PD-L1 treatment. **Result:** Moderate correlation between tPD-L1 and PD-L1 mRNA (r=0.62, *P*<0.001), weak correlation between tPD-L1 and sPD-L1 (r=0.37, *P*=0.007) and weak correlation between PD-L1 mRNA and sPD-L1 (r=0.32, *P*=0.02) were found. Most clinicopathologic features had no significant correlation with PD-L1 mRNA and sPD-L1 expression. Interestingly, patients without metastasis had higher PD-L1 mRNA and sPD-L1 expression than counterparts. Further, patients with over 2.03-fold PD-L1 mRNA increase (n=11) during treatment experienced improved progression-free survival (PFS) than those with less than 2.03-fold increase (n=13), these patients also had higher best overall response (bOR) rate (45.45% vs. 7.69%). By comparison, the dynamic changes of sPD-L1 expression had no significant correlation with PFS and bOR.

Conclusion: Our study demonstrates that plasma PD-L1 mRNA expression was significantly correlated with tissue PD-L1 expression, and provides proof for the application of plasma PD-L1 mRNA as a predictor for anti-PD-1/anti-PD-L1 treatment.

Keywords: dynamic changes, anti-PD-1/anti-PD-L1 treatment, PD-L1 mRNA



a, The correlation between tPD-L1 and plasma PD-L1 mRNA (n=51). **b,** The correlation between tPD-L1 and sPD-L1 (n=51). **c,** Plasma PD-L1 mRNA expression in patients with (n=33) and without (n=18) metastasis. **d,** sPD-L1 expression in patients with (n=33) and without (n=18) metastasis. **e,** Kaplan–Meier PFS of patients with high (n = 11) and low (n = 13) fold changes of plasma PD-L1 mRNA within 2 months. **f,** Kaplan–Meier progression-free survival of patients with high (n = 12) and low (n = 12) fold changes of plasma sPD-L1 within 2 months. **g,** bOR rate for patients with high and low fold changes of plasma PD-L1 mRNA . **h,** bOR rate for patients with high and low fold changes of plasma sPD-L1. tPD-L1, tissue PD-L1; sPD-L1, soluble PD-L1; PFS, progression-free survival; bOR, best overall response.
* Tissue PD-L1 expression were measured by immunohistochemistry with SP142 (1.0 : <1%, 2.0 : 1%-99%, 3.0 : ≥50%). Plasma PD-L1 mRNA and self-designed plasma external reference PLACON (DOI: 10.16016/j.1000-5404.201812172) were detected by quantitative real-time PCR. Plasma soluble PD-L1 expression were measured by ELISA kit.

POSTERS

P1.04-30 PIONEER STUDY: PRECISION IMMUNO-ONCOLOGY FOR ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH PD1/L1 ICI RESISTANCE

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Background: In the management of advanced Non-Small Cell Lung Carcinoma (NSCLC), both PD1/L1 immune checkpoint inhibitors (ICIs) have been shown to increase overall survival (OS) over standard second-line chemotherapy. While this long-term increase in OS is driven by about 20% of patients, others display disease progression during the first weeks (w.). PIONeeR aims to understand, through a strategy based on a comprehensive biomarkers assessment, and overcome, through rescue IO strategies, the resistance to ICIs. **Method:** Stage IV or recurrent NSCLC patients (n=450), with an archived pre-ICI tumor block, planned for a standard 2nd or 3rd line ICIs monotherapy, will be screened. If eligible, after signing an informed written consent, they will be blood-sampled, every cycle throughout the 18 w. post C1D1, and systematically be re-biopsied (primitive or metastasis tumor) at 6 w. of treatment. Efficacy of ICIs will be assessed by RECIST, after 6, 12 and 18 w. Feces will be self-collected by patients, before and during ICIs, to analyze impact of gut microbiome in resistance to ICIs. Characterization of the specific immune contexture of each patient to potentially predict the efficacy of ICIs will be based on the investigation of tumors and their microenvironment (Immunoscore® IC & Multiplex ImmunoHistoChemistry, Tumor Mutational Burden –T cell clonality- ctDNA investigation), effector immune cells, cytokines and endothelial activation (ELISA-Flow cytometry). Protocol's legal and ethical authorizations were obtained on February 2018 (NCT03493581), patient inclusions were enhanced on April 2018 with the activation of 3 main centers; 10 satellites centers were opened at Q4 2018, inclusions are expected to be completed at Q4 2020. Patients who will progress between 6 and 18 w. (n=150) will be randomized within a precision immuno-oncology experimental masterprotocol using a Bayesian, adaptive design (4 combinations of PDL1i and NKG2Ai, STAT3i, ATRi or CD73i or a control arm). Legal authorizations were obtained on December 2018 (NCT03833440), the inclusion period is expected to last 24 months, from the beginning of Q2 2019.Descriptive statistics will be used to characterize distributions of marker's expression and to evaluate their predictive value on treatment response and prognostic value on Progression Free Survival., in both protocols. The primary endpoint of the randomized clinical trial is the 12-week Disease Control Rate, assessed in each arm of treatment. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: PD1/L1 inhibitors, primary resistance, predictive biomarkers

P1.04-31 IMMUNOSENESCENCE CORRELATES WITH POOR OUTCOME FROM PD-(L)1 BLOCKADE BUT NOT CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: CD28, CD57 and KLRG1 on circulating T-lymphocytes have been identified as markers of immunosenescence. The characterization of a senescent immune phenotype (SIP) in advanced NSCLC (aNSCLC) and its impact on anti-PD(L)-1 (IO) or platinum-based chemotherapy (PCT) treatments are unknown. **Method:** The percentage of circulating $CD8^+CD28^-CD57^+KLRG1^+$ T-lymphocytes (SIP) was assessed by flow cytometry on fresh blood from aNSCLC patients treated with IO or PCT. A SIP cut-off was identified by log-rank maximation method. Correlations with categorical or continuous variables were performed by logistic regression or t-test. Survival curves were estimated with Kaplan Meier and compared with log-rank. **Result:** In the IO cohort, 43 patients were evaluated for SIP: 32% ≥ 65 years, 92% non-squamous, 51% with tumoral PD-L1 expression ≥1%, 93% chemotherapy pretreated. Disease control rate (DCR), median PFS and OS and FU were 57%, 4.6 (95% CI 0.5; 8.8) months, 13 (95% CI 2.8-23.2) months, and 14 (95% CI 8.8-19.8) months, respectively. SIP median value was 15.4% (min 1.6%, max 57.7%). 32% of patients had >21.72% $CD28^-CD57^+KLRG1^+CD8^+$ lymphocytes (SIP^+). SIP was not significantly associated with clinical characteristics. SIP changed according to IO response by T-sne algorithm (Figure 1A). Compared to SIP^-, SIP^+ patients had significantly lower DCR (81% vs 28%, p=0.002), PFS [7.3 (95% CI 4.1; 10.4) vs 1.7 (95% CI 1.2; 2.3), p=0.02] and OS [NR (95% CI 6.04; NR) vs 2.4 (95% CI 1.7; 3.1), p=0.01]. SIP was significantly associated with specific immune populations [higher peripheral activated ($Ox40^+ICOS^+PD1^+$) T-regulatory ($CD25^{high}CD127^{low}$) cells, TEMRA ($CCR7^-CD45RA^+$) $CD8^+$ and T-helper 1 ($CXCR5^-CXCR3^+CCR4^-CCR6^-CCR10^-$) $CD4^+$] (Figure 1B). The PCT cohort included 61 patients, 43% SIP^+. No significant difference in DCR, PFS or OS were observed according to SIP.

Fig 1A. T-sne algorithm (unsupervised analysis)

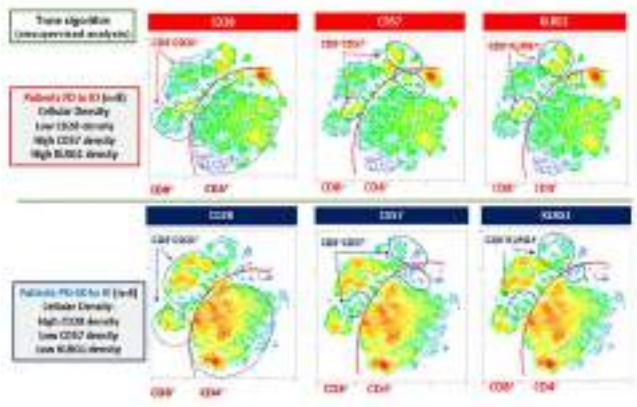
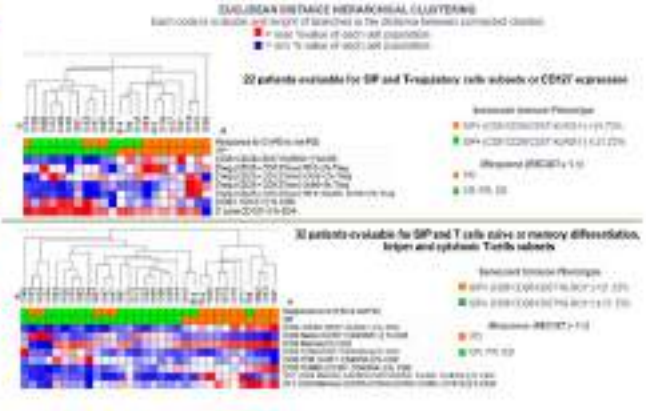


Fig 1B. Heatmap hierarchical clustering



Conclusion: Immunosenescence is observed in 32% of aNSCLC patients before IO and correlates with specific immune phenotypes. Immunosenescence predicts lower DCR, PFS and OS from IO but not from PCT.

Keywords: immunosenescence, NSCLC, Immunecheckpoint blockade

POSTERS

P1.04-32 KI67$^+$PD-1$^+$ CENTRAL MEMORY CD8 T-CELL FREQUENCIES PREDICT RESPONSE UPON NIVOLUMAB+IPILIMUMAB IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: New treatment options for malignant pleural mesothelioma (MPM) are urgently needed, as the only standard treatment, chemotherapy, has only modest activity in the majority of the patients. Recent clinical trials with checkpoint inhibitors have shown promising results in MPM patients who progressed after first line platinum-based chemotherapy. We reported on 2 phase II clinical trials which assessed nivolumab (aPD-1) monotherapy (NIVOMES) and the combination of nivolumab + ipilimumab (INITIATE). At the 12-week time point, the disease control was 47% for nivolumab and 68% for the combination. Here we report on differences in T cell subsets present in the peripheral blood at baseline and during treatment in both trials. **Method:** Peripheral blood of 31 MPM patients enrolled in NIVOMES and 38 MPM patients enrolled in INITIATE was collected at baseline and 6-weeks after start of treatment. T-cell subsets frequencies and the expression of Ki67 and PD-1 on these subsets were determined by flow cytometry. **Result:** An increased proportion of proliferating Ki67$^+$ T-cells was found after 6-weeks of combination treatment with nivolumab/ipilimumab, which was not observed 6-weeks after treatment with nivolumab monotherapy. Increased proliferation was particularly observed in the effector memory (EM) and central memory (CM) CD4$^+$ T-cells and EM CD8$^+$ T-cells. Additionally, patients with a clinical response on combination therapy had a significantly higher frequency of PD-1$^+$ Ki67$^+$ CM CD8$^+$ T-cells and effector memory re-expressing RA (EMRA) CD8$^+$ T-cells compared to non-responders at baseline. These differences were not seen in patients that responded to nivolumab monotherapy. No alterations in the frequencies of either activated or naïve regulatory T cells (Tregs) were found in both treatment groups comparing baseline to 6 weeks. **Conclusion:** Our results indicate that specifically in patients that respond to combination therapy the frequency of PD-1$^+$Ki67$^+$ CM CD8 T-cells at baseline was significantly increased, whereas combination therapy in both responding and non-responding patients increased proliferation of memory T-cell subsets. This indicates that addition of ipilimumab to nivolumab treatment reinvigorates T-cell responses in general, whereas responding patients present with elevated immune activation already at baseline. In conclusion, we were able to select MPM patients that are most likely to benefit from combination therapy of nivolumab and ipilimumab at baseline.

Keywords: Mesothelioma, Checkpoint inhibitors, immunomonitoring

P1.04-33 DEEP PHENOTYPING OF IMMUNE POPULATIONS REVEALS BASELINE PREDICTORS OF PEMBROLIZUMAB EFFICACY IN NSCLC ON KEYNOTE-001

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Background: Medical treatment of lung cancer has irreversibly changed since the development of immune checkpoint inhibitors like pembrolizumab. However, immune biomarkers of efficacy are still lacking. Preliminary data in melanoma showed that a high baseline blood level of classical monocytes was associated with improved outcome in patients treated with programmed cell death-1 (PD-1) inhibitors. This led us to explore the immune landscape of non-small cell lung cancer (NSCLC) patients treated with pembrolizumab on KEYNOTE-001 using high-dimensional mass cytometry. **Method:** We analyzed 38 advanced NSCLC patients treated with pembrolizumab on KEYNOTE-001 at UCLA. Mass cytometry (CyTOF) was performed on baseline peripheral blood mononuclear cells (PMBC). We used a panel of 31 antibodies defining major immune populations of myeloid cells (plasmacytoid and myeloid dendritic cells, myeloid-derived suppressor cells, classical and CD16$^+$ monocytes), lymphoid cells (B cells, NK cells, T_{Reg}, γδ T-cells, sub-populations of CD4$^+$ and CD8$^+$ T-cells), selected co-stimulatory (CD28, ICOS, 41BB), co-inhibitory molecules (PD-1, PD-L1, TIM3, LAG3, CTLA-4) and cytotoxicity molecules (perforin, granzymeB). Unsupervised clustering combined with predictive regression model (Citrus algorithm, false discovery rate = 1%) was used to detect immune populations differing between patients that experienced an objective response on trial, as assessed by immune-related response criteria (responders) *vs* those that did not (non-responders). Classical manual gating (FlowJo software) was used to confirm the Citrus results. **Result:** Among the 38 patients analyzed via CyTOF, 27 patients had sufficient viable cells for analysis. Citrus algorithm comparing responders (n=7) and non-responders (n=20) revealed significant frequency differences in specific subtypes of three immune populations: monocytes, CD4$^+$ and CD8$^+$ T-cells. Manual gating confirmed that responders (*vs* non-responders) had increased frequency (%CD45$^+$) of classical monocytes perforin$^+$ granzymeB$^+$ (5.54% *vs* 2.55%, p=0.029), central memory CD4$^+$ T-cells ICOS$^+$ CD28$^+$ PD1$^+$ (1.29% *vs* 0.83%, p=0.06) and over-expression of 41BB (mean metal intensity (MMI)=0.15 *vs* MMI=0.09, p=0.006) and perforin (MMI=108.4 *vs* MMI=70.7, p=0.004) in effector memory CD8$^+$ T-cells. **Conclusion:** Mass cytometry in the blood reveals that a high baseline frequency of activated and cytotoxic monocytes, CD4$^+$ and CD8$^+$ T-cells predicted for pembrolizumab efficacy in advanced NSCLC. Preliminary analyses correlating immune cell populations and overall survival are ongoing and suggest a similar increase in the three immune cell populations found to be higher in responders *vs* non-responders.

Keywords: Pembrolizumab, biomarkers, mass cytometry

P1.04-34 EFFICACY AND SAFETY OF FIRST-LINE PEMBROLIZUMAB MONOTHERAPY IN ELDERLY PATIENTS (AGED ≥ 75 YEARS) WITH NON-SMALL CELL LUNG CANCER

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Background: Pembrolizumab is effective as first-line treatment for advanced non-small cell lung cancer (NSCLC) patients expressing high programmed death-ligand 1 (PD-L1). However, it is unclear whether the efficacy of first-line pembrolizumab treatment in elderly patients (aged ≥75 years) is similar to that in non-elderly patients expressing high PD-L1. Therefore, we aimed to investigate the efficacy and safety of first-line pembrolizumab monotherapy in elderly patients with NSCLC expressing high PD-L1. **Method:** Between February 2017 and February 2018, 128 patients (comprising 47 elderly) with advanced NSCLC expressing high PD-L1 received first-line pembrolizumab monotherapy at 10 Japanese institutions. Baseline characteristics, efficacy of pembrolizumab treatment, and adverse events were recorded. **Result:** Overall, 47 patients (40 men and 7 women) (median age, 79 [range, 75–88] years) were included in our analysis. In these patients who received first-line pembrolizumab monotherapy, the overall response, disease control rates, median progression-free survival (PFS), and overall survival (OS) were 53.1%, 74.4%, 7.0 months, and not reached, respectively. Common adverse events included anorexia, fatigue, skin rash, and hypothyroidism. Two treatment-related deaths due to pneumonitis and infection were noted. First-line pembrolizumab monotherapy with non-progressive disease (PD) was associated with better PFS. Pembrolizumab monotherapy with good performance status and non-PD was also linked to better OS. **Conclusion:** First-line pembrolizumab monotherapy among elderly patients with NSCLC expressing high PD-L1 was effective and safe and showed outcomes equivalent to those in non-elderly patients. First-line pembrolizumab monotherapy without PD, and with good performance status and non-PD, might be associated with better PFS and OS, respectively.

Keywords: advanced non-small cell lung cancer, Elderly patients, first-line pembrolizumab monotherapy

P1.04-35 IDENTIFICATION AND CHARACTERIZATION OF A UNIQUE KLRG1-EXPRESSING SUBSET OF CD4+FOXP3+ TREGS IN NON-SMALL CELL LUNG CANCER

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Background: It is well established that CD4+FOXP3+ T regulatory cells (Tregs) contribute to dampening anti-tumor responses. Despite our improved understanding of their role in cancer, there remains a knowledge gap with respect to the clonal composition and heterogeneity of tumor-infiltrating Tregs in solid cancers. **Method:** We addressed this outstanding issue by conducting comprehensive phenotypic profiling of Tregs present in lung adenocarcinomas of a genetically engineered mouse model of non-small cell lung cancer (NSCLC) as well as those in resected tumors of NSCLC patients. **Result:** Multi-parameter flow cytometric analysis revealed that unlike the peripheral tissues, the tumor harbors a distinct sub-population of Tregs that express the co-inhibitory receptor, KLRG1. Compared to their negative counterparts, the KLRG1+ Treg subset exhibited heightened expression of a number of Treg signature proteins as well as higher levels of activation and memory molecular markers suggesting that they are a highly activated and differentiated Treg pool that is recruited to, or induced in the tumor microenvironment. Consistent with this phenotype, these KLRG1+ Tregs were superior in their capacity to suppress T cell proliferation relative to the KLRG1- cells. **Conclusion:** Collectively, these findings demonstrate that the tumor microenvironment in non-small cell lung cancer harbors a unique Treg sub-population that is characterized by dominant expression of KLRG1, and which represents a clonal pool with the most potent inhibition of T cell responses. These studies highlight the installment of distinct Treg subsets in NSCLC that have implications for regulation of anti-tumor responses.

Keywords: Tumor Immunology, Tregs, Non-Small Cell Lung Cancer

P1.04-36 AN IN VIVO INFLAMMATORY LOOP POTENTIATES KRAS BLOCKADE

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Background: Several reports from different groups suggest that novel KRAS inhibitors are not effective *ex vivo*, but the mechanism(s) responsible for this are unknown. We performed complex experiments that highlight the huge discrepancy between the marked *in vivo* and the minimal *in vitro* effects of KRAS inhibitors. Furthermore, we identified and validated the mechanism of the *in vivo*-restricted actions of KRAS inhibitors in immunocompetent mice, which can be translated to successful new treatments for patients with *KRAS*-mutant cancers. **Method:** We treated tumor cells with defined *KRAS* mutation status with KRAS inhibitors deltarasin, cysmethynil, and AA12 and used different *in vitro* assays as readout. Additionally *KRAS* silencing and overexpression were done using shRNA and $KRAS^{G12C}$ vectors and included in the experimental setup. In parallel C57BL/6 wildtype mice or deficient in interleukin (IL)-1β (*Il1b-/-*) or chemokine receptors (*Ccr2-/-*, *Cxcr1-/-*, *Cxcr2+/-*) received s.c. *KRAS*-mutant or wild-type tumor cells followed by saline or deltarasin treatments. Microarrays were done using a large set of *Kras*-mutant and *Kras*-wildtype cell lines. **Result:** We identified that KRAS inhibitors exerted comparable effects against cancer cells *in vitro* irrespective of *KRAS* status. However, mice only with *KRAS*-mutant tumors responded selectively to deltarasin treatment. Similar *in vivo*-restricted effects were evident after genetic manipulation of KRAS. Microarrays identified a 42-gene signature specific to *Kras*-mutant cancer cells and responsive to *Kras* manipulation, which contained *Kras*, *Ccl2*, *Il1r1*, *Ccl7*, and *Cxcl1*. Deltarasin was effective in halting *KRAS*-mutant flank tumors in *Wt*, *Cxcr1-/-*, and *Cxcr2+/-*, but not in *Ccr2-/-* and *Il1b-/-* mice. qPCR results revealed a strong regulation of *Il1r1/IL1R1* mRNA expression depending of *Kras/KRAS* mutation status and drug treatment. Thereby, KRAS inhibition can be effective *in vivo* via blockade of the positive feedback loop of KRAS-CCL2-IL1ß. **Conclusion:** Inflammatory signaling loops are synthetic lethality targets for *KRAS* mutant tumors and only druggable by KRAS inhibitors *in vivo*. Hence *in vitro* drug screens may be suboptimal settings for anti-KRAS drug discovery.

Keywords: KRAS, inflammation, Drug resistance

P1.04-37 DIOSCIN ELICITS ANTI-TUMOR IMMUNITY BY INHIBITING MACROPHAGES M2 POLARIZATION VIA JNK AND STAT3 PATHWAYS IN LUNG CANCER

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Background: Tumor associated macrophage (TAM) is an important component in tumor microenvironment. Generally, TAM exhibits the function of M2-like macrophage, which is closely related to angiogenesis and tumor progression. Dioscin, a natural steroidal saponin, has shown its powerful anti-tumor activity recently. However, the mechanism of dioscin involved in immune-regulation is still obscure. Our study aimed to find the potentional anti-tumor role of dioscin in macrophages polarization regulation in lung cancer. **Method:** Flow cytometry was used to analyze the percentage of M1 macrophages($CD86^+F4/80^+$ or $NOS2^+F4/80^+$) and M2 macrophages($CD209^+F4/80^+$ or $CD206^+F4/80^+$) with dioscin treatment in vivo and *in vitro*. Real-time quantitative PCR was used to detect the expression of Arg-1, CD206 and NOS2, IL-6 mRNA. The level of IL10 and IL-12 secreted by macrophages was also analyzed using flow cytometry. Phagocytosis was determined by the amount of fluorescence-labeled latex beads internalized by BMDMs with microscopy and Flow cytometry. JAK-STAT and MAPK signaling pathways were detected by Western-Blot method. **Result:** We observed dioscin induced macrophages M2-to-M1 phenotype transition *in vitro* and inhibited IL-10 secretion. Meanwhile, the phagocytosis of macrophages was enhanced. In subcutaneous lung tumor models, dioscin inhibited the augmentation of M2 macrophage populations. Furthermore, dioscin down-regulated STAT3 and JNK signaling pathways in macrophages *in vitro*. Additionally, condition mediums from dioscin-pretreated macrophages inhibited the migration of 3LL cells and the tube-formation capacity of HUVEC cells. **Conclusion:** Dioscin may act as a new anti-tumor agent by inhibiting TAMs via JNK and STAT3 pathways in lung cancer.

Keywords: dioscin, macrophages polarization, anti-tumor

P1.04-38 EFFICACY AND SAFETY OF IMMUNOTHERAPY IN ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Most trials with Immune Checkpoint Inhibitors (ICIs) for Non-Small Cell Lung Cancer (NSCLC) included only small subgroups of patients (pts) aged ≥65. As NSCLC is often diagnosed in pts aged ≥70, real-world data about efficacy and safety of IO in elderly pts are essential. **Method:** We retrospectively collected data about all pts with advanced NSCLC treated with IO at our Institution between April 2013 and March 2019. All ICIs administered for ≥1 cycle were admitted. Pts were stratified for age as follows: <70 year-old (yo), 70-79 yo, ≥80 yo. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analyses were performed with Cox model. **Result:** We reviewed 290 cases, with a median age of 67 (range: 29-89). Pts aged<70, 70-79 and ≥80 yo were 180, 94 and 16, respectively. Two hundred five pts received an anti-PD1, 77 an anti-PDL1, 8 an anti-CTLA4 or a combo-IO. Clinical/pathological variables were uniformly distributed across age classes, except for a higher rate of males (p 0.0228) and squamous histology (p 0.0071) in the intermediate class. Response Rate (RR) was similar across age groups (21.5% vs 22.3% vs 18.8% for pts aged<70 vs 70-79 vs ≥80 yo, respectively; p 0.9470). Median PFS did not differ according to age (2.8 vs 3.5 vs 2.6 mos for pts aged<70 vs 70-79 vs ≥80 yo, respectively; p 0.2020). Similarly, median OS was similar across age classes (9.1 vs 11.3 vs 9.6 mos for pts aged<70 vs 70-79 vs ≥80 yo, respectively; p 0.9144). These results did not change after stratification for sex (p 0.516 for PFS, p 0.5154 for OS) and histology (p 0.9057 for PFS, p 0.1002 for OS). The incidence of toxicity was comparable across subgroups (grade ≥2 adverse events in 35.8% vs 32.7% vs 37.5% for pts aged<70 vs 70-79 vs ≥80 yo, p 0.6493). The only variables influencing outcome at both univariate and multivariate analyses were performance status (p<0.0001 for PFS, p 0.0192 for

OS), number of metastatic sites (p 0.0842 for PFS, p 0.0235 for OS) and IO line (p<0.0001 for both PFS and OS), regardless age group. **Conclusion:** Advanced age is apparently not associated to a reduced efficacy of IO in our case series. Furthermore, no toxicity concern emerges even among the eldest pts. Therefore, to our opinion ICIs should be considered irrespective of age, provided an optimal PS at baseline. Of note, IO is often the only therapeutic option applicable to these cases considering the toxicity of chemotherapy.

Keywords: Non small cell lung cancer, Immunotherapy, Elderly patients

P1.04-39 MOLECULAR CHARACTERISTICS, IMMUNOPHENOTYPE, AND IMMUNE CHECKPOINT INHIBITOR RESPONSE IN BRAF NON-V600 MUTANT LUNG CANCERS

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Background: Targeted therapy for Class I *BRAF* mutant lung cancers (V600) is well described and there is growing literature on their response to immune checkpoint inhibitors (ICI). In contrast, the molecular characteristics, immunophenotype, and response rates of class II and III *BRAF* mutations are not well defined. **Method:** Patients with *BRAF* Class I, II, III mutant and variants of unknown significance (VUS) lung cancers detected on NGS (MSK-IMPACT) from 1/2014-1/2018 were identified. PD-L1 by immunohistochemistry (E1L3N) was evaluated. Tumor mutation burden (TMB; mut/Mb) was determined by MSK-IMPACT. Best objective response to ICI was assessed by RECIST v1.1. Time to treatment discontinuation (TTD) and overall survival (OS) were assessed. Statistical analysis was performed with Fisher's exact and Kaplan-Meier. *BRAF* V600 lung cancers were used as a comparator and analyzed separately from *BRAF* non-V600. **Result:** 6.0% (177/2962) of lung cancers harbored a *BRAF*-mutation. Median TMB of *BRAF* non-V600 mutant lung cancers was 10.8 mut/Mb (n=136) overall compared to 4.9 mut/Mb in V600 (n=41; p<0.0001) and 5.9 mut/Mb in *BRAF* wild-type patients (n=2785; p<0.0001). 69% (127/177) of *BRAF*-mutant cases were metastatic (29 Class I, 36 Class II, 23 Class III, and 39 VUS). 57% of patients were female, 82% were smokers, and 90% were adenocarcinoma. More smokers were seen in the BRAF V600 group than in the non-V600 group (n = 16 vs 88 respectively, p<0.0001). PD-L1 expression in 49 non-V600 cases with available tissue was 0%, 1-49%, and ≥50% in 59% (n=29), 31% (n=15), and 10% (n=5) respectively. 7 *BRAF* V600 cases with PDL1 testing had expression of 0%, 1-49%, and ≥50% in 2, 3, and 2 cases, respectively. No *BRAF* V600 cases had concurrent *RAS/NF1*-alterations compared to 11 non-V600 (p=0.07). 36 patients with *BRAF* non-V600 mutations received ICI (nivolumab (n=25), pembrolizumab (n=5), atezolizumab (n=2), ipilimumab/nivolumab (n=4); median line of therapy=2) with an ORR of 22% (8/36). 10 *BRAF* V600 mutant lung cancer patients received ICI (nivolumab (n=5), pembrolizumab (n=2), atezolizumab (n=1), ipilimumab/nivolumab (n=2); median line of therapy=2) with an ORR of 10% (1/10). There was no difference in ORR between non-V600 and V600 patients that received ICI (p=0.66). TTD in *BRAF* non-V600 was 3.2 months compared to 1.4 months for *BRAF* V600 mutant lung cancer patients (HR 0.59, p=0.26). Median TMB in patients with *BRAF* non-V600 mutations that responded vs those who did not was 13.2 and 10.8 mut/Mb respectively (p=0.92). One response to ICI was seen in a *BRAF* V600 with TMB of 19.3. OS of *BRAF* non-V600 patients was 1.7 years compared to 2.5 years in V600 (HR 1.25, p=0.38). OS was higher in *BRAF* non-V600 lung cancer patients who received ICI (2.4 years) compared to those that did not (1.2 years; HR 0.60, p=0.04). **Conclusion:** The molecular characteristics and immunophenotype of *BRAF* non-V600 mutant lung cancers is typified by high TMB and low PD-L1 expression, with reasonably higher response rates and improved OS to later line ICI compared to *BRAF* V600. Further studies of immunotherapy in this oncogene subset is warranted.

Keywords: Immune Checkpoint Inhibition, Tumor Mutation Burden, BRAF non-V600 mutant lung cancer

P1.04-40 SERUM PERFORIN LEVELS DURING THE FIRST CYCLE OF ANTI-PD-1 ANTIBODY THERAPIES IN NON-SMALL CELL LUNG CANCER

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Background: Blockade of PD-1 pathways by anti-PD-1 antibodies restore the function of exhausted T cells and release perforin and granzyme B which induce cytotoxic activity against tumor cells. We examined serum perforin and granzyme B as biomarkers of response to nivolumab and pembrolizumab in non-small cell lung cancer (NSCLC) patients. **Method:** Advanced NSCLC patients treated with nivolumab or pembrolizumab were studied. Serum were collected on days 1, 2, 8 and 15 for nivolumab and on days 1, 2, 8, 15 and 22 for pembrolizumab. Concentration of perforin and granzyme B was determined by enzyme-linked immunosorbent assay (ELISA). Best objective response was evaluated by Evaluation Criteria in Solid Tumors (RECIST) 1.1. **Result:** Sera from 40 patients with nivolumab and 26 patients with pembrolizumab were analyzed. Optimal cutoff levels for baseline concentration of perforin (day 1) were determined by efficacy. The calculated optimal cutoff levels were 5450.46 pg/ml with nivolumab (area under the receiver-operating-characteristic curve [AUC], 0.703) and 6631.16 pg/ml with pembrolizumab (AUC, 0.806). With nivolumab, median progression-free survival (PFS) was 6.8 months (95% confidence interval [CI], 2.8 to 3.7) in high concentration group (85%) versus 0.7 months (95% CI, 0.13 to not reached) in low concentration group (15%; hazard ratio [HR] for disease progression or death, 0.24; 95% CI, 0.09 to 0.68, p=0.007). Median overall survival (OS) was 14.9 months (95% CI, 10.2 to not reached) in high concentration group versus 1.8 months (95% CI, 0.13 to not reached) in low concentration group (HR for death, 0.19, 95% CI, 0.05 to 0.78, p=0.022). With pembrolizumab, median PFS was 6.7 months (95% CI, 3.5 to not reached) in high concentration group (73%) versus 0.7 months (95% CI, 0.37 to 5.7) in low concentration group (26%; HR for disease progression or death, 0.31; 95% CI, 0.11 to 0.89; p=0.03). Median OS was not reached (95% CI, 7.9 to not reached) in high concentration group versus 2.1 months (95% CI, 0.57 to not reached) in low concentration group (HR for death, 0.2; 95% CI, 0.05 to 0.77; p=0.018). Ratios of sequential perforin levels to baseline levels were analyzed, however, their AUC were not high enough, considered as low predictive power. Serum granzyme B was difficult to measure by ELISA. **Conclusion:** With anti-PD-1 antibody therapies, in patients with advanced NSCLC, higher baseline serum perforin levels before treatment were associated with significantly longer progression-free and overall survival.

Keywords: advanced non-small cell lung cancer, anti-PD1 antibody therapy, perforin

P1.04-41 IMMUNOTHERAPY CONCOMITANT TO RADIOTHERAPY: A MULTICENTRIC RETROSPECTIVE STUDY ON 179 PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy (IT) has enhanced the treatment armamentarium for aNSCLC. Radiobiological studies and initial clinical reports suggest a potential synergistic effect of radiotherapy

(RT) and IT. Aim of the study is to investigate the safety of cytoreductive RT (palliative or ablative) delivered in association with Nivolumab (NIVO), Pembrolizumab (PEM) or Atezolizumab (ATE) in aNSCLC setting. **Method:** We analyzed 179 consecutive pts affected by aNSCLC treated with a combination of RT and IT with NIVO/PEM or ATE from January 2015 to February 2019. One hundred eighteen patients were male and 61 female. Mean age was 65 (range 38-81). Adenocarcinoma was diagnosed in 101 of patients, while squamous cell carcinoma constituted 43.6% of our population. Eleven patients received IT as first line therapy, while the other 168 pts received at least a first line of systemic therapy before IT. One hundred thirty patients received NIVO, 42 PEM and 7 ATE. Concerning RT, 109 patients were treated before first cycle of IT (within 40 days), 49 pts during IT and the remaining 21 received RT immediately after the last IT session (within 40 days) due to disease progression (DP). **Result:** After a mean follow up (FUP) of 24.1 months (range 3-142), 63/179 patients were still alive. During FUP 115 patients (62.4%) experienced DP after RT-IT. One and 3-year Overall Survival were 60.3%±3.8%SE and 26,7%±4,5%SE, respectively. RT was delivered in 96 cases to bone metastasis, in 49 to brain mts, in 11 to lung nodules, in 12 to lymph nodes, in 6 to surrenalic gland and in 5 pts to other sites. RT was delivered to 109 patients as a pure palliative treatment (8-36 Gy in 1-12 fractions), to 49 pts using stereotactic ablative doses (18-54 Gy in 1-5 fractions) and to 21 with high dose moderately-hypofractionated schedules(24-51 Gy in 3-17 fractions) . In 107 patients, RT was planned using a 3D conformal approach, while in 72 an inverse planning system was used (IMRT/VMAT/Tomotherapy). Mean number of IT administrations was 11 (2-58). No patient had an interruption of systemic therapies during or after RT. Severe acute toxicities (Grade 3 by 4.0 CTCAE scale) were reported only in three cases because of the RT treatment: 1 case of radiodermitis and two lung toxicities. Known systemic side effects from IT were observed in 44 pts, 12 of whom with ≥G3 : 6 pneumonitis, 3 colitis, 2 thyroid toxicities, 1 oesophageal toxicity, 1 pt asthenia. **Conclusion:** RT and IT with checkpoint inhibitor NIVO/PEM/ATE represent a safe, well tolerated and efficient multimodal treatment in aNSCLC, with the available data suggesting also potential, synergistic effects on local and systemic disease in aNSCLC pts even when non-radical RT doses are prescribed. Ongoing studies set out to understand the optimal timing, RT doses and ideal combination between RT and IT in aNSCLC.

Keywords: radiotherapy, Immunotherapy, advanced NSCLC

P1.04-42 TUMOR MICROENVIRONMENT IS ASSOCIATED WITH EFFICACY OF PD-1/PD-L1 INHIBITORS IN PATIENTS WITH PRIMARY PULMONARY LYMPHOEPITHELIOMA-LIKE CANCER

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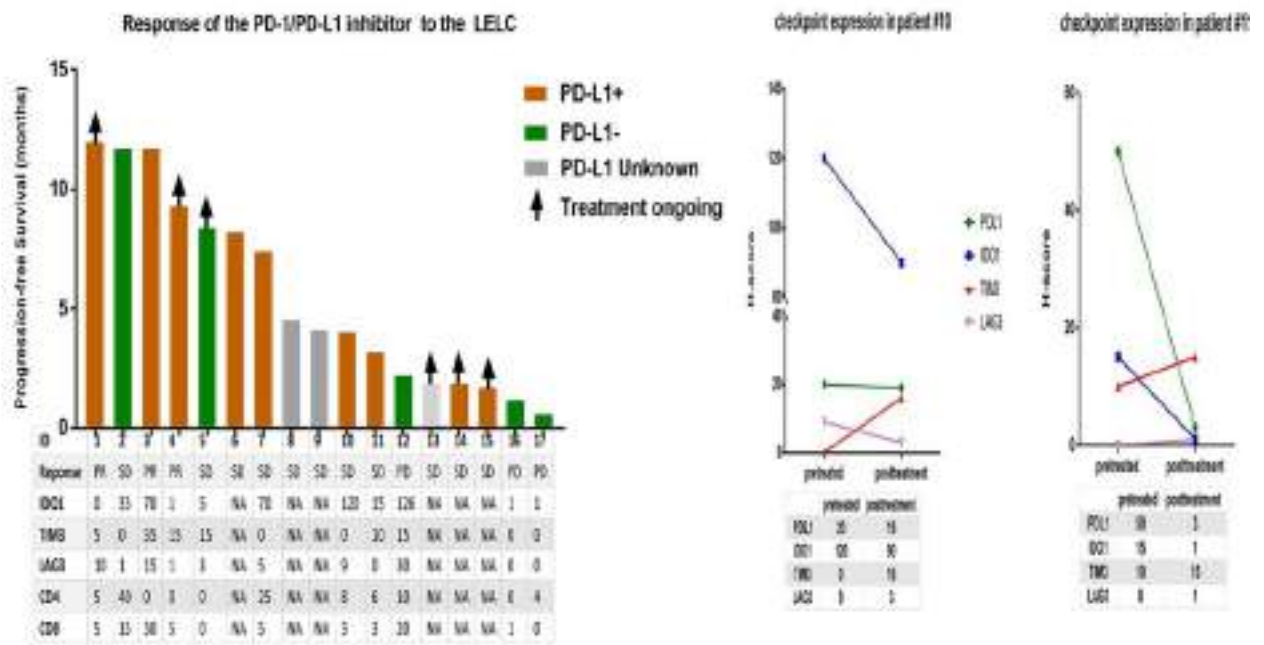
Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is Epstein-Barr (EB) virus related subtype of non-small-cell lung cancer. Evidence of immunotherapy in LELC is scarce. The role of immune markers in tumor microenvironment and their relation with the efficacy of PD-1/PD-L1 inhibitors in LELC remain poorly explored.Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is Epstein-Barr (EB) virus related subtype of non-small-cell lung cancer. Evidence of immunotherapy in LELC is scarce. The role of immune markers in tumor microenvironment and their relation with the efficacy of PD-1/PD-L1 inhibitors in LELC remain poorly explored. **Method:** A total of seventeen patients treated with PD-1/PD-L1 inhibitors in Guangdong Lung Cancer Institute were enrolled. We detected multiple immune markers including PD-L1, IDO1, TIM3, LAG3, CD4 and CD8 by immunohistochemistry in eleven of these patients. Dynamic changes of the checkpoint biomarkers in two patients (#10 and #11) treated with PD-1 inhibitors were analyzed. Tumors with 1% TPS (tumor proportion staining) were defined as PD-L1 positive. H-score of PD-L1, IDO1, TIM3 and LAG3 was calculated by multiplying percentage of positively stained cells and intensity score (0, absent; 1, weak; 2, moderate; 3, strong). For CD4 and CD8, the H-score equals the percentage of staining positive lymphocytes among all nucleated cells. **Result:** In the 17 patients, most of them suffered from lines of chemotherapy (only two patients (2/17, 11.8%) received PD-1/PD-L1 inhibitors as the first line therapy). There are eight males and nine females. The median age was 47 years (range from 13 to 63). All of them were stage IIIB and IV. Thirteen of seventeen patients received single agent PD-1/PD-L1 inhibitor. PD-1/PD-L1 inhibitor showed an 82.4% disease control rate and 17.6% objective response rate. The median progression free survival was 7.4 months. The overall survival was not reached. Biomarkers of IDO1, LAG3, and TIM3 were not mutually exclusive with PD-L1, and could be highly expressed in responder patients to PD1/PD-L1 inhibitors. Notably, TIM3 expression was up-regulated at disease progression in two patients treated with PD-1 inhibitor.



Conclusion: PD-1/PD-L1 inhibitors had preliminary good activity, and TIM3 up-regulation might be a mechanism of resistance to PD-1 inhibitors in advanced pulmonary LELC.

Keyword: lymphoepithelioma-like carcinoma; PD-1/PD-L1 inhibitors; Tumor micro environment; TIM3;

P1.04-43 PD-RAD: A TRANSLATIONAL STUDY INVESTIGATING PD-L1 EXPRESSION AFTER RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER - TRIAL IN PROGRESS

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Background: Radiotherapy (RT) is delivered to 30-50% of NSCLC patients. However, over half of patients progress following RT and mechanisms of resistance are poorly understood. RT has immune-modulatory properties such as the ability to upregulate tumour PD-L1 expression and can recalibrate the immune contexture. Blockade of the PD-1/PD-L1 axis has been shown to enhance the efficacy of RT in several pre-clinical models and the recent PACIFIC trial. Exploiting immuno-regulatory effects of RT therefore has the ability to enhance local and distant anti-cancer effects of RT, especially when combining RT with immunotherapies such as anti-PD-1 or costimulatory agonists. **Method:** PDRAD is a prospective UK multi-centre feasibility study of paired pre- and post-treatment biopsies in NSCLC patients receiving palliative or radical RT. The study will recruit up to 30 patients with inoperable disease that is accessible to core biopsy by CT or bronchoscopy within the proposed RT field. Patients with archival baseline histology containing sufficient tumour material are eligible. Consented patients undergo a repeat biopsy in the second week of RT (fig.1). Blood samples will be collected at baseline, repeat biopsy, and following RT to assess immune changes that may correlate with the tumour microenvironment (TME). PDRAD opened to recruitment in November 2018 and will continue recruitment over 16 months. Research aims include investigating: •Feasibility and acceptability of obtaining paired biopsies •Changes in the immune contexture in irradiated tumour and 'out of field' sites •Immune changes in the TME and peripheral blood •Interim feasibility results after recruitment of 15 patients will be presented at World Lung.

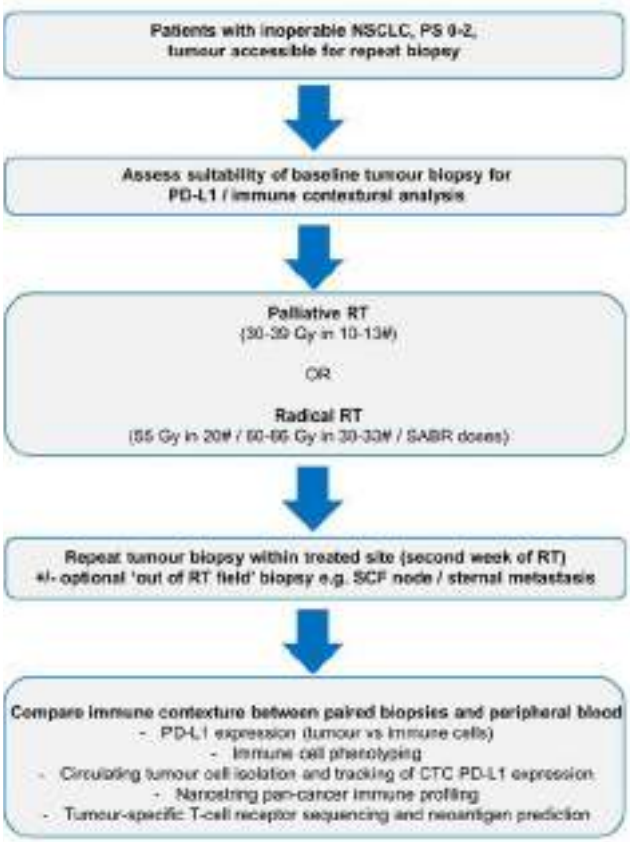

Fig. 1: Trial design

Result: Section not applicable **Conclusion:** We are at a pivotal point in evolving our knowledge of how the TME may influence responses to RT. The PDRAD study will help to influence further clinical trials, including combination studies with immunotherapies and predictive and prognostic biomarker development within the field.

Keywords: radiotherapy, Repeat biopsy, Immune contexture

P1.04-44 RADIOMICS FOR PREDICTING RESPONSE TO FIRST-LINE ANTI-PD1 THERAPY IN ADVANCED NSCLC

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Background: Radiomics is the high-throughput extraction of quantitative imaging features from medical images that can reflect underlying tumour pathophysiology. Imaging biomarkers have the potential to improve disease characterisation and predict patient outcomes. In this study, the utility of radiomic features to predict response and survival to first-line immune check-point inhibition with pembrolizumab in advanced non-small cell lung cancer (NSCLC) was explored. **Method:** Patients with Stage IIIB/IV NSCLC treated with first-line pembrolizumab and PD-L1 ≥50% were retrospectively identified and stratified by Best Overall Response (BOR) by RECIST 1.1. Patients with the primary tumour in situ and a contrast-enhanced CT thorax/abdomen (minimum 5mm CT slice thickness) at baseline were included. The single largest thoracic lesion was segmented in the diagnostic image using the Pinnacle radiotherapy treatment planning system. All tumour delineations were supervised by a highly experienced certified senior radiologist. Lesions <1cm, inflammatory and indeterminate lesions were excluded from delineation. A total of 47 radiomic features including shape, first-order and texture features were extracted from the segmented tumour using PyRadiomics. No pre-processing of the images was performed. Highly correlated features (r>0.85) were removed from further analysis. Least Absolute Shrinkage and Selection Operator (LASSO) feature selection was performed to find informative features that could predict either best overall response or overall survival. Univariate logistic regression and cox proportional hazard models were then used for an initial assessment of the potential of these features in predicting response and survival respectively. **Result:** Sixteen patients with evaluable

best overall response (partial response n=9, progressive disease n=7) were selected for the initial discovery-cohort. Mean age was 68 years with 63% adenocarcinoma histology. From the 47 features extracted, 32 were highly correlated to each other and were removed from further analysis. For predicting best overall response, LASSO selected 5 features with univariate logistic regression suggesting that tumour surface area to volume ratio might be informative (p=0.057, AUC of 0.83 (95% CI 0.61-1.0)). With respect to overall survival, LASSO selected 3 features with univariate cox regression suggesting the first-order feature skewness might be predictive (HR = 0.27, 95% CI 0.08-0.88, p=0.03). When split on the median skewness value the Kaplan-Meier plot showed a significant survival difference between high and low risk patients (p=0.007). **Conclusion:** Radiomic features extracted from baseline contrast-enhanced CT scans may have the potential to predict response and survival in patients treated with first-line pembrolizumab in advanced NSCLC. We emphasize the exploratory nature of these results given the very limited number of patients in the study. We are expanding this discovery cohort to further investigate and validate these results. Updated results will be presented at the meeting.

Keywords: Radiomics, Immunotherapy, NSCLC

P1.04-45 IMMUNE-ONCOLOGY GENE EXPRESSION PROFILES ALLOW LUNG CANCER PATIENTS' STRATIFICATION AND IDENTIFICATION OF RESPONDERS TO IMMUNOTHERAPY

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Background: Immune-checkpoint inhibitors (ICI) represent a new standard of care for Non-Small Cell Lung Cancer (NSCLC) patients. Beyond tumor PD-L1 protein expression, other biological parameters are emerging as potential predictive biomarkers. We evaluated high-throughput immune-related Gene Expression Profiles (GEP) in tumor tissue from ICI-treated patients, correlating immune activation data with clinical response to immunotherapy. **Method:** RNA was isolated from tumor tissues of 44 metastatic NSCLC patients treated with Nivolumab (as 2nd or 3rd line therapy) and collected from different Italian centers. The nCounter® PanCancer IO360™ Panel was applied on NanoString platform to analyze 770 genes involved in key immuno-oncology pathways. Clinical-pathological data, as well as best response to ICI treatment, have been collected. **Result:** Patients were dichotomized as responders (7 Partial Response and 19 Stable Disease) and non-responders (18 Progressive Disease). A pre-identified T-cell inflamed signature was evaluated at single gene level and the expression of *CCL5, CD27, CD276, CMKLR1, CXCL9, CXCR6, LAG3, NKG7, PDCD1LG2, PSMB10, TIGIT* was higher in the responder group, although not reaching statistical significance. Moreover, higher *STING, CGAS* and *IRF3* genes expression level appeared to be more commonly associated with non-responder patients. Considering the disease stage at the time of diagnosis, a different gene panel (CCL5, CD27, CD274, CD8A, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PSMB10, TIGIT) resulted to be more expressed in early and locally advanced (16 from stage I to IIIA) compared to metastatic (28 stage IV) tissue samples. **Conclusion:** A trend in differential expression patterns was observed between responders and non-responders NSCLC patients treated with Nivolumab and additional analyses on this cohort could reveal specific pathways able to predict unresponsiveness to ICI treatment. Different disease stage seems also to influence immune-related GEPs.

Keywords: gene expression profile, predictive biomarker, Immunotherapy

P1.04-46 PD-1 INHIBITOR PLUS CHEMOTHERAPY AS 2ND/SUBSEQUENT LINE SETTING DEMONSTRATE SUPERIOR EFFICACY OVER PD-1 INHIBITOR ALONE IN PTS OF ADVANCED NSCLC

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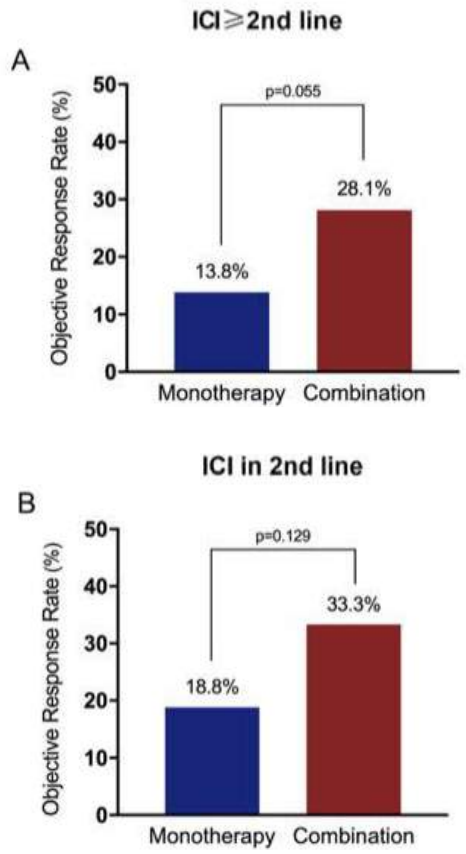
Background: PD-1/PD-L1 inhibitors have become standard of care as the 2nd-line setting and also approved as 1st line setting when combined with doublet chemotherapy in patients with advanced NSCLC. This study aims to compare the efficacy of PD-1 inhibitor plus chemotherapy with PD-1 inhibitor alone as 2nd/subsequent lines setting in patients with advanced NSCLC **Method:** Patients who received PD-1 inhibitor monotherapy or PD-1 inhibitor plus chemotherapy as 2nd/subsequent lines setting in Shanghai Pulmonary Hospital, Tongji University were retrospectively collected. Detailed clinicopathologic characteristics and therapeutic outcomes were analysis. **Result:** From January 2016 to February 2019, 148 patients who meet the criteria were included. Among them, 116 were in PD-1 inhibitor monotherapy group and 32 were in PD-1 inhibitor plus chemotherapy group. Chemotherapy regimens were pemetrexed(n=9), docetaxel(n=2), nab-paclitaxel(n=18) and gemcitabine(n=3). The baseline characteristics such as age, gender, smoking status, histology, PD-1 mono-antibodies, line of therapy were similar in the 2 groups. Combination group showed a favorable ORR (28.1% vs. 13.8%, p=0.055) and a significantly longer PFS(median 4.9 vs 2.5 months, p=0.005) compared with ICI monotherapy. Overall survial (OS) data was immature in the cutoff date of follow up. In the subgroup of 96 patients (monotherapy group n=69/ Combination group n=27) who were included as 2nd line setting, PD-1 inhibitor plus chemotherapy had significantly higher ORR(ORR:33.3% vs 18.8%, p=0.129) and longer PFS(median PFS: 4.9 vs 2.9 months, p=0.041).



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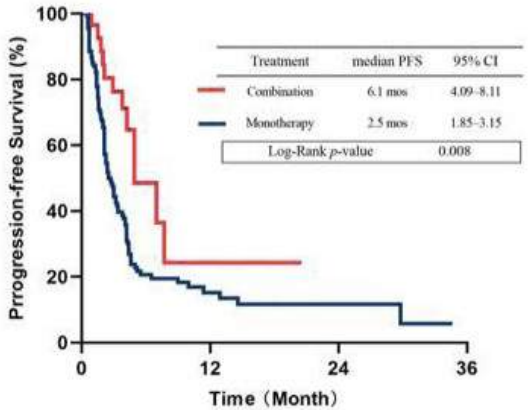

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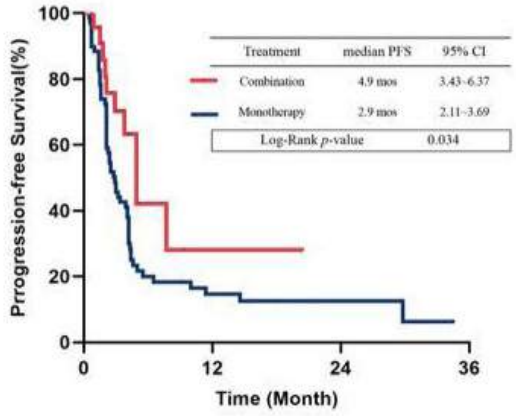

Conclusion: PD-1 inhibitor plus chemotherapy as 2nd/subsequent lines setting demonstrated superior efficacy over PD-1 inhibitor alone in patients with advanced NSCLC.

Keyword: immunotherapy, chemotherapy, NSCLC

P1.04-47 TUMOR MUTATION BURDEN THROUGH HYBRID CAPTURE – CIRCULATING TUMOR DNA MAY PREDICT RESPONSE TO IMMUNOTHERAPY IN NSCLC

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Background: Immunotherapy has become the therapy backbone for patients with NSCLC. Currently, prediction to therapy response is based on tissue biopsy biomarkers such as PD-L1 expression, tumor mutation burden (TMB), genomic alterations in *EGFR/ ALK/ROS1* and *KRAS/TP53/STK11* mutations, all competing for limited tissue biopsy samples. Therefore, we investigated whether these biomarkers can be detected from a non-invasive plasma sample. Challenges of assessment of TMB with cell-free DNA next-generation sequencing (NGS) include the limited size of liquid biopsy gene panels and the fact that low shedding of tumor DNA into circulation may fail to detect hypermutated tumors. **Method:** In this retrospective study, data was collected from 100 NSCLC patients treated in medical centers in Israel and USA between 2014 and 2018. NGS on ctDNA was used to evaluate whether mutational burden influence the response to immunotherapy in these patients. Response to immunotherapy was defined by a cutoff of four months of progression free survival (PFS). Liquid biopsy tests were obtained three months or less before immunotherapy treatment start. **Result:** Overall, 100 NSCLC patients underwent NGS on ctDNA. Clinical treatment information and full clinical data was available for 66 patients. 23 patients underwent liquid biopsy tests within a range of 3 months or less before immunotherapy initiation. 9 patients were considered responders and 14 patients progressors by a cutoff of 4 months PFS. Preliminary results showed that in the group of responders, the median TMB was 5 with a standard deviation of 5.49. An average TMB of 2.3 was calculated for the group of progressors with a standard deviation of 1.44. ctDNA signature will be further presented based on a 73-gene ctDNA NGS panel that adjusts for the degree of tumor shedding. **Conclusion:** ctDNA collection was feasible in 66 patients, amongst which 23 underwent liquid biopsy testing 3 months or less before immunotherapy treatment initiation. As the preliminary data is promising on this pilot cohort, we are planning on expending the cohort study and presenting a complex analysis that includes multifactorial mutation load approach that integrates TMB and prediction to immunotherapy response.

Keyword: Advanced NSCLC, Immunotherapy, cfDNA, Immuno-oncology

P1.04-48 PREDICTION OF TUMOR DOUBLING TIME OF LUNG ADENOCARCINOMA USING RADIOMICS MARGIN CHARACTERISTICS

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Background: Because shape or irregularity along the tumor perimeter can result from interactions between the tumor and the surrounding parenchyma, there could be a difference in tumor growth rate according to tumor margin or shape. However, no attempt has been made to evaluate the correlation between margin or shape features and tumor growth. Thus, the purpose of our study was to identify the tumor doubling time (DT) of lung adenocarcinomas (ADCs) through margin-related radiomic features. **Method:** We evaluated 52 lung ADC patients who had at least two computed tomographic (CT) examinations before curative resection. Volume-based DTs were calculated based on CT scans, and patients were divided into two groups according to the growth pattern of their ADCs (gradually growing tumors [GP I] vs. growing tumors with a temporary decrease in DT [GP II]). CT radiomic features reflecting margin characteristics were extracted, and radiomic features reflective of tumor DT were selected. **Result:** Among the 52 patients, 41 (78.8%) were assigned to GP I and 11 (21.2%) to GP II. Of the 94 radiomic features extracted, eccentricity, surface-to-volume ratio, LoG uniformity (σ = 3.5), and LoG skewness (σ = 0.5) were ultimately selected for tumor DT prediction. Selected radiomic features in GP I were surface-to-volume ratio, contrast, LoG uniformity (σ = 3.5), and LoG skewness (σ = 0.5), similar to those for total subjects, whereas the radiomic features in GP II were solidity, energy, and busyness. **Conclusion:** This study demonstrated the potential of margin-related radiomic features to predict tumor DT in lung ADCs. The results of this study may help predict tumor aggressiveness and behavior in patients with lung ADC and contribute to the development of treatment strategies

Keywords: lung adenocarcinoma, Radiomics, Tumor doubling time

P1.04-49 QUANTITATIVE COMPUTED TOMOGRAPHY (CT) BASED TEXTURE ANALYSIS (QTA) MIGHT IDENTIFY RESPONDERS TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Quantitative computed tomography (CT) based texture analysis (QTA) can characterize tumor heterogeneity, that might be associated with tumor infiltrating immune cells, including T-cells, a hallmark of ongoing immune surveillance with potential therapeutic importance. Therefore, QTA might represent prognostic

and predictive biomarker in terms of immunotherapy administration. In this study, we investigate the potential of tumoral QTA and a novel machine learning approach to differentiate responders from non-responders using baseline pre-treatment CT imaging in advanced-stage NSCLC patients treated with immune checkpoint inhibitors. **Method:** The QTA was applied separately on 50 contrast and 50 non-contrast CT images of histologically confirmed NSCLC patients. All patients included were treated with second-line immunotherapy (nivolumab, pembrolizumab or atezolizumab). Three-dimensional tumor segmentation was performed using the 4.10 version of 3D Slicer, and a total of 104 CT parameters from each CT image was obtained. For data pre-processing and standardization, we used the Sklearn machine learning library in Python programming language, reducing the number of CT parameters by Principal Component Analysis (PCA). The components thus obtained were further analyzed with hierarchical cluster analysis. According to QTA, responders were differentiated from non-responders based on naïve Bayes and k-means clustering. Response was defined as complete response, partial response, or stable disease at the first follow-up CT scan after immunotherapy initiation while non-response was defined as either visible signs of progression at time of or death prior to first follow-up CT scan. To verify the accurateness of the machine learning algorithms, leave-one-out cross-validation was performed. **Result:** Overall, we analyzed the CT scans of 88 advanced-stage NSCLC patients including 40 woman and 48 men. PCA identified eight major principal components which characterize the 104 CT features with an accuracy of 90%, suggesting no loss of essential CT-related information. We further evaluated these eight principal components and hierarchical cluster analysis clearly identified two major subgroups both in the contrast and non-contrast CT image group. According to the QTA, based on naïve Bayes clustering, the machine learning algorithm was able to differentiate responders from non-responders with an accuracy of 66.6% in the contrast CT image group but was not predictive in the non-contrast group. K-means clustering also showed an accuracy of 66.6%, thus confirming the results of the naïve Bayes clustering. **Conclusion:** Advanced-stage NSCLC patients can be classified into two major subgroups according to their CT features principal components with hierarchical cluster analysis using both contrast and non-contrast CT images. The clinical relevance of these principal component related subgroups should be further investigated in future prospective studies. By evaluating the contrast CT images, machine learning algorithms based on naïve Bayes and k-means clustering may predict the response to immunotherapy, however, further studies on "Big Data" are needed to define the exact prognostic value of QTA in NSCLC patients regarding immunotherapy administration. Application of QTA to prognostication for progression-free survival and overall survival is in progress.

Keyword: quantitative texture analysis, NSCLC, immunotherapy

P1.04-50 REAL WORLD EFFICACY OF PEMBROLIZUMAB OF AS A 1ST LINE TREATMENT IN METASTATIC NON-SMALL CELL LUNG CANCER WITH PD-L1 HIGH EXPRESSION

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Background: Pembrolizumab has demonstrated its usefulness as a primary treatment for metastatic non-small cell lung cancer (NSCLC) in Keynote-024 and Keynote-042. However, there is little information on the usefulness of pembrolizumab in clinical practice. The purpose of this study is to examine whether the efiicacy reported in Keynote-024 and Keynote-042 is reproduced in real world setting. **Method:** This study is retrospective multicenter trial. From Feb, 2017 to Dec, 2018, patients with histologically diagnosed, advanced, metastatic or recurrent NSCLC, TPS score of 50% or greater, and PS 0 or1, received pembrolizumab at 1st line were enrolled in this study. Clinical data were collected from electronic medical records and pharmacy databases. **Result:** Seventy-four consecutive patients received pembrolizumab monotherapy at seven centers between Febrary 2017 and December 2018. The median age was 72 years (range 51-89), 55 males, 59 smokers, 48 had adenocarcinomas. Nine patients had clinical stage III disease, 55 had IV, and 10 postoperative relapses. The antitumor effect was 6 cases for CR, 27 cases for PR, and 20 cases for SD. Overall response rates and disease control rates were 44.6% (95% confidence interval(CI): 33.3-55.9) and 71.6% (95%CI: 61.3-81.9), respectively. Progression-free survival and overall survival were 7.7 months (95%CI: 4.4-11.0) and 18.5 months, respectively. Immune-related adverse events were observed in 33 cases (44.6%). ILD was noted in 13.5% of cases. Two treatment related deaths were observed. **Conclusion:** In conclusion, our initial results in this real world cohort show pembrolizumab as a single agent therapy is a safe, effective treatment. Our results suggest that the results of Keynote-024 and Keynote-042 studies colud be reproduced in clinical practice.

Keywords: Pembrolizumab, 1st line treatment, PD-L1 high expression

P1.04-51 TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS FOR ADVANCED NSCLC IN ELDERLY AND FRAIL PATIENTS. A REAL-LIFE EXPERIENCE

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Background: Immune checkpoint inhibitors (ICIs) has changed the standard treatment in advanced stage non-small cell lung cancer (NSCLC). However, patients above 75 years and patients in performance status (PS) 2 are underrepresented in randomized clinical trials. Hence, the efficacy and safety of treatment in these large subgroups of patients remains unclear. We report a real-life study of such patients treated with immunotherapy in a second-line setting. **Method:** Data from consecutive patients with advanced NSCLC who had 2nd line treatment with ICIs at the University Hospitals in Copenhagen during November 2015 to March 2019 were obtained from medical records. Treatment efficacy and safety was evaluated, and treatment related adverse events (AEs) were registered. **Result:** A total of 224 NSCLC patients were treated with either nivolumab or pembrolizumab: The median follow up time of was 12.3 months. The median progression free survival (PFS) was 4.9 months, and median overall survival (OS) was 12.9 months CI [9.7-14.6]. The median age was 67.7 years, while 45 patients (20%) were 75 years or older. There were no significant difference when comparing patients ≥ 75 years *vs.* < 75 years with respect to PFS (5.3 *vs.* 4.9 months, p = 0.81) nor in OS (14.2 *vs.* 12.8 months, p = 0.93). PFS and OS were correlated with PS: The PFS was 7.7, 4.7 and 2.0 months (p = 0.0003) in PS 0, PS 1 and PS 2, respectively. OS was 20.9, 12.0 and 3.0 months (p > 0.0001) in PS0, PS1 and PS 2, respectively. AEs were reported in 183 patients (82%), among whom 44 patients (20%) experienced grade 3-5. There were no difference in AEs in younger patients compared to older ≥ 75 years (p = 0.18). The incidence of grade 3-5 AEs was significantly higher among patients in PS 2 (35%) compared to PS 0-1 (17%), (p < 0.001). **Conclusion:** NSCLC patients ≥ 75 years had efficacy and safety profiles in second-line ICIs comparable to those of younger patients. However, treatment with ICIs in patients with PS 2 was associated with a significant lower PFS and OS. The high risk of seriously AEs in patients with PS 2 is of concern and warrants further investigation.

Keywords: Lung cancer, Elderly patients, Immunotherapy

P1.04-52 THE ROLE OF BLOOD BIOMARKERS IN RADIATION THERAPY FOR THORACIC MALIGNANCIES

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Background: Radiation (RT) of malignant tumors has the potential to induce immunomodulatory and vascular effects, which can influence the anti-tumor immunity and normal tissue radiosensitivity. We prospectively evaluated the role of different chemokines and

cytokines in patients treated with radiotherapy for different thoracic malignancies concerning survival (OS) and development of radiation induced lung toxicity (RILT). **Method:** Fifty-six patients with lung cancer (n=41), esophageal cancer (n=14) or thymoma (n=1) treated either with conventionally fractionated (n=43) or hypo-fractionated (n=13) radiotherapy were enrolled prospectively in the study. The serum levels of IL-10, IFN-γ, IL-12p70, IL-13, IL-1β, IL-4, IL-6, IL-8, TNF-α, bFGF, Flt-1, PlGF, VEGF, VEGF-C, VEGF-D were analysed by multiplex array (MesoScale Discovery) and measured in a USA CLIA-certified core at MGH Boston.at predefined time points: before, during and at the end of treatment as well as in the first and second follow-up. Toxicities were scored according to common toxicity criteria for adverse events. **Result:** We observed an upregulation of IL-10, IFN-γ, PlGF, VEGF-D and a downregulation of IL-8, TNF-α, VEGF, VEGF-C during and at the end of radiotherapy. IL-6 was upregulated during radiotherapy and downregulated at the end of treatment and Flt-1 was downregulated during radiotherapy and upregulated at the end of treatment. Furthermore, the baseline concentrations of several chemokines correlated with OS such as IFN-γ, IL-13, IL-6, TNF-α, but couldn't be sustained after Bonferroni correction. On the contrary a higher IL-13 concentration during radiotherapy (p<0.000, HR 19.456, 95% CI 4.254-89.070), IL-6 (p<0.000, HR 1.055, 95% CI 1.024-1.086), IL-1β (p=0.004, HR 11.200, 95% CI 2.160-58.074), IL-8 (p=0.009, HR 1.014, 95% CI 1.003-1.024) and bFGF (p<0.000, HR 1.170, 95% CI 1.075-1.274) and of the IL-6 at the first follow up (p=0.001, HR 1.140, 95% CI 1.057-1.229) correlated with OS. Seventeen patients (30%) developed radiologic signs of RILT Grade≥1 but only two of them (3.6%) developed clinical symptoms (Grade 2). We could not find any association between the different serial blood biomarkers and a higher incidence of RILT. **Conclusion:** In our study early changes in blood biomarkers during radiotherapy could indicate an early immune response and might play a role on the outcome of the threatmentbut they don't seem to play a significant role in the development of early stage (grade 1) RILT.

Keywords: Immuno biomarkers, Thoracic radiation

P1.04-53 A HIGH PD-L1 EXPRESSION IN NON-SMALL CELL LUNG CANCER CORRELATES WITH EXPRESSION OF SPOP AND CD8 TUMOR-INFILTRATING LYMPHOCYTES

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Background: Immunotherapy that targets PD 1 pathway has emerged as a novel treatment modality for malignant diseases. Clinical trials have reported durable responses and long-term remissions using PD-1/PD-L1. However, despite promising clinical results, checkpoint blockade therapies are only successful in a subset of patients. Thus, it is crucial to more fully understand the mechanisms behind immunotherapies. Recently, it has been reported that PD-L1 expression can be regulated at both transcriptional and post-transcriptional levels, including HIF-1, STAT3, NF-κB, AP-1, cyclin-dependent kinase 4 (CDK4) and speckle-type POZ protein (SPOP). In this study, we focused on the regulation of PD-L1 expressionin lung cancer, and we investigated the association between the expression of PD-L1 and biomarkers in regard to clinical outcomes. **Method:** We investigated CDK4, CDK6 and SPOP expression of lung cancer, and CD4 and CD8 expression of tumor-infiltrating lymphocytes (TILs) by immunohistochemistry of 52 patients with non-small cell lung cancers who had undertaken an operation or chemotherapy from May 2008 to December 2018 and analyzed PD-L1 expression (negative:<1%, low expression:1-49%, high expression:≥50%). The staining intensity of CDK4, CDK6 and SPOP was scored as 0 (negative), 1 (weak), 2 (medium), and 3 (strong). Extent of staining was scored as 0 (0-10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), and 4 (76-100%) according to the percentages of the positive staining areas in relation to the whole cancer area. For CD4+ and CD8+ cells, a numbers of stained cells were counted semi-quantitatively in high-powered fields (400x). A numbers of CD8+ cells in tumor tissue were scored as 0 (0-5 cells/HPF), 1 (6-10 cells/HPF), 2 (11-25 cells/HPF), 3 (26-50 cells/HPF), and 4 (51- cells/HPF). The observed protein expression levels and TILs counts were analyzed for correlation to PD-L1 expression and clinicopathological parameters. **Result:** PD-L1 expression was observed in 33 (64%) patients of lung cancer, being low in 19 (37%) and high in 14 (27%). The positive rate of expression of SPOP was 42% in tumors with negative expression of DP-L1, 53% low expression and 14% high expression. That of CDK4, CDK6 and CD8 in tumor tissue was 79%, 79%, 57% and 53%, 63%, 43%, and 41%, 41%, 92%, respectively. The positive rate of SPOP of CDK4 positive group was significantly higher than that of CDK4 negative group (50% vs 7%, p=0.005). The positive rate of SPOP of high PD-L1 expression group was significantly lower than negative and low expression groups (14% vs 47%, p=0.03). CD8+ cell counts showed positive relation to PD-L1 expression. **Conclusion:** In previous report, CDK4/6 inhibitors treatment decreased SPOP protein abundance and elevated PD-L1 protein. Our data supported those findings that PD-L1 expression is regulated by CDK4 and SPOP. Then combination treatment with CDK4/6 inhibitors and PD-1/PD-L1 immune checkpoint blockade may have potential to enhance therapeutic efficacy for cancers.

Keyword: PD-L1, SPOP, CDK4

P1.04-54 INTER-TUMOR HETEROGENEITY OF PD-L1 EXPRESSIONS IN NON-SMALL CELL LUNG CANCER

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Background: Following to approval of Pembrolizumab for patients with advanced NSCLC, PD-L1 IHC 22C3 pharmDx (Dako) was adopted as a companion diagnostic test. While PD-L1 IHC 28-8 pharmDx (Dako) was established as a complementary diagnostic for Nivolumab. Recently many groups demonstrated the intra-tumor heterogeneity of these PD-L1 expressions, but there have been a few reports about the intra-patient or inter-tumor heterogeneity. We aimed to investigate the inter-tumor heterogeneity of PD-L1 IHC 22C3 and 28-8 pharmDx (Dako). **Method:** Between December 1, 2014 and May 7, 2018, total 517 patients with NSCLC underwent surgical resection at our hospital. We excluded all patients with no informed consent, with no lymph node metastasis, with chemotherapy/radiotherapy before surgery and with never enough volume of material for genetic testing. Finally 35 formalin-fixed paraffin-embedded primary tumors with paired metastatic lymph nodes were available in this study. After staining by PD-L1 IHC 22C3 and 28-8 pharmDx (Dako) respectively, we counted tumor cells exhibiting membrane staining and calculated Tumor Proportion Score (TPS). Afterward, all cases were classified into three subgroups as follows; No Expression (TPS: <1%), Low Expression (TPS: 1-49%) and High Expression (TPS: ≥50%). **Result:** Average age of 35 patients was 66.8 years old and there were 10 females (28.6%), 10 never smokers (28.6%), 27 adenocarcinomas (77.1%) and 11 tumors with EGFR mutation. The number of cases in No Expression, Low Expression and High Expression in 22C3 were 7 (20.0%), 22 (62.8%) and 6 (17.1%) in primary tumor, meanwhile 18 (51.4%), 13 (37.1%) and 4 (11.4%) in metastatic lymph node, respectively. The concordant rate was 28.6% between TPS subgroups in primary tumor and that in metastatic lymph node. About 28-8 antibody, No Expression, Low Expression and High Expression were 8 (22.9%), 21 (60.0%) and 6 (17.1%) in primary tumor, meanwhile 18 (51.4%), 11 (31.4%) and 6 (17.1%) in metastatic lymph node, respectively. The concordant rate was 31.4% between TPS subgroups in primary tumor and that in metastatic lymph node. **Conclusion:** Our result demonstrated apparent discrepancy of TPS between primary tumor and metastatic lymph node in both PD-L1 IHC 22C3 and 28-8.

Keywords: Checkpoint inhibitors, Immunotherapy, Programmed death ligand 1

P1.04-55 COMPARISON OF PD-L1 EXPRESSION STATUS BETWEEN PURE-SOLID VERSUS PART-SOLID TUMORS IN LUNG ADENOCARCINOMAS

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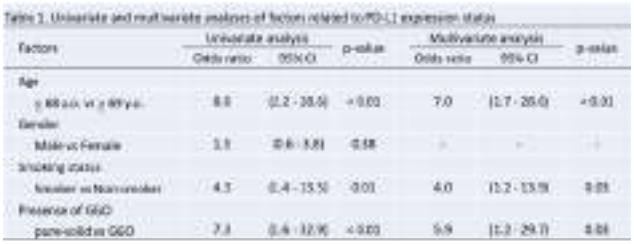
Background: Recent studies have reported clinicopathological and prognostic differences between lung adenocarcinomas with ground-glass opacity (GGO) versus those without GGO (pure-solid tumors). However, it is unknow if the expression status of PD-L1 protein differs between these two groups. **Method:** One-hundred twenty-four stage IA – IB lung adenocarcinoma patients who received pulmonary resection between 2007 – 2009 were included in this study. PD-L1 staining was performed in our previous study

using E1L3N antibody. PD-L1 status was classified as positive if 1% or more tumor cells showed membrane staining; and was classified as strong positive if 50% or more tumor cells did so. **Result:** Among 124 lung adenocarcinoma patients, 45 had lung adenocarcinomas with GGO and 79 had pure-solid lung adenocarcinomas. We observed no significant differences between these two groups in terms of clinical factors (gender, age, and smoking status). However, the rates of PD-L1 positive tumors (4% vs 25%, p < 0.01) and PD-L1 strong positive tumors (2% vs 16%, p = 0.02) were significantly lower in lung adenocarcinomas with GGO. In multivariate analyses, these correlations between the presence / absence of GGO and PD-L1 expression status were still evident as shown in Table 1.



Conclusion: Lung adenocarcinomas with GGO were less frequent to express PD-L1 compared to pure-solid lung adenocarcinomas.

Keywords: Biomarker, immunohistochemistry, PD-L1

P1.04-56 LANDSCAPE OF TUMOR MUTATIONAL BURDEN IN INDIAN NSCLC PATIENTS

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Background: Tumor mutational burden (TMB) can be defined as the total number of nonsynonymous mutations present in a tumor. High mutation load correlates with an immunogenic tumor microenvironment with increased expression of tumor specific neo-antigens that can be targeted by activated immune cells. Recent evidences have shown that certain tumor types such as NSCLCand melanoma with high tumor mutation rate respond well to immune check point inhibitors. TMB of a certain tumor type is associated with neoantigen load and outcome on immune check point inhibitors. The study focuses on using TMB as a predictive biomarker for response of Immune check point inhibitors. **Method:** The study population comprised of 53 NSCLC patients who had undergone comprehensive genomic profiling (CGP) using commercially available NGS test (Positive Select). **Result:** TMB calculation is done by measuring the number of somatic mutations occurring in the sequenced genes and extrapolating to the genome as a whole. In the present study, hybrid-capture based targeted next generation sequencing was used to estimate TMB as the total number of synonymous and non-synonymous mutations present at ≥5% allele frequency (after filtering) in the sequenced tumor genome. Results are expressed as mutations/megabase. Targeted sequencing of 350-cancer related genes was carried out on ctDNA/FFPE from the patients using the Illumina Next-seq platform. The target region includes >5000 coding exons of canonical transcript isoforms, >100 exons of noncanonical transcripts, as well as 35 introns of 15 recurrently rearranged genes. The bioinformatics analysis of the raw data was done using our trademark TEST pipeline to call out all four categories of genomic variants; SNVs, Indels, CNVs and Structural variants. The mean age of the patient population is 57 ± 11.25 years. The patient population had 34% females and rest were males. Most of the patients were recorded with metastatic disease. The analysis was performed on circulating tumor DNA sample (92% patients) and FFPE blocks (8% patients). Out of the 53 subjects, 4 (7.54%) patients were found to have TMB >10 mutations/megabase and were categorized as eligible candidates for showing a higher likelihood of benefit from immune check point inhibitors. Among the four samples showing high TMB, only one of the sample showed high microsatellite instability with the TMB being 11.12 mutations/megabase.

Important Actionable genomic alterations detected in NSCLC patients having high TMB

Patient Number	Actionable mutations	TMB (mut/megabase) and MSI status	Therapy recommendations
I	*KDR* [p.Q472H]	TMB=21.68 mut/megbase MSI=low	VEGF Inhibitors and immune check point inhibitors
II	*CDKN2B* [loss]	TMB= 33.4 mut/megbase MSI=low	CDK4/6 inhibitors and immune check point inhibitors
III	*MAP2K1* [p.Q56P-Subclonal]	TMB= 11.12 mut/megbase MSI=high	Immune check point inhibitors
IV	*PTEN* [C211*], *NOTCH4* [amplification]	TMB=20.44 mut/megabase MSI=low	mTOR inhibitors and immune check point inhibitors

Conclusion: The prevalence of high TMB was found in 7.5% Indian NSCLC patients. Testing for TMB and MSI in the above cases provided an option for treating the patients with immune check point inhibitors along with targeted therapy.

Keyword: Tumor Mutation Burden, NSCLC, NGS

P1.04-57 METRONOMIC DOSING OF CHEMOTHERAPY ALTERS ANTITUMOR IMMUNITY AND SYNERGIZES WITH PD-1/PD-L1 INHIBITION IN NON-SMALL CELL LUNG CANCER

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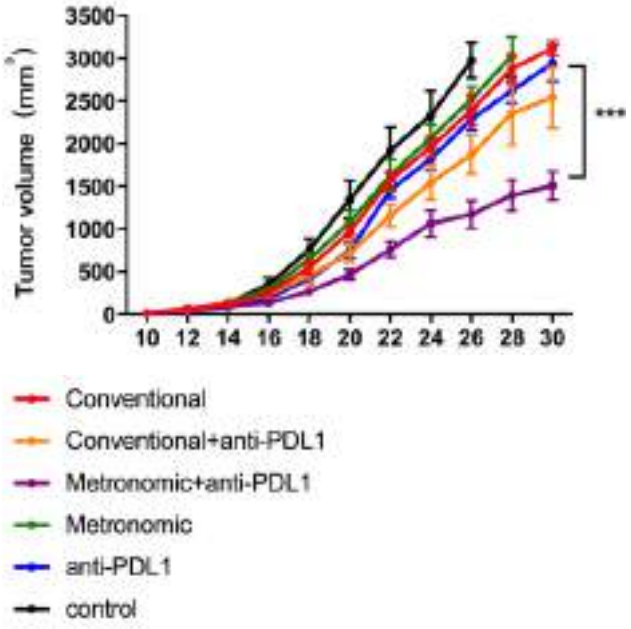
Background: The combination of immune checkpoint blockade with chemotherapy is currently under investigation as a promising strategy for the treatment of non-small cell lung cancer. Although it has been reported that metronomic dosing of cisplatin can be immune stimulating, the impact of its combination with anti-PD-1/PD-L1 immunotherapy for the treatment of lung cancer remains to be evaluated. Therefore, the current study aimed to explore whether combining low-dose continuous chemotherapy and anti-PD-L1 treatment can induce synergistic antitumor effect by enhancing antitumor immune response in murine lung cancer. **Method:** We evaluated the antitumor effects of conventional dose of cisplatin and low-dose metronomic dose of cisplatin as monotherapy or in combination with anti-PD-L1 monoclonal antibody in a murine lung cancer model using Lewis lung cancer cells (LLC). And the changes of immune components in tumor were tested in different treatment groups by flow cytometry and immunohistochemistry. **Result:**



The results showed that low-dose metronomic use of cisplatin could eradicate Foxp3⁺ regulatory T cells (Tregs) and myeloid derived suppressive cells (MDSCs). Furthermore, combining low-dose cisplatin and anti-PD-L1 therapy could not only increase the inflitration of $CD8^+$ T cells ,especially IFN-γ^+CD8^+ T cells, but also significantly reduce the expression of PD-1 and PD-L1. In a syngeneic mouse model of NSCLC, we observed that concurrent use of low-dose cisplatin and anti–PD-L1 delayed tumor growth and enhanced survival. **Conclusion:** Low-dose continuous cisplatin treatment can modify tumor immune microenvironment by eliminating immunosuppressive components like Tregs and MDSCs and enhance antitumor immune response, which can be enhanced by PD-1/PD-L1 blockade and therefore induced a synergistic anti-tumor effect.

Keywords: Lung cancer, Immunotherapy, Chemotherapy

P1.04-58 UNCOVERING THE TUMOR MICROENVIRONMENT OF KRAS-DRIVEN LUNG ADENOCARCINOMA: THE LINK BETWEEN TH17 SIGNALING AND B CELL

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Background: Non small cell lung cancer, been histologically classified into adenocarcinoma (AD) and squamous cell carcinoma, is one of the most deadly malignancy worldwide. Lung AD (LUAD) could benefit of a plethora of target therapies and, in the last few years, also of immunotherapies. Here we focused on a cohort of LUAD aiming to gain insights into the immune contexture of such a malignancy. **Method:** 20 patients affected by advanced LUAD, previously analyzed through the CE-IVD Oncomine solid tumor DNA kit, have been included in our cohort. DNA and RNA were isolated from 6 μm thick FFPE sections usingthe QIAamp DNA/RNA FFPE Tissue Kit (Qiagen). Two custom panels were designed using Ion Ampliseq Designer Tool. DNA and RNA libraries were prepared according to manufacturer's instructions. Torrent suite variant caller and Vardict tool were used to call variants, subsequently annotated with Annovar. RNA raw read counts were analyzed by DESeq2 R package. TIMER web-tool was used to deconvolve immune-cytotype composition and LUAD-TCGA dataset has been used to validate our findings. Immune infiltration results were validated with immunohistochemistry in an independent cohort. **Result:** We explored the mutational status of 41 genes and the expression of 94 genes, related to immune-checkpoint, inflammation and stromal microenvironment. Surprisingly, we found that our cohort has a very low mutational burden if we consider our panel as its surrogate. Regarding gene expression data, we identified 31 genes significantly deregulated in tumor tissues compared with a pool of normal pleura samples. Unsupervised hierarchical clustering of the deregulated genes is able to identify two clusters of tumor samples, differently enriched in alterations in actionable. In particular, we identified a cluster enriched in patients carrying KRAS alterations. GO/KEGG enrichment displayed terms related, as expected, to T cell differentiation but more interestingly term linked to Th17 lymphocytes. Thus, we perform in silico deconvolution through TIMER algorithm. Estimation performed on our gene expression matrix showed that, after stratification based both on cluster and KRAS mutational status, B cell infiltration is lower in KRAS-mutated enriched cluster. Notably, also in LUAD-TCGA dataset, B cell infiltration is significantly low in KRAS mutated patients. Such a finding has been validated in situ through immunohistochemistry in an independent cohort. Moreover, cases in LUAD-TCGA with low B cell infiltration have a significantly worse overall survival than those with higher levels. In our cohort we observed that cases belonging to cluster enriched in KRAS-mutated patients have a poor outcome. **Conclusion:** LUAD driven by KRAS mutation represents an unmet clinical need, being refractory to pharmacological inhibition. Our results link KRAS mutations to composition and in particular to B cell infiltration. The role of B cell in tumor microenvironment of lung cancer has been previously explored, demonstrating that low level of infiltration is related to short survival. Interestingly, we found that deregulated genes are enriched in GO/KEGG terms related to Th17, which, through CXCL13 signaling, support B cell recruitment. Thus, the present findings could be helpful in a better definition of immunotherapeutic approaches for KRAS mutated patients.

Keywords: KRAS, LUAD, B-Cell

P1.04-59 MODIFIED GLASGOW PROGNOSTIC SCORE PREDICT SURVIVAL AMONG NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint (ICP) inhibitors improved survival among patients (pts) with metastatic non-small cell lung cancer (mNSCLC). Modified Glasgow Prognostic Score (mGPS) is an inflammation-based score with prognostic value in lung cancer. We investigated predictive value of pre-treatment mGPS among mNSCLC pts treated with ICP inhibitors. **Method:** Data of mNSCLC pts treated with ICP inhibitors at Hospital São João, Porto, Portugal, were retrospectively collected. Pre-treatment mGPS was calculated using pre-treatment albumin and C-reactive protein. Survival was estimated with Kaplan-Meier method and curves were compared by log-rank test. Multivariate analysis was performed using Cox proportional hazard model. **Result:** 77pts were included, 71.4% were male and mean age was 66.2±9.7 years old. Most of pts had previous smoking history (77.9%) and an ECOG 0 or 1 (83.1%). Concerning tumour features, 69.5% were adenocarcinoma and 28.6% squamous cell carcinoma with a mean of PD-L1 expression of 47.6±34.3%. 10.4% had a driver mutation. Nivolumab was used in 71.4% and pembrolizumab in 28.6%. Partial response was achieved in 27.3%, stable disease in 31.2% and 39.0% had disease progression. Overall, progression-free survival (PFS) and overall survival (OS) were 5.0 (95% CI, 2.0-7.9) and 15.0 (95% CI, 8.4-21.6) months (mo), respectively. Adverse effects (AE) occurred in 26.0%. A lower mGPS was associated with superior OS (0: not reached; 1: 7.0 mo; 2: 3.0 mo, p=0.002) and PFS (0: not reached; 1: 4.0 mo; 2: 2.0 mo, p<0.001). In addition, ECOG 0-1was associated with superior OS (16.0 vs 3.0mo, p=0.011) and PFS (6.0 vs 2.0mo, p=0.023), comparing to ECOG 2-3. Better survival was also verified in pts with AE occurrence (OS: p=0.001 and PFS: p<0.001) and in pts with lower number of metastatic sites (OS: p=0.004 and PFS: p<0.001). In a multivariate model, adjusting for ECOG, number of metastatic sites and AE occurrence, lower mGPS was associated to a better survival, regarding OS (p=0.004) and PFS (p=0.002). **Conclusion:** Pre-treatment mGPS influenced OS and PFS and may represent a useful tool to predict survival in pts with mNSCLC treated with ICP inhibitors.

Keywords: Nsclc, Immune Checkpoint Inhibitors, mGPS

P1.04-60 IMPACT OF METASTATIC LOCATION ON SURVIVAL IN STAGE-IV NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH IMMUNOTHERAPY

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Background: Emerging preclinical data suggests that the heterogeneity in the metastatic site-specific tumor immune microenvironment, as well as organ specific mutational diversity, may impact antitumor response to immune checkpoint inhibition (ICI). However, there is a paucity of clinical data describing the efficacy of ICI across metastatic compartments. Therefore, we sought to elucidate the impact of the metastatic location on survival in ICI treated stage-IV NSCLC. **Method:** We conducted a retrospective review of 140 stage-IV NSCLC patients treated with ICI between 4/2015 to 12/2018 at East Carolina University Cancer Center. Any non-skeletal lesion >0.5 cm on computerized tomography at an extrapulmonary site was considered as metastasis. Bone liesions were identified based on bone scan or positron emission tomography. ICI consisted of nivolumab, pembrolizumab, atezolizumab, Nivolumab+ ipilimumab and concurrent chemo+ ICI. Targeted next-generation sequencing (NGS) using Caris life sciences platform was used to determine tumor molecular profile. PD-L1^{pos} was defined as ≥ 1% staining using 22c3 Dako assay. Tumor mutational burden (TMB) was measured by counting all somatic non-synonymous missense mutations using targeted NGS (592 genes). TMB-high (H) was defined as ≥ 10 mut/Mb. Chi-Square test compared categorical variables. Kaplan Meier method was used for progression-free survival (PFS) and overall survival (OS) analysis. **Result:** Median age at treatment was 64 years. Bone (Bo-44.3%) was the most common metastatic site followed by brain (Br-37.9%) and liver (L-17.1%). Majority of patients had an oligometastatic disease (58.6%) with Br only metastasis present in 30.0% and Bo only metastasis in 26.4%. L only metastasis was rare (4.3%) but more commonly associated with bone involvement (L+Bo) in 17.7%.TMB was assessed in 34.3% and PD-L1 in 46.4%. NGS identified TMB-high to be more prevalent in patients with Br metastasis compared to no-Br disease (84.6 vs 52.1%; p=0.02). Across metastatic sites, Br only metastasis had a greater proportion of TMB-high compared to Bo only (85.0 vs 33.3 %; p=0.01). L+Bo had lower median PFS vs. Br alone (3.2 vs 8.3 months; p<0.01) and a trend towards inferior PFS vs. Bo alone (3.2 vs 4.1 months; p=0.08). L+Bo also had shorter OS compared to Br alone (3.2 vs 10.2, p<0.01) and Bo alone (3.2 vs.8.8; p=0.047). Patients with >1 metastatic site had inferior PFS (9.4 vs 11.8 months ;p=0.04) and inferior OS (3.70 vs 11.0 months; p=0.01). 30.7% of the patients were treated with concurrent chemo+ICI. In the entire cohort, compared to ICI alone, concurrent chemo+ICI had significantly better median PFS (9.2 vs 4.3 months; p<0.01) and OS (Not reached vs 5.2 months; p <0.001). In patients with an oligometastatic disease, chemo+ICI also demonstrated improved OS for both Br only (Not reached vs 6.7 months; p=0.01) and Bo only disease (Not reached vs 4.8 months;p=0.06). **Conclusion:** Our data demonstrate non-uniform responses to ICI based on the site of metastasis and the number of metastatic sites. We observed Br to have a higher proportion of TMB-high with improved survival when treated with concurrent chemo+ICI. Further studies to identify metastatic site-specific biomarkers to optimally guide ICI related treatment decisions are required.

Keywords: Non-Small Cell Lung Cancer, Immune Checkpoint Inhibition, metastatic sites

P1.04-61 NEUTROPHIL-LYMPHOCYTE RATIO: A PREDICTIVE BIOMARKER OF IMMUNOTHERAPY IN LUNG CANCER?

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Background: Identifying predictive biomarkers of immunotherapy in advanced non-small cell lung cancer (NSCLC) is essential to select the patients that could benefit more from this revolutionary therapy. Besides PD-L1 expression, neutrophil-lymphocyte ratio (NLR) has been explored as a potential predictor of clinically meaningful outcomes. Aim: Assess if NLR is an independent predictor of response to immunotherapy in advanced NSCLC. **Method:** Retrospective study of patients with locally advanced or metastatic NSCLC treated with immunotherapy in the second or further lines setting in a Multidisciplinary Thoracic Tumor Unit between 2015 and 2018. Pre-treatment NLR was calculated from baseline peripheral blood cell counts. NLR was categorized as a binary variable: "low" (<5) or "high" (≥5). Cox regression models were used for overall survival (OS) and progression-free survival (PFS) analysis. **Result:** From a total of 63 patients, 49 were treated with nivolumab and 14 with pembrolizumab. At the beginning of immunotherapy, baseline patient characteristics were: men: 79.4%; median age (IQR): 62 (56-70) years; ever smokers: 82.5%; ECOG PS 0-1: 82.5%; adenocarcinoma: 63.5%; squamous cell carcinoma: 31.7% and NSCLC-NOS: 4.8%; stage IV: 76.2%; PD-L1 expression <1%: 47.6%. Twenty three patients (36.5%) received immunotherapy in the third or further lines of treatment. Median PFS and OS were 5 months (2-10) and 8 months (4-13), respectively. After adjusting for gender, age, tobacco habits, ECOG PS, histology and PD-L1 expression, "high" NLR was an independent predictive factor of worse PFS (HR 2.22; 95% CI 1.06-4.66; p 0.035) and OS (HR 2.74; 95% CI 1.19-6.30; p 0.017). **Conclusion:** In our cohort, patients with NLR≥5 had a higher risk of disease progression and death compared to those with NLR<5. NLR is an inexpensive and affordable biomarker that could help to predict response to immunotherapy. Further large prospective studies are needed to validate this biomarker and to establish the optimal cut-off level.

Keywords: Neutrophil-Lymphocyte Ratio, advanced non-small cell lung cancer, Immunotherapy

P1.04-62 NOMOGRAM BASED ON MULTIVARIABLE REGRESSION MODEL ESTIMATES THE OVERALL SURVIVAL OF NIVOLUMAB FOR PREVIOUSLY TREATED ADVANCED NSCLC

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Background: Nivolumab (Nivo) has demonstrated with its efficacy against metastatic non-small cell lung cancer (NSCLC). However, it has been also reported that Nivo does not show beneficial effects in approximately 80% of patients. The predictive ability of biomarkers still is yet unclear; thus identifying biomarkers which better predict overall survival (OS) of such patients treated with Nivo is crucial. In this study, we conducted multivariable cox regression analysis including biomarkers and clinical factors measured at the time of initiating treatment with Nivo to assess predictive ability of OS of patients. Results of the multivariable analysis were elucidated with a nomogram which estimates the OS of Nivo in previously treated patients with advanced NSCLC. **Method:** In this study, data for 201 patients treated with nivolumab during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We collected clinical data at the time of nivolumab treatment commencement, and we evaluated two programmed cell death ligand 1 (PD-L1) immunohistochemistry (IHC) assay systems (22C3 and 28-8). **Result:** The median age at the time of administration nivolumab was 68 years, 135 patients were male, 157 patients had a smoking history, and 152 patients had a performance status (PS) score of 0–1. 39 patients had EGFR (37) or ALK (2) mutation positive. For 22C3 and 28-8, 36.3% and 36.8% of patients were negative, 17.4% and 14.4% had PD-L1 status of 1-49%, and 11.9% and 14.9% had PD-L1 status of ≥50%, 34.3% and 33.8% had PD-L1 status of missing, respectively. Kendall's rank correlation coefficient between 22C3 and 28-8 was 0.8414. The median OS of all patients was 333 (95% confidence interval (CI): 116-520) days. In the multivariate analysis, PS score ≥2 (hazard ratio (HR): 2.23; 95%CI: 1.36-3.66 p<0.001), high LDH level at baseline (HR: 1.13 95%CI: 1.03-1.24; p=0.008, and progression disease (PD) of pre-treatment response (HR: 3.64 95%CI: 2.29-5.79 p<0.001) were significantly associated with poor OS. There was not significant distance between PD-L1 status and OS of Nivo. Based on these analyses, we created the nomogram to estimate the OS of Nivo in previously treated patients with advanced NSCLC. **Conclusion:** PS score ≥2, high LDH levels at baseline, and PD of pre-treatment response were predictive of poor

OS of Nivo, moreover the nomogram might be useful to estimate the OS of Nivo in previously treated patients with advanced NSCLC. (UMIN-ID: UMIN000025908)

Keywords: nivolumab, Nomogram, Non-Small Cell Lung Cancer

P1.04-63 CORRELATION OF MUTATIONS IN TP53, CDKN2A AND PIK3CA WITH VISTA EXPRESSION IN PLEOMORPHIC LUNG CARCINOMA

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Background: Pleomorphic Lung Carcinoma (PC) is a rare subtype of NSCLC poorly responsive to systemic therapy. VISTA is an immune checkpoint that negatively regulates T-cells and offers an alternative therapeutic approach to immune checkpoint manipulation. It has increased expression in the tumour microenvironment. We aimed to identify the genomic associations of PC with VISTA immunohistochemistry (IHC) expression and establish its correlation with PD-L1 IHC expression. **Method:** Histopathological assessment and diagnosis was confirmed for 42 cases of resected PCs from the Royal Brompton Hospital histopathology diagnostic archive. DNA was isolated and a targeted capture panel for next generation sequencing performed. Samples were stained with H&E to confirm diagnosis, VISTA (D1L2G) and PD-L1 (28-8) and scored as the proportion of positively stained cells. Normal lung acted as control. **Result:** VISTA was increased in tumour infiltrating immune cells compared to background lung and tumour (median: 33% (0-85) vs. 0% (0-15); vs. 0% (0-11); P<0.001). VISTA was upregulated on infiltrating immune cells of cases with variants in *TP53* (n=25, median 52.5% vs. 24% P=0.008) and *CDKN2A* (n=4, median 57.5% vs. 30%; P=0.068) but was reduced in cases with *PIK3CA* mutations (n=4; median 7% vs. 35%; P=0.029). There was no association of VISTA with PD-L1 expression (spearman rank: -0.19; P=0.22). Figure 1: Percent of VISTA staining of immune cells according to tumour mutation

		VISTA IHC		
	N =	Median	Range	
TP53 mutant	25	42.5	5 - 85	P = 0.008
TP53 wild-type	17	24	5 - 64	
CDK2NA mutant	4	57.5	37.5 - 69	P = 0.068
CDK2NA wild-type	38	30	5 - 85	
PIK3CA mutant	4	7	5 - 42.5	P = 0.029
PIK3CA wild-type	38	35	6 - 85	

Conclusion: VISTA is raised in infiltrating immune cells of tumours with *TP53* and *CDKN2A* mutations. This may suggest dampening of the immune reaction to tumours defective in cell cycle control. Conversely, tumours with PIK3CA mutations had reduced VISTA expression by infiltrating immune cells. VISTA and PD-L1 exhibited no association in their levels of expression and therefore offers a therapeutic opportunity.

Keywords: VISTA, PD-L1, Pleomorphic lung carcinoma

P1.04-64 THE OPPOSITE ROLE OF PD-L1 EXPRESSION IN EGFR MUTANT LUNG CANCER TREATED WITH PD-1 INHIBITOR BEFORE AND AFTER EGFR TKI: PILOT STUDY

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Background: Standard treatment of EGFR mutant lung cancer is EGFR tyrosine kinase inhibitor (TKI). But PD-1 inhibitor in EGFR mutant lung cancer is also effective treatment option. PD-L1 expression is suggested as predictive biomarker for drug efficacy, but in EGFR mutant lung cancer, PD-L1 expression change after TKI have not been established and their role in PD-1 inhibitor treatment was not studied well. **Method:** This study evaluated 18 EGFR mutant lung cancer patients treated with PD-1 inhibitor at St. Vincent hospital from April 2016 to January 2019. Following baseline data were recorded at the time of PD-1 inhibitor treatment: Age, Sex, ECOG performance status, PD-1 inhibitor type, line of treatment, lymphopenia, NLR (neutrophil-lymphocyte ratio), hyponatremia, presence of brain, liver and bone metastasis, EGFR status, PD-L1 expression. Progression free survival (PFS) and overall survival (OS) was evaluated and Cox survival analysis was used for these analyses. **Result:** Median age was 61 years old and female was predominant (66.7%). Nivolumab and pembrolizumab was treated in 11 (61.1%) and 7 (38.9%) patients, respectively. Lymphopenia (<1,000/microleter) was 8 (44.4%) and high NLR (≥ 3) was 9 (50.0%). Hyponatremia (135 mEq/L) was noted in 5 (27.8%) and metastasis of brain, liver and bone were 9 (50%), 5 (27.8%) and 8 (44.4%). Median PFS and OS were 42 days and 102 days, respectively. Although high PD-L1 expression (SP263 ≥10%) before EGFR TKI is not significant predictive factor (Hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.09-2.45, P-value: 0.368) for PFS, high expression of PD-L1 before EGFR TKI tend to have favorable outcome. But, high PD-L1 expression (SP263 ≥10%) after EGFR TKI is associated with poor PFS outcome (HR: 2.20, 95% CI: 0.42-11.53). Regarding OS, high PD-L1 expression (SP263 ≥10%) before EGFR TKI is associated with prolonged survival (HR: 0.47, 95% CI, 0.09-2.41, P-value: 0.362), although it is not statistically significant. But, high PD-L1 expression after EGFR TKI tend to have shorter survival (HR: 3.34, 95% CI: 0.64-17.51, P-value: 0.154). **Conclusion:** The role of PD-L1 expression between before EGFR TKI and after EGFR TKI is opposite. This study is small study as a pilot setting and further studies are needed to evaluate these findings.

Keywords: NSCLC, PD-L1 expression, EGFR TKI

P1.04-65 MICROENVIRONMENT-DERIVED ADAM28 IMPACTS THE ONSET OF LUNG CANCER

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Background: ADAM28 expression is upregulated in non-small cell lung carcinoma and correlated with cell proliferation and metastatic dissemination. Moreover, *in vivo* studies have shown that knockdown of ADAM28 in tumor cells decreased the primary tumor growth and formation of lung metastasis. Besides, ADAM28 is thought to be an important regulator of inflammatory signaling pathways as it sheds the pro-inflammatory cytokine, *pro-TNF-alpha*. ADAM28 protease also interacts with integrins and the P-selectin glycoprotein ligand-1 leading to inflammatory cell migration. Altogether, these findings suggest that ADAM28 contributes to cellular mechanisms leading to cancer development and progression. **Method:** This study aims to characterize the effects of microenvironment-derived ADAM28 on lung metastasis formation. To achieve this purpose, we generated *ADAM28*$^{-/-}$ mice into two different mouse strains (C57BL/6 and BALB/c). Lung metastatic dissemination was assessed in both *ADAM28*$^{-/-}$ and wild-type (WT) mice after intravenous injection of Lewis Lung Carcinoma cells, B16K1 melanoma cells or 4T1 breast carcinoma cells. As ADAM28 promotes leukocyte transendothelial migration, lymphocyte subtypes implicated in tumor cytotoxicity or in regulation of immune response were studied by flow cytometry. **Result:** An unexpected increased tumor burden was found in lungs of *ADAM28*$^{-/-}$ mice as compared to WT mice. Flow cytometry analysis revealed that less CD8$^+$ T were infiltrated within lungs of *ADAM28*$^{-/-}$ tumor-bearing mice. Moreover, a reduced CD8$^+$ T cell population was observed in the spleen of naïve *ADAM28*$^{-/-}$ mice that is not caused by an impaired T cell maturation in the thymus. *Ex vivo* assays demonstrated that intrinsic properties of CD8$^+$ T cells from *ADAM28*$^{-/-}$ mice were not affected by ADAM28 deficiency as their proliferation, migration and activation was similar. Besides, we found no expression of ADAM28 in isolated CD8$^+$ T cells from the spleen of *ADAM28*$^{-/-}$ and WT mice. Therefore, we hypothesized that ADAM28 indirectly modulates the anti-tumor cytotoxic immune response. We also found that ADAM28 depletion is associated with a reduced infiltration of NK cell within lungs of *ADAM28*$^{-/-}$ tumor-bearing mice. **Conclusion:** Our results demonstrate a protective effect of microenvironment-derived ADAM28 by regulating the tumor-associated immune response.

Keyword: ADAM28, lung cancer, CD8

POSTERS

P1.04-66 THE PERCENTAGE OF PD-L1 BESIDES 50% POSITIVITY PREDICTS OBJECTIVE RESPONSE TO PEMBROLIZUMAB IN NON-SMALL CELL LUNG CANCER

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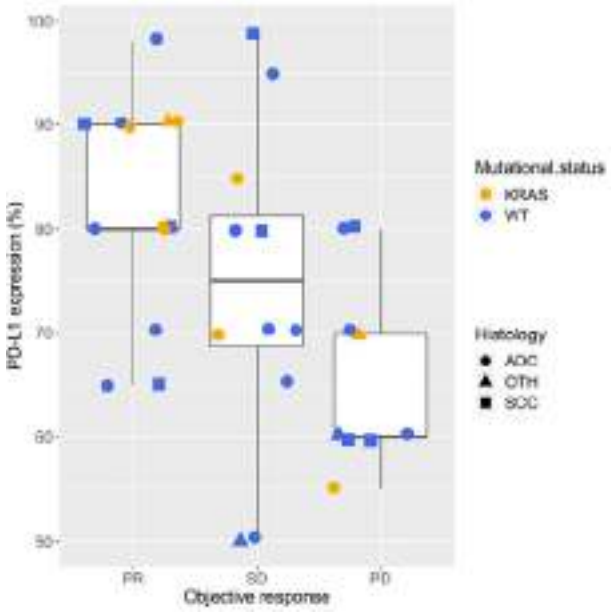
Background: Pembrolizumab is the first-line standard of care for advanced Non-Small Cell Lung Cancer (NSCLC) that have a PD-L1 expression level greater than 50%. In this prospective monocentric study, we evaluated how the expression levels of PD-L1 above 50% impact on the objective response rate. **Method:** Thirty-four advanced NSCLC patients with a PD-L1 expression level greater than 50% treated with Pembrolizumab in first-line setting between 2017 and 2019 were enrolled in this study. Patient and tumor characteristics were correlated with treatment outcomes. Patients clinical evaluation has been performed every 3 months from the beginning of treatment. Responses were defined according to the Response Evaluation Criteria in the Solid Tumors guidelines, version 1.1. Tumor assessments were performed locally. The mutational status of *KRAS, BRAF, NRAS, PIK3CA, ALK, ERBB2, DDR2, MAP2K1, EGFR* and *RET* was determined using a Mass Spectrometry assay. PD-L1 expression levels among the objective response groups were compared by Kruskal-Wallis test. A logistic regression model was used to evaluate the impact of PD-L1 expression levels above 50% on the objective response using mutational status, age, smoking habits, presence of toxicities, performance score and histology as confounders. **Result:** Thirteen patients had partial response (PR), 12 stable disease (SD) and nine progression disease (PD). Nine out of 34 tumours harboured *KRAS* mutations; no alterations were found in the other tested genes. PD-L1 expression levels were different among the objective response groups (P=0.01) with the PR and PD groups having the highest (median 80%, IQ range 80-90%) and the lowest (median 60%, IQ range 60-70%) expression respectively (Figure 1). In the multivariate analysis, PD-L1 level was the only significant predictor of objective response (P=0.03) with an odds ratio of 0.91 (95%CI 0.81-0.98).



Conclusion: In our series, PD-L1 expression above 50% confirmed to be an imperfect biomarker; however, the higher is the expression level the better is the objective response. For this reason, it could be relevant to provide clinicians with the exact PD-L1 percentage. Further investigations are warranted to define the best cut-off to select patients for monotherapy or combination with chemotherapy.

Keyword: lung cancer, PD-L1, immunotherapy

P1.04-67 FIRST-LINE IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) – A NETWORK META-ANALYSIS BY PD-L1

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Background: Emerging trials suggested survival benefits of first-line immune checkpoint inhibitors (ICIs) alone or in combination with chemotherapy in advanced NSCLC. However, little is known about the head-to-head comparisons of different ICIs and their relative effects at different PD-L1 expression levels. Here, we compared overall survival (OS) with ICIs head-to-head in a network meta-analysis and computed rankings of ICIs by PD-L1 expression levels. **Method:** PubMed and conference abstracts were searched for randomized clinical trials evaluating first-line ICI alone or in combination with chemotherapy in advanced NSCLC. We excluded studies assessing other trigger biomarkers (e.g. TMB). Bayesian network meta-estimates were computed by pooling reported OS hazard ratios (HRs) on the logarithmic scale and incorporation of both within and between studies heterogeneity. Treatment rankings by PD-L1 expression levels were compared in terms of surface under the cumulative ranking curve (SUCRA), probability best, probability better than chemotherapy, and posterior HR with corresponding 95% credible interval (CrI). **Result:** Seven trials were included in network meta-analysis. Pembrolizumab+chemotherapy was ranked to have the best OS benefit with HR ≤0.60 and >99% probability to outperform standard chemotherapy across all PD-L1 expression categories. Atezolizumab+chemotherapy and pembrolizumab monotherapy showed >95% probability to outperform standard chemotherapy in PD-L1≥50%. Nivolumab monotherapy showed little to no benefit across PD-L1 categories. Head-to-head comparisons of pembrolizumab+chemotherapy versus pembrolizumab monotherapy were HR 0.76 (0.48-1.19) for PD-L1≥50%. Detailed meta-estimates by PD-L1 expression for ICI alone or in combination with chemotherapy versus standard chemotherapy are provided in table below.

Treatment	PD-L1 expression	OS HR (95% CrI)	Probability better than standard chemotherapy
Pembrolizumab+chemotherapy	≥50%	0.51 (0.34-0.75)	> 99%
	1-49%	0.56 (0.39-0.81)	> 99%
	≥1%	0.55 (0.41-0.73)	> 99%
	<1%	0.60 (0.42-0.85)	> 99%
Atezolizumab+chemotherapy (include immune-cell cut-offs)	≥50%	0.70 (0.47-1.05)	96%
	1-49%	1.03 (0.74-1.42)	43%
	<1%	0.83 (0.66-1.06)	93%
Pembrolizumab	≥50%	0.67 (0.53-0.83)	> 99%
	1-49%	0.92 (0.69-1.23)	73%
	≥1%	0.81 (0.63-1.04)	95%
Nivolumab	≥50%	0.90 (0.60-1.36)	70%
	≥1%	1.08 (0.80-1.46)	30%

Conclusion: Pembrolizumab+chemotherapy demonstrated best survival benefit compared to other ICIs across all PD-L1 expression levels in the first-line treatment of advanced NSCLC.

Keywords: Pembrolizumab, Atezolizumab, cost-effectiveness

P1.04-68 LIVER METASTASES PREDICTS POORER PROGNOSIS IN ADVANCED NSCLC PATIENTS WHO RECEIVING NIVOLUMAB MONOTHERAPY

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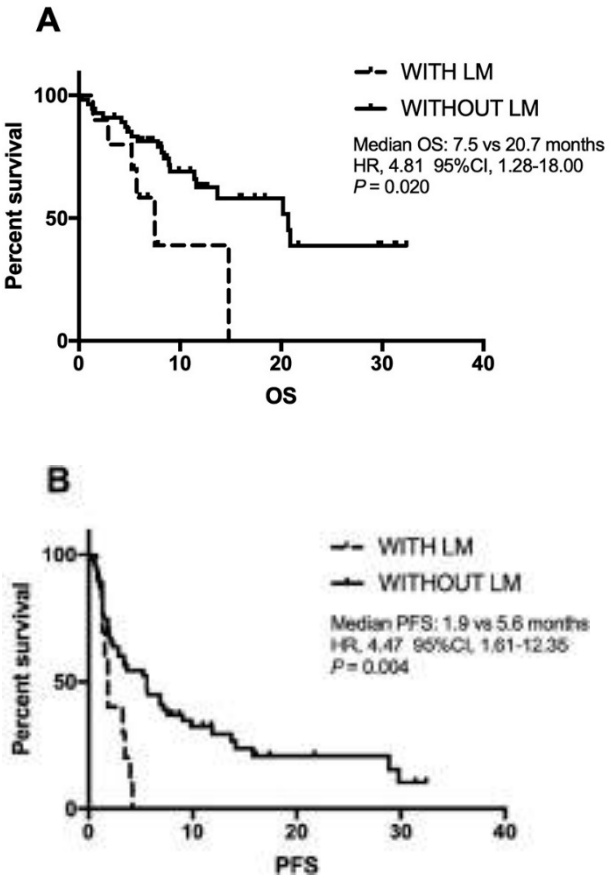
Background: Nivolumab is a fully human IgG4 monoclonal antibody targeting the programmed death-1 (PD-1). It's a standard second-line treatment for advanced NSCLC. Liver metastases(LM) is one of the worst prognostic NSCLC metastatic sites, but the attention to LM is far lower than brain metastases and bone metastases. **Method:** Patients with stage IIIB-IV NSCLC treated with second-line or later nivolumab monotherapy were retrospectively collected from January 2016 to July 2018. The patients were divided into two cohorts based on the presence or absence of LM at the time of first dose. Study endpoints included OS and PFS. **Result:** 65 patients were included, including 10 patients with and 55 patients without LM. Baseline characteristics of the two cohorts were comparable, as shown in the below table.

Characteristic	*All*	*LM (n=10)*	*Without LM (n=55)*	*P-Value*
Sex(Female/Male)	16/49	2/8	14/41	0.999
Mean age (years)	59.0±10.2	60.1±8.0	58.8±10.5	0.713
ECOG PS				0.999
0-1	59	9	50	
⩾2	6	1	5	
Histologic subtype				0.203
Squamous carcinoma	26	2	24	
Adenocarcinoma	36	7	29	
Others	3	1	2	
Stage				0.999
IV	62	10	52	
IIIB/IIIC	3	0	3	
Lines of therapy				0.673
2nd Line	53	9	44	
⩾3rd Line	12	1	11	
Driver gene status				0.580
EGFR mutations	4	0	4	
KRAS mutations	4	1	3	
Other mutations	5	0	5	
Driver gene negative	27	6	21	
Unknown	25	3	22	
Other metastatic sites				0.958
Central nervous system	24	4	20	
Bone	20	2	18	
Adrenal gland	6	0	6	
Intrathoracic	47	6	41	
Other/unspecified	9	1	8	

The median OS of the patients with and without LM was 7.5 and 20.7 months, respectively(HR =4.81:95%CI, 1.28-18.00:p=0.020). Their median PFS was 1.9 and 5.6 months, respectively(HR =4.47:95%CI, 1.61-12.35:p=0.004). COX multivariate regression analysis suggested LM was an independent prognostic factor. Kaplan-Meier curves of OS and PFS were shown in the below figure.



Conclusion: The outcome of advanced NSCLC patients with LM treated with Nivolumab monotherapy is relatively poor compared with those without LM.

Keywords: Non-Small Cell Lung Cancer, liver metastases, nivolumab

P1.04-69 MODELLING THE IMMUNOSUPPRESSIVE DIFFERENCE OF SBRT AND CRT BY SIMULATING THE DOSE TO CIRCULATING LYMPHOCYTES IN NON-SMALL CELL LUNG CANCER

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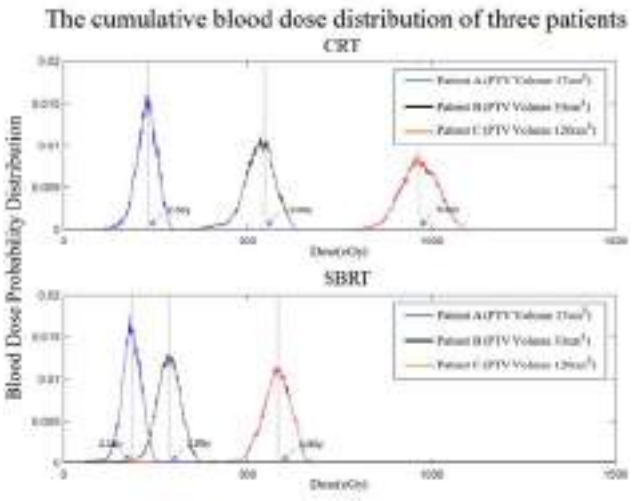
Background: Radiation-dose delivered to circulating lymphocyte (CL) has detrimental effect on immune system for cancer patients. Our study established a model to compare the cumulative dose on CL of patients with conventional fractionation radiotherapy (CRT) and stereotactic body radiation therapy (SBRT) in lung cancer with different target volume. **Method:** The improved model is based on convolution algorithm suggested by Yovino(Cancer Investigation, 2013). The current blood DVHs of each organ were multiplied with treatment field DVH to generate original DVHs. During one second, 0.6% of whole-body blood circulates through each organ and rest body according to blood circulating pattern and then new DVHs of organ were generated. The new DVHs would be used for next second's calculation with treatment field DVH. Conventional fractionated non-small cell lung cancer plan 60Gy (30 fractions*2.0Gy) and SBRT plan 50Gy (5fractions*10Gy) are constructed for three patients with different target volumes. The primary endpoint is peak cumulative blood dose (PCBC). **Result:** PCBC of three patients with CRT and SBRT were calculated as Figure 1. PCBC with CRT to circulating lymphocyte (CL) were 2.5Gy, 5.6Gy, 9.5Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively. And PCBC with SBRT to circulating lymphocyte (CL) were 2.1Gy, 2.9Gy, 6.0Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively. PCBC gap of SBRT to circulating lymphocyte (CL) was decreased 0.4Gy, 2.7Gy, 3.5Gy in PTV-volume 17cm^3, 33cm^3, 120cm^3, respectively.



Conclusion: An improved simulation-model was established, SBRT, compared to CRT, will lead to decreased cumulative dose on CL, which may cause less impact on immune system with the enlargement of PTV-volume.

Keywords: Immunosuppressive, Stereotactic body radiation therapy (SBRT), Conventional fractionation radiotherapy (CRT)

P1.04-70 APPLICATION OF TUMOR KINETICS FOR EVALUATION OF HYPERPROGRESSION IN IMMUNE CHECKPOINT INHIBITOR TREATMENT FOR NON-SMALL CELL LUNG CANCER

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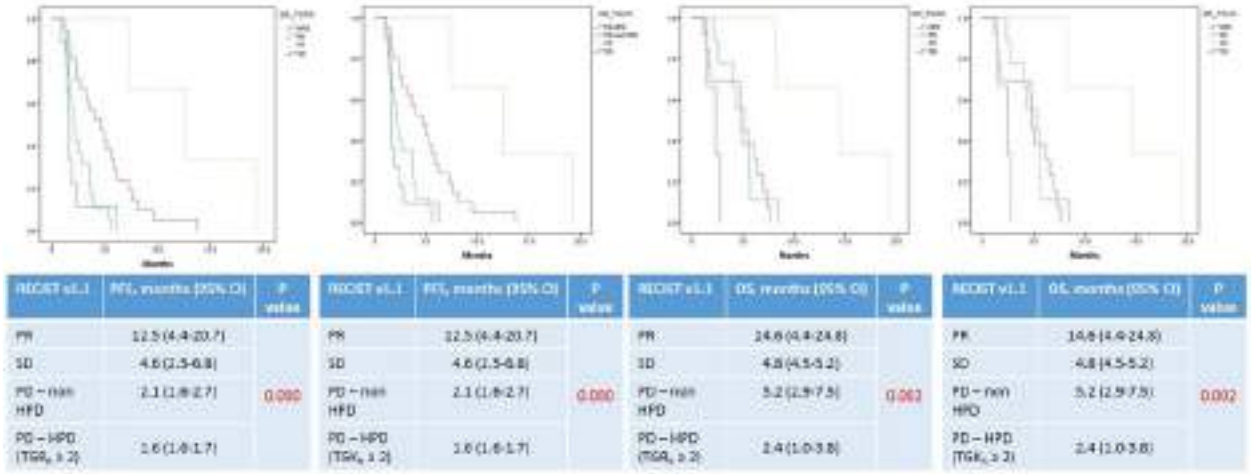
Background: Immune checkpoint inhibitors (ICIs) have suggested substantial options for treatment in advanced non-small cell lung cancer (NSCLC) without driver oncogenes. However, existing criteria for response assessment have limitations in differentiating categories of disease progression upon ICI treatment: primary resistance, pseudoprogression or hyperprogression (HPD). This study was aimed to investigate a real-world feasibility of pre- and on-treatment tumor kinetics for ICIs-specific response assessment in NSCLC. **Method:** We retrospectively recruited stage III/IV NSCLC patients treated with anti-PD-1/PD-L1 monotherapy after failure of first-line platinum-doublet chemotherapy (n=91) between June 2016 and October 2018. Based on medical records from response-evaluable patients, we analyzed tumor kinetics prior and upon ICI treatment using ratio of tumor growth rate (TGR ratio, TGR_R), tumor growth kinetics (TGK ratio, TGK_R) and difference in TGR (delta TGR, ΔTGR), respectively. HPD was defined as $TGR_R \geq 2$, $TGK_R \geq 2$ and ΔTGR >50%. **Result:** After excluding 18 patients without CT scan after start of ICIs, 73 patients were enrolled. Of response-evaluable patients, 47 patients (64%) stopped ICI treatment due to disease progression or death. Overall response rate by RECIST v1.1 was 16.4% (12/73) and disease control rate was 62% (45/73). HPD patients was 12% (9/73) and 15% (11/73) when defined by TGR_R and TGK_R, respectively. There was no HPD patients defined by ΔTGR. HPD patients classified by each criterion were associated with shorter median progression-free survival (PFS) according to iRECIST ($TGR_R \geq 2$, 1.6 vs 2.1 months, p<0.001; $TGK_R \geq 2$, 1.6 vs 2.1 months, p<0.001) and median overall survival (OS) than non-HPD-PD patients ($TGR_R \geq 2$, 2.4 vs 5.2 months, p=0.002; $TGK_R \geq 2$, 2.4 vs 5.2 months, p=0.002). HPD was not associated with age, sex, histology, stage, brain metastasis, nor PD-L1 expression at baseline. There was no pseudoprogression in patients classified as HPD.



RECIST v1.1	PFS, months (95% CI)	P value
PR	12.5 (4.4-20.7)	
SD	4.6 (2.5-6.8)	
PD – non HPD	2.1 (1.8-2.7)	0.000
PD – HPD ($TGR_R \geq 2$)	1.6 (1.0-1.7)	

RECIST v1.1	PFS, months (95% CI)	P value
PR	12.5 (4.4-20.7)	
SD	4.6 (2.5-6.8)	
PD – non HPD	2.1 (1.8-2.7)	0.000
PD – HPD ($TGK_R \geq 2$)	1.6 (1.0-1.7)	

RECIST v1.1	OS, months (95% CI)	P value
PR	24.6 (4.4-24.8)	
SD	4.8 (4.5-5.2)	
PD – non HPD	5.2 (2.9-7.5)	0.002
PD – HPD ($TGR_R \geq 2$)	2.4 (1.0-3.8)	

RECIST v1.1	OS, months (95% CI)	P value
PR	24.6 (4.4-24.8)	
SD	4.8 (4.5-5.2)	
PD – non HPD	5.2 (2.9-7.5)	0.002
PD – HPD ($TGK_R \geq 2$)	2.4 (1.0-3.8)	

Conclusion: HPD defined by pre- and on-treatment tumor kinetics was observed in 12-15% of patients with advanced NSCLC treated with second-line ICI monotherapy, and correlated with shorter PFS and OS. TGR and TGK could classify HPD patients from non-HPD PD with similar discriminability. Further studies are needed to investigate clinical and molecular determinants that distinguish HPD from non-HPD PD and pseuoprogression.

Keywords: Immune Checkpoint Inhibitors, hyperprogression, tumor kinetics

POSTERS

P1.04-71 TUMOR BURDEN IS NOT ASSOCIATED WITH EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN ADVANCED LUNG CANCER

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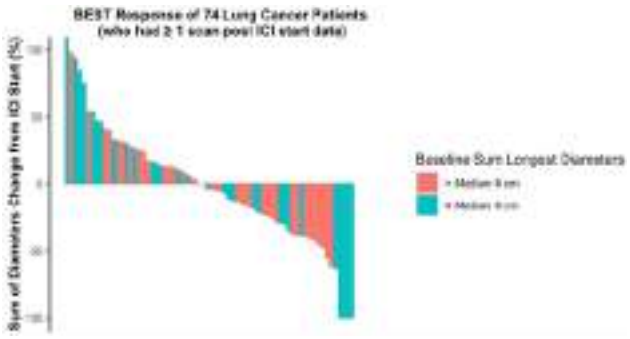
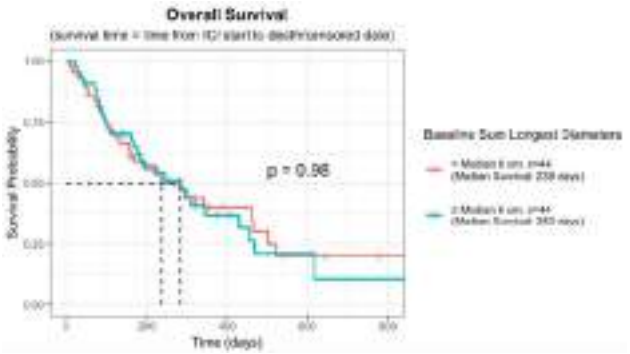
Background: Tumor bulk has long been cited as an impediment to efficacy of certain immunotherapeutic agents, such as vaccines. However, the association between tumor burden and efficacy of immune checkpoint inhibitors (ICI) is unknown. **Method:** We prospectively enrolled patients with diverse cancer types treated with immune checkpoint inhibitors on a registry trial. Demographic, disease, and treatment data were collected on patients with advanced non-small lung cancer (NSCLC). Imaging studies (predominantly computed tomography) were reviewed, and tumor dimensions were recorded according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Associations between tumor number and dimensions, and radiographic response, progression-free survival (PFS), and overall survival (OS) were determined using log-rank tests, cox proportional-hazard regression, and logistic regression. **Result:** Eighty-nine patients treated with ICI (without concurrent or sequential chemotherapy or radiation therapy) were included in the analysis. Median baseline sum of largest diameters (BSLD) was 6 cm; median baseline largest single diameter was 3 cm; median number for both target and non-target lesions was 2. There was no significant difference between cases with BSLD ≤6 cm and >6 cm for response rate (OR=1.06; *P*=0.94) (Figure 1), PFS (HR 0.99; 95% CI, 0.60-1.64; *P*=0.97), or OS (HR 0.99; 95% CI, 0.59-1.68; *P*=0.98) (Figure 2). No significant differences were observed for these endpoints when cases were considered according to largest single diameter, number of target lesions, or number of non-target lesions.





Conclusion: Although tumor burden was considered a potential mediator of efficacy of vaccines and other early immunotherapies, it does not appear to impact outcomes from ICI.

Keywords: Computed tomography, Lung cancer, Immunotherapy

P1.04-72 TUMOR MUTATIONAL BURDEN AS A POTENTIAL PREDICTIVE BIOMARKER OF RESPONSE TO PD-1/PD-L1 BLOCKADE IN NON-SMALL CELL LUNG CANCER

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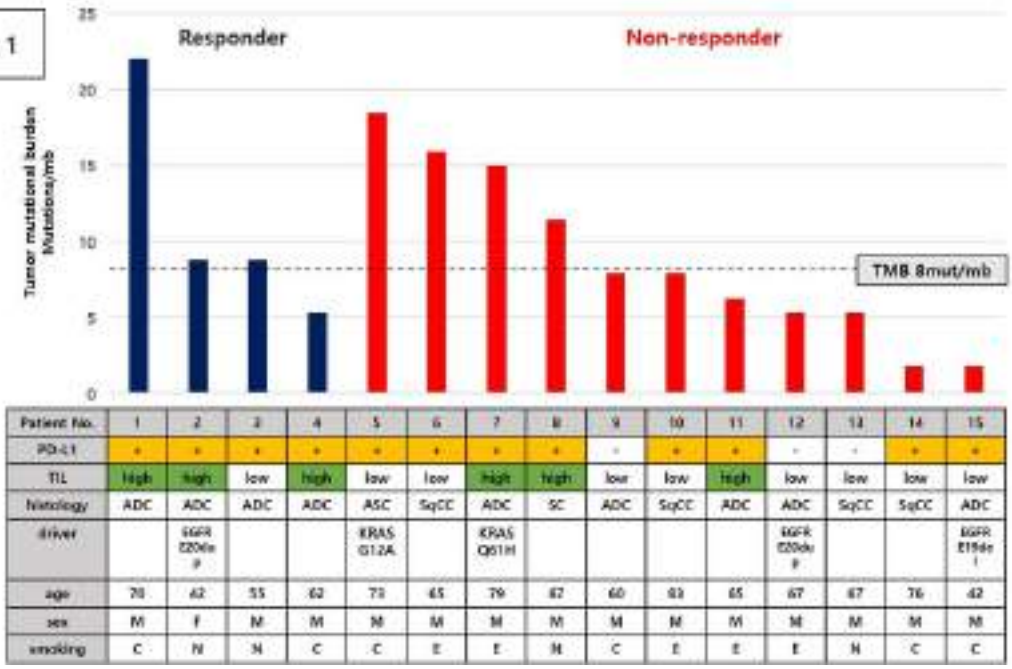
Background: There is an unmet need for biomarkers that will identify patients more likely to respond to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). We aimed 1) to investigate the impact of tumor mutational burden (TMB) on outcomes of NSCLC patients treated with ICIs, 2) to determine the relationship between TMB, PD-L1 expression, and tumor-infiltrating lymphocytes (TILs), and 3) to present an algorithm that can best predict ICI therapy response through a combination of biomarkers. **Method:** We performed targeted deep sequencing on 22 primary and 8 paired metastatic NSCLC from 15 patients treated with ICIs (two primary samples from 7 patients). **Result:** The median TMB across all samples was 9.46 mutations/Mb (IQR 1.762–22.03). Applying the cutoff of TMB to 8 mutations/Mb, which best predicts ICI response using receiver operating characteristic curves, 46.7% and 53.3% were high and low TMB group, respectively. There was no correlation between TMB, PD-L1 expression, and TILs. The response rate (RR) to ICIs for patients with high versus low TMB was 3/7 (42.8%) versus 1/8 (12.5%; p>0.05) (Figure 1). The median TMB for responders (n=4) versus nonresponders (n=11) treated with ICIs was 11.2 versus 8.8 mutations/mb. When patients were classified into four groups according to TMB (Figure 2), PD-L1 positivity, and TIL, 50% (2/4) of the patients with $TMB^{hi}PD\text{-}L1^{pos}TIL^{hi}$ showed clinical benefit to ICI. One of the two patients who did not respond to ICI despite $TMB^{hi}PD\text{-}L1^{pos}TIL^{hi}$ group was sarcomatoid carcinoma and one was KRAS-mutant adenocarcinoma. In patients with $TMB^{hi}PD\text{-}L1^{neg}TIL^{low}$ and $TMB^{low}PD\text{-}L1^{pos}TIL^{hi}$, the RR was 40% (2/5). All of $TMB^{low}PD\text{-}L1^{neg}TIL^{low}$ group were non-responder (0/6)

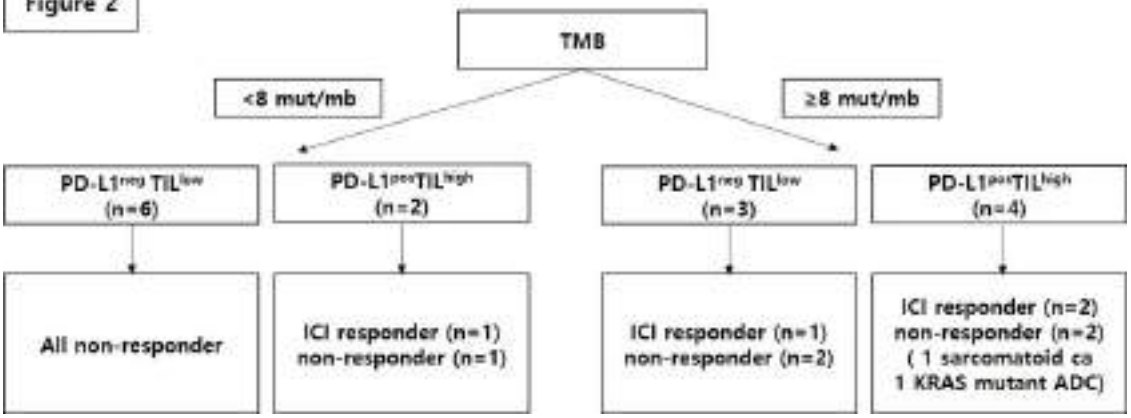
POSTERS

Figure 1



Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PD-L1	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+
TIL	high	high	low	high	low	low	high	high	low	low	high	low	low	low	low
histology	ADC	ADC	ADC	ADC	ASC	SqCC	ADC	SC	ADC	SqCC	ADC	ADC	SqCC	SqCC	ADC
driver		EGFR E20del			KRAS G12A		KRAS Q61H					EGFR E20del			EGFR E19del
age	70	62	55	62	73	65	79	67	60	83	65	67	67	76	42
sex	M	F	M	M	M	M	M	M	M	M	M	M	M	M	M
smoking	C	N	N	C	C	E	E	N	C	E	E	E	N	C	C

Figure 2



Conclusion: TMB can be a potential predictive biomarker of response to ICI treatment in NSCLC patients. An algorithmic approach, which takes into account the integration of TMB, PD-L1 expression, and TIL, may be more effective in screening ICI response groups.

Keywords: tumor mutational burden, predictive biomarker, Non-Small Cell Lung Cancer

P1.04-73 SMALL CELL TRANSFORMATION OF NON-SMALL CELL LUNG CANCER (NSCLC) ON IMMUNE CHECKPOINT INHIBITORS: CASE REPORT AND LITERATURE REVIEW

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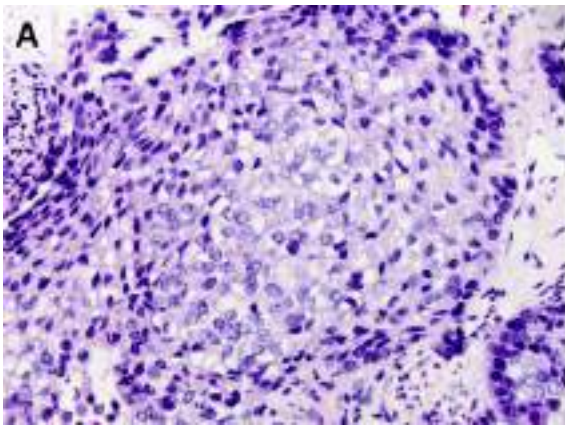
Background: Histological transformation of oncogene-driven lung adenocarcinoma to small cell lung cancer (SCLC) following treatment with tyrosine kinase inhibitors (TKI) is a well-described phenomenon. However, it is unknown whether a similar transformation may drive acquired resistance to immune checkpoint inhibitors (ICPi) in NSCLC by altering tumor-related immune evasion. **Method:** We present a case of a patient with NSCLC treated at our institution with transformation to SCLC during second line therapy with nivolumab. We conducted a review of the literature to identify similar cases and patient outcomes. **Result:** This is a case of a 69 year-old woman with a 35 pack-year tobacco history presenting with stage IV squamous cell lung cancer (figure 1A). Her disease progressed within 4 weeks of first line carboplatin/gemcitabine and she was transitioned to next line nivolumab with sustained partial response lasting 18 months. She then developed rapid, bulky progression of mediastinal disease. Biopsy showed transformation to SCLC (figure 1B). Comparison of genomic profiling results from the initial NSCLC diagnosis and SCLC transformation revealed similar tumor profiles (*TP53 R283fs*62*). Absence of *RB1* loss and initial protracted response to nivolumab suggested that transformation likely occurred as a result of treatment-induced selection pressure. The patient had a near complete response following 4 cycles of carboplatin/etoposide and remained alive 7 months post-transformation. Review of the literature revealed 7 reported cases where SCLC transformation was thought to result from acquired resistance to ICPi (Table 1). **Conclusion:** We add to the emerging evidence of transformed SCLC as an acquired resistance mechanism following ICPi treatment in advanced NSCLC. Although only a few reports are available at this time, the real-world frequency may well be under-estimated due to relative infrequency of post-progression biopsies in NSCLC patients not being treated with TKIs. The underlying genomic/epigenetic mechanisms that may explain acquired resistance with neuro-endocrine transformation remain to be elucidated.



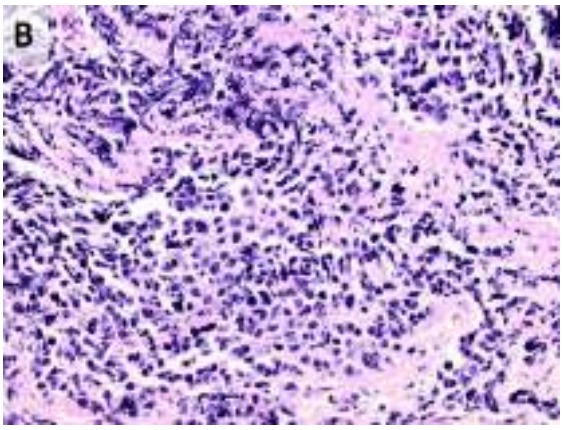


Table 1. Summary of literature on NSCLC cases transformed to SCLC on ICPi

Serial No. (Reference)	Original histology	Original genomic profile	ICPi details	Genomic profile of transformed SCLC	Outcome post SCLC transformation
1 (Index case)	Squamous cell carcinoma	*TP53* mutation	Nivolumab (2nd line, 47 cycles)	*TP53* R283fs*62 mutation	Alive 7 months post SCLC
2 (Iams *et al,* JTO 2018)	Adeno-carcinoma	*KRAS* G12C mutation	Nivolumab (2nd line, 33 cycles)	*KRAS* G12C mutation, *TP53* R273C mutation	Died 16 months post SCLC
3 (Iams *et al*, JTO 2018)	Adeno-carcinoma	*KRAS* G12C mutation	Nivolumab (2nd line, 36 cycles)	*TP53* S315S mutation, *RB1* splice site mutation	Died 11 months post SCLC
4 (Imakita *et al*, Respir Med Case Rep. 2017)	Poorly differentiated carcinoma	Neg for *EGFR / Alk*	Nivolumab (2nd line, 3 cycles)	Not described	Died 2 months post SCLC
5 (Abdallah *et al*, Lung Cancer [Auckl]. 2018)	Adeno-carcinoma	Neg for *EGFR / Alk*	Nivolumab (2nd line, 5 cycles)	Not described	Response after 2 chemotherapy cycles
6 (Abdallah *et al*, Lung Cancer [Auckl]. 2018)	Squamous cell carcinoma	Not described	Pembrolizumab (1st line, 30 cycles)	Not described	Alive 18 months post SCLC
7 (Bar *et al*, JCO 2018)	Squamous cell carcinoma	Not described	ICPi (16 months)	Not described	Poor response to chemotherapy
8 (Bar *et al,* JCO 2018)	Squamous cell carcinoma	Not described	ICPi (6 months)	Not described	Poor response to chemotherapy

Keywords: Immune Checkpoint Inhibitors, Small cell transformation, Acquired resistance

P1.04-74 CHARACTERISTICS OF T CELL RECEPTOR REPERTOIRE OF LUNG CANCER PATIENTS

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Background: As the importance of T cell receptor (TCR) repertoire gains appreciation, particularly given their potential utility for cancer immunotherapeutic prognostication, the characteristics of TCR repertoire are needed. We detected the complementarity determining region 3 (CDR3) by TCR sequence to describe diversity and changes in human's immune system with age and difference clinical stage . **Method:** The TCRβ repertoire of 19 stage IV lung cancer patients and 77 stage I/II/III lung cancers patients was analyzed. Genomic DNA was extracted from peripheral blood and used to amplified and sequenced the CDR3 region of rearranged TCRβ genes. Finally, we got the relative frequencies of patients T cell clones. Shannon index was calculated on the clonal abundance of all productive TCR sequences. The normalized Shannon index was determined by dividing Shannon index by the natural logarithm of the number of unique productive TCR sequences. **Result:** Diversity of the TCR repertoire can be measured using the Shannon index. Analysis had been made to test the diversity relationship among a cluster of clinical features, such as stages, age and gender. Diversity were significantli decreasing with clinical stages(p=0.0482). Comparison of the diversity between stage IV and stage I/II/III patients, we found stage IV lung cancer has more lower diversity(p=0.0048). In these patients, diversity had showed a significantli correlation with age(r=-0.3036, p=0.0026). Diversity was significantly lower in patients 55 years of age or older compared to younger patients (p=0.0083). **Conclusion:** These results suggest that patients with advanced cancer exhibit limited TCR repertoire diversity and that this diversity is further limited in patients with advanced clinical stage and older age. Interestingly, these factors are often associated with a poor immune status.

Keyword: TCR repertoire, clinical stage, immune system

P1.04-75 IMMUNE-RELATED ADVERSE EVENTS AND THE NEUTROPHIL TO LYMPHOCYTE RATIO AS PREDICTORS OF CLINICAL RESPONSE TO IMMUNOTHERAPY

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Background: Several immune checkpoint inhibitors (ICPis) have been approved for the treatment of non-small cell lung cancer (NSCLC). PD-L1 expression seems to correlate with activity of ICPis; however, it is not a completely accurate biomarker. Therefore, other clinical or molecular predictors of response are needed. **Method:** The purpose of this study was to assess the value of immune-related adverse events (irAEs) and the neutrophil to lymphocyte ratio (NLR) in predicting response to ICPis. Furthermore, since Hispanics (H) are often not stratified in clinical trials, we sought to evaluate if incidence of irAEs and the baseline NLR were similar between H and non-Hispanic (NH) patients (pts). This was a retrospective review of 70 pts diagnosed with NSCLC and treated with ICPis at our institution between July 2014 and 2017. The electronic medical record was utilized to collect pt demographics, occurrence of irAEs, baseline NLR (categorized as < 5 or ≥ 5), progression free survival (PFS) and overall survival (OS). The data cutoff date was March 31, 2019. **Result:** The median age of the pts was 65.5 years (range 51 to 89 years). The male to female ratio was 1.2. There were 19 H and 51 NH pts. Most of the pts were treated with single agent ICPis. The irAEs positive group had increased median PFS (7.5 vs 2.1 months; p-value 0.001) and OS (14.7 vs 4.7 months; p-value 0.001) compared to the irAEs negative group. OS at 12 months was 58.1% in the irAEs positive group compared to 20.5% in the irAEs negative group (p-value 0.001). There was a non-statistically significant trend towards improved outcomes in pts with baseline NLR < 5 vs ≥ 5. The overall incidence of irAEs was similar between H and NH pts; however, hypothyroidism was observed more frequently in H than NH pts (45% vs 20%; p-value 0.020). Baseline NLR < 5 vs ≥ 5 was similar between H and NH pts. **Conclusion:** Occurrence of irAEs might be useful in identifying potential responders to ICPis. H pts on ICPis might be at a higher risk for developing hypothyroidism. Since our total number of pts is small, these findings should be further evaluated in prospective studies.

Keywords: Minorities, Immunotherapy, NonSmallCellLungCancer

P1.04-76 PREDICTIVE FACTORS OF EARLY THERAPEUTIC FAILURE TO IMMUNOTHERAPY IN PATIENTS WITH METASTATIC NSCLC

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Background: Immunotherapy helped to improve the outcomes of patients diagnosed with metastatic NSCLC. Nevertheless, survival curves show that some patients do not benefit from treatment and progress rapidly. Identifying factors capable of predicting early failure to immunotherapy is clinically useful. We determined factors associated with disease progression before nine weeks of treatment with anti-PD1. **Method:** We retrospectively reviewed the medical records of patients with metastatic NSCLC treated in second or more line with anti-PD1 at AC Camargo Cancer Center-Brazil, from January 2006 until April 2018. Altogether, 87 patients were identified and had pre-treatment (data collected within 30 days of immunotherapy initiation) characteristics collected. Univariate analysis was performed using binomial logistic regression (disease progression occurring till 9 weeks versus after); variables with p value < 0.20 were selected for multivariate analysis. A multivariate model to predict disease progression (DP) until 9 weeks was developed using the likelihood ratio test and Akaike Information Criteria (AIC). Median follow-up was estimated using reverse Kaplan-Meier method. Median progression-free (mPFS) and overall survival (mOS) were obtained from Kaplan-Meier curves. **Result:** Median follow-up was 18 months (95% CI 14.0-20.3), mPFS was 3.3 months (95%CI 2.1-3.7) and mOS was 15.8 months (95%CI 7.5-25.5). Univariate analysis demonstrated that the number of metastatic sites (OR=1.79; 95%CI 1.25-2.68; p=0.002), hemoglobin level (OR=0.791; 95%CI 0.55-0.88; p=0.003), monocyte count (OR=1.24; 95%CI 1.08-1.47; p=0.004), platelet count (OR=1.44; 95%CI 1.01-2.14; p=0.051), dNLR (derived neutrophil to lymphocyte ratio) (OR=1.19; 95%CI 0.95-1.54; p=0.14), ECOG (OR=2.43; 95%CI 1.00-6.048; p=0.051), T stage (OR=2.15; 95%CI 0.78-6.14; p=0.14), N stage (OR=4.26; 95%CI 1.51-14.13; p=0.010) and treatment line (OR=0.53; 95%CI 0.22-1.25; p=0.15) were significantly associated with early treatment failure. The final multivariate model demonstrated that N stage (OR=8.14; 95%CI 1.50-44.11; p=0.015), the number of metastatic sites (OR=2.10; 95%CI 1.24-3.55; p=0.005), hemoglobin level (OR=0.62; 95%CI 0.44-0.89; p=0.010), monocyte count (OR=1.44; 95%CI 1.12-1.84; p=0.004) and dNLR (OR=1.40; 95%CI 1.03-1.91; p=0.029) are independent factors associated with DP until 9 weeks of treatment. **Conclusion:** N stage, the number of metastatic sites, hemoglobin level (g/dL), the monocyte count and the dNLR are factors independently associated with early disease progression (until 9 weeks from immunotherapy initiation). This can help to better select metastatic NSCLC patients for anti-PD1 therapy in second line.

Keywords: Immunotherapy, NSCLC, Early Progression

P1.04-77 EFFICACY OF ANTI-PD-1/L1 THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER WITH PREEXISTING AUTOIMMUNE MARKERS

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Background: Targeting therapies against the programmed cell death protein-1/ligand 1 (PD-1/L1) pathway has become a standard for patients with advanced non-small cell lung cancer (NSCLC). However, most clinical trials have not evaluated its safety and efficacy in patients with autoimmune diseases or with preexisting autoantibodies. Antinuclear antibodies (ANAs) are a spectrum of autoantibodies that target various nuclear and cytoplasmic components of the cells. Rheumatoid factors (RFs) are antibodies (immunoglobulin M) that react with immunoglobulin G. They are usually used as serological markers for autoimmune diseases. Recently, the relationship between these antibodies and some types of cancers has been identified, suggesting that autoantibodies might be associated with carcinogenesis and represent a state of pre-autoimmunity. Preexisting autoantibodies have been reported to be a surrogate marker of the efficacy of immunotherapy, but the trend is different by reporting. **Method:** To examine the effects of preexisting autoantibodies in anti-PD-1/L1 therapy, clinical data including ANAs and RF were reviewed retrospectively in patients with advanced NSCLC who received monotherapy with a PD-1/L1 inhibitor. Survival outcome was estimated with the Kaplan-Meier method and was compared between patient groups with the log-rank test. **Result:** In this retrospective analysis, we evaluated 275 patients with advanced NSCLC who received nivolumab, pembrolizumab or atezolizumab monotherapy, at Osaka International Cancer Institute in Japan between December 2015 and December 2017. The median age was 68 (range 27 to 80 years). 199 were men. ANAs were analyzed in 176 of 275 (64%) patients, and RF were analyzed in 161(56%). 68 of 176 (38.6%) were positive for ANAs (more than 1:40 serum dilution) and 21 of 161(13%) were positive for RF (more than 15IU/ml). None of the patients had active symptoms of an autoimmune disease. The median Time to Treatment Failure (TTF) was significantly shorter in patients positive for RF, 1.9 (95%CI, 0.5-2.9) months, than in those without RF, 3.5 (95%CI, 2.0-4.3) months. No significant differences in Overall Survival (OS) (12.5 versus 19.8 months) were observed between patients with or without RF, but OS in patients positive for RF tended to be shorter. Although no significant differences in OS (21.1 versus 19.4 months) and TTF (3.6 versus 2.8 months) were observed between patients with or without preexisting ANAs, OS in patients strongly positive (more than 1:160 serum dilution) for ANAs tended to be shorter compared to mildly positive patients (1:40, 1:80 serum dilution) (22.2 versus 12.7 months). **Conclusion:** The presence of preexisting RFs may be a factor for poor prognosis in NSCLC patients undergoing anti PD-1/L1 therapy. There was no significant difference between patients with and without ANAs, but high titer of ANAs may be a factor in poor OS.

Keywords: autoantibodies, programmed cell death 1/ ligand 1, Non small cell lung cancer

P1.04-78 EFFICACY OF CHECKPOINT INHIBITORS IN COMBINATION WITH CHEMOTHERAPY FOR FIRST-LINE TREATMENT OF ADVANCED NON-SQUAMOUS NSCLC

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Background: Checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab, or atezolizumab) have created a fundamental paradigm shift in the management of non-small cell lung cancer (NSCLC). In recent years, many randomized clinical trials (RCT) have combined different checkpoint inhibitors with various standard chemotherapy regimens as first-line treatment of advanced non-squamous NSCLC. In general, these trials have included patients across different levels of PD-L-1 expression. The purpose of our study is to consolidate the efficacy of checkpoint inhibitors in combination with chemotherapy for first-line treatment of advanced non- squamous NSCLC. **Method:** We systematically conducted a comprehensive literature search using PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019. RCTs of first-line chemotherapy +/- immunotherapy in patients with advanced non-squamous NSCLC were incorporated in the analysis. A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q -statistic. Random effects model was applied. **Result:** A total of 3228 patients with advanced non-squamous NSCLC from 6 RCTs (Keynote – 021,189, IMpower – 130, 132, 150, and Lynch et al.) and a subgroup of another RCT (Checkmate-227) were included. The study arm used standard chemotherapy regimens in combination with ipilimumab, pembrolizumab, atezolizumab, or nivolumab while control arm used only standard chemotherapy regimens. The randomization ratio was 2:1 in IMpower-130 and Keynote-189 studies and 1:1 in other studies. The I^2statistic for heterogeneity was 15, suggesting some heterogeneity among RCTs. The pooled HR for PFS was statistically significant at 0.61 (95% CI: 0.55-0.67; P < 0.00001), and the pooled HR for OS was noted at 0.78 (95% CI: 0.65- 0.94; P = 0.01).The PFS benefit was observed in all PD-L1 categories, including PD-L1 negative/ tumor proportion score (TPS) of less than 1% cohort (HR, 0.67; 95% CI: 0.53- 0.84; P = 0.0005), PD-L1 low/ TPS ≥1-49% cohort (HR, 0.62; 95% CI: 0.52- 0.74; P < 0.00001) and PD-L1 high/ TPS ≥ 50% cohort (HR, 0.42; 95% CI: 0.33- 0.52; P < 0.00001). **Conclusion:** Our study showed that first-line checkpoint inhibitors in combination with chemotherapy significantly improved PFS and OS compared to standard chemotherapy in patients with advanced non-squamous NSCLC and the PFS benefit was consistent regardless of PD-L1 expression.

Keywords: Checkpoint inhibitors, advanced non-squamous NSCLC, first-line treatment

P1.04-79 CD73 EXPRESSION IN LUNG ADENOCARCINOMAS AND IMMUNOLOGICAL AND MOLECULAR ASSOCIATIONS

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Background: Immune checkpoints inhibitors (ICI), in monotherapy or combination with chemotherapy, are the standard of care for lung adenocarcinoma (ADC) patients. Unfortunately, only a restricted number of patients will respond to ICI. Combination therapies such as CD73 inhibitors, are being studied with the goal to achieve synergic effects. CD73 is a membrane-bound protein with immunosuppressive functions. We previously reported that higher immune cell infiltration was associated mainly to CD73 basolateral (BL) expression, in this abstract, we show the correlation of CD73 expression at luminal (L) and BL membrane of ADC malignant cells (MCs), with annotated clinicopathological characteristics, immune and molecular biomarkers. **Method:** CD73 IHC expression (clone D7F9A) was evaluated in 106 archived ADCs from patients that underwent surgical treatment without neoadjuvant therapy between February 1999 and February 2012 at MD Anderson Cancer Center (Houston, Texas, USA). We scored % and H-score of CD73 expression at the luminal (L) and basolateral (BL) membrane, we calculated the Total (T) CD73 as the average of L and BL, and classified ADCs in three groups: 'T High' (TH) (upper quartile for all tumors); 'T Low' (TL); 'T Neg' (TN) (<1%). We correlated T, L and BL expression and the three groups with clinicopathological characteristics, mutational status of KRAS and EGFR, TP53, STK11 and Tumor mutation burden (TMB), and cell densities of CD3, CD8, CD68, CD45RO, FOXP3, and Granzyme B, and PD-L1 expression (clone E1L3N) in MCs. **Result:** T CD73 expression was found in 76%; BL in 60% and L in 57%; among ADCs with luminal membrane present (n=72), L CD73 was present in 83%. T+ and L+ expression was more frequent in never smokers (p=0.02 and p=0.003). Also higher frequency of L+ was found in older patients (>65) (p=0.01), tumors with non-solid histology patterns (p<0.001), EGFR mutation (p=0.048), non-mutated p53 (p=0.002), negative PD-L1 (p=0.03), and low TMB (<10 mut/MB) (p=0.001). Higher levels of L expression were found in KRAS mutated tumors (p=0.049). Higher BL expression positively correlated with p53 mutated tumors (p=0.038), PD-L1+ in MCs (p=<0.0001), and higher TMB (p=0.040). Our group analyses revealed that TH and TN were associated with ADCs from patients with >30 pack-year of smoking history (p=0.04), presence of any-solid histology pattern (p=0.03), p53 mutation (p= 0.005) and higher TMB (p=0.003) compared with TL. TH also had higher frequency of PD-L1+ tumors, and a higher cell density of CD3 (p=0.0001), CD8 (p=0.001), CD68 (p=0.048), CD45RO (p=0.036), FOXP3 (p=0.053), and Granzyme B (p=0.024) compared to TL and TN. TN showed higher frequency of STK11 mutation (p=0.034). **Conclusion:** Based on the CD73 expression we defined subsets of lung adenocarcinomas that have distinct histological, molecular and immunological characteristics that may play a role in the response to ICI. Our characterization could help us to understand patient's response to ICI, and identify patients that could potentially benefit from combination therapies.

Keywords: CD73, Lung neoplasms, immune profiling

P1.04-80 IMMUNOTHERAPY-RELATED THROMBOSIS: CONSIDERATIONS AND ASSOCIATED FACTORS IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Widespread use of immune checkpoint inhibitors (ICIs) for the treatment of lung cancer has exposed a large number of patients to these medications, increasing the incidence of rare adverse reactions such as thromboses. The present study elaborates on factors related to the occurrence of these events. **Method:** In a retrospective cohort study, a total of 48 patients, 24 who experienced thrombosis and 24 matched controls who underwent evaluation after initiation of ICIs therapy for advanced/metastatic NSCLC, were included. Clinical and pathological as well as serum inflammatory and coagulation markers were evaluated. **Result:** Among the 48 patients, 46% (n=26) were female, median age was 62 years old and all patients had an ECOG performance score of < 2. The

median overall survival reached by the cohort was 22.47 months. Among patients who developed thrombosis there were 8 cases of deep venous thrombosis (DVT) (33%), 13 pulmonary embolisms in addition to DVT (62.5%) and 1 case of brain venous sinus thrombosis (4.2%). Apart from expected thrombosis markers such as D dimer, differences in inflammatory and immune related markers between patients who experienced thrombosis and those who did not, were observed. Abnormal values were found in the thrombosis group for B2glycoprotein 1 (33% vs 0%, OR= 4.08, [95%CI 1.65 - 12.1], p= 0.005), B2glycoprotein 1 IgG (29.2% vs 0%, OR= 4.64, [95%CI 1.73 – 16.9], p= 0.007), C Reactive protein (83.3% vs 12.5%, OR= 35, [95%CI 7.9 - 213], p< 0.001), B2microglobulin (62.5% vs 8.3%, OR= 14, [95%CI 3.11-103.7], p = 0.002), Prothrombin time (41.7% vs 4.2%, OR= 2.4, [95%CI 1.64 -3.69], p =0.01) and C Coagulation protein (50% vs 16.6%, OR =1.79, [95%CI 1.53 – 2.91], p <0.001). **Conclusion:** Abnormalities in antiphospholipid antibodies, C reactive protein, B2microglobulin and coagulation in patients who suffered thrombosis during ICI treatment suggest that this phenomenon could be the result of immune and auto-inflammatory induced intravascular dysfunction.

Keywords: Non small cell lung cancer, Inmunooncology, Thrombosis

P1.04-81 CHARACTERIZATION OF HISPANIC PATIENTS WHO EXPERIENCED HYPERPROGRESSION DURING TREATMENT FOR ADVANCED NSCLC WITH IMMUNOTHERAPY

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Background: Immunotherapy related hyperprogression is poorly characterized in Latin American patients. In this study we sought to characterize and identify factors associated with the presentation of hyperporgression after initiation of immunotherapy in patients with advanced non-small cell lung cancer (NSCLC). **Method:** A multicenter international retrospective study on 110 patients was conducted. Clinical variables as well as routine blood studies were recorded before initiation of treatment. Regression analysis was used to find associations. A random forest tree analysis (RFTA) based on continuous and discrete variables was used to subcategorize patients based on occurrence of hyperprogression. **Result:** Median age was 64 years (Range 34-90) and 59.8 % were male patients. ECOG performance status was >1 on 8.8% of patients. Median overall survival was 12.7 months (95% CI 9.67-14 months) and progression-free survival of 4.27 months (95% CI 3.97-5.0). 44 hyperprogressors were documented (19.8%, [95%CI 14.5-25.1%]). Median time to progression was approximately 5 weeks after initiation of treatment. Factors associated included albumin and hemoglobin levels (p = 0.046 and 0.037 respectively), presence of CNS (p= 0.0009) and bone metastasis (p = 0.004) and weight loss (p= 0.004). RFTA revealed that a leucocyte count over 5.300 cells/dl was present in all hyperprogressors. **Conclusion:** Hyperprogression is a phenomenon after initiation of immunotherapy which is associated with clinical and paraclinical variables. These associations could be used to withhold certain agents and prevent its occurrence in NSCLC treatment.

Keywords: hyperprogression, Latin America, Immunotherapy

P1.04-82 TOXICITY AS A CLINICAL MARKER FOR EFFICACY OF IMMUNOTHERAPY IN NSCLC: A MULTICENTRIC EXPERIENCE FROM ARGENTINA

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Background: Immunotherapy (IO) has become standard of care in NSCLC. Immune-related adverse events (irAEs) have shown to be associated with survival benefit in several tumor types in small reports. However, its predictive role as a clinical marker for efficacy to PD-1 inhibition in NSCLC remains uncertain. **Method:** We conducted a retrospective analysis of patients (pts) with NSCLC treated with IO at six centers between Nov 2013 and Feb 2019. We categorized patients in two groups (irAEs and no-irAEs group) and evaluated overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). A 6-week cutoff was established to evaluate the impact of early vs. late onset of irAEs. Correlations were assessed using Fisher's exact tests. Kaplan-Meier was used to estimate survival rates and compared using log-rank. **Result:** A total of 269 NSCLC pts treated with ICIs were included, 48 pts (17.8%) developed Grade 3-4 irAEs. Among them, median age 66 years [range 47 - 86], 31 (65%) were male, 42 (87.5%) current or former smoker and 42 (87.5%) had PS 0-1, PDL-1 tumor proportion score (TPS) was ≥ 50% in 17/26 pts (65.4%), 5 pts (11%) received baseline corticoids; 15 pts (31%) were treated in first-line. No statistical significant differences in baseline characteristics were observed. Median follow-up from IO was 15.8 months [95%CI 12.1 – 19.7]. Median number of cycles to toxicity was 5 [range 1 – 60]. Most common grade 3-4 events were pneumonitis (n=12), adrenal insufficiency (n=7), thyroiditis (n=7), rash (n=6) and nephritis (n=6). There were 5 (10%) treatment-related deaths. Patients with irAEs had significantly higher ORR and DCR vs. no-irAEs: 48% (23/48) vs. 26.7% (59/221) p=0.005 and 83% (40/48) vs. 58% (128/221) p<0.001, respectively. Similarly, median PFS and OS were significantly prolonged in pts with irAEs vs. no-irAEs: 17.1 months [95%CI 8.1 – 25.9] vs. 6.6 months [95%CI 4.9 – 8.3] p=0.02 and 29.4 months [95%CI NR] vs. 12.9 months [95%CI 10.0 – 15.9] p=0.01, respectively. Early onset of irAEs (≤6 weeks) had significantly shorter PFS and OS vs. late onset (>6 weeks): 2.43 months [95%CI 0 - 9.02] vs 21.0 months [95%CI 14.57 - 27.44] p=0.006 and 3.94 months [95%CI NR] vs NR p=0.010, respectively. **Conclusion:** In our cohort, we observed a correlation between irAEs and efficacy in NSCLC patients treated with IO. This potential predictive value needs to be validated in larger prospective cohorts to drive definitive conclusions.

Keywords: Inmunotherapy, NSCLC, toxicity

P1.04-83 COMBINING IMMUNE GENE POLYMORPHISM AND IMMUNE PROFILE PREDICTS BRAIN METASTASES AND DEATH IN A BRAZILIAN COHORT OF NON-SMALL CELL LUNG CARCINOMA

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Background: Combining immunotherapies such as anti–PD-1 and anti–CTLA-4 agents, which target complementary pathways in the cancer-immunity cycle, might result in additive or synergistic antitumor activity, and has been suggested to improve survival of patients with advanced non-small cell lung carcinomas (NSCLC). This study was conducted to investigate whether polymorphisms of immune checkpoints genes is associated with the tumor immune cell profile and with the risk of brain metastases and death of patients with advanced stage NSCLC. **Method:** A total of 75 NSCLC patients were enrolled. The specimens included 37 (50%) adenocarcinomas (ADC), 25 (33%) squamous cell carcinomas (SqCC), and 13 (17%) large cell carcinomas (LCC). Using multiplex immunofluorescence

(mIF) and image analysis, we evaluated programmed death ligand 1 (PD-L1) expression in malignant cells (MCs), CD68+ macrophages, and cells expressing the immune markers CD3, CD8, CD57, CD45RO, FOXP3, PD-1, and CD20. We used high-throughput next-generation sequencing (NGS) to evaluate single nucleotide variants (SNVs) in immune checkpoints genes CD274 (PD-L1), CTLA-4, PDCDL1LG2 (PD-L2), LAG3 and B7H4 (VTCN1) in NSCLC by TruSeq Custom Amplicon Panel (Illumina, Inc., San Diego, CA). A total of five single nucleotide polymorphisms (SNPs) were selected: rs2297136G/A (PD-L1), rs231775A/G (CTLA-4), rs7854303C/T (PD-L2), rs870849T/C (LAG3) and rs10754339G/A (B7H4). Cell phenotype data were then integrated with clinicopathologic characteristic and next-generation sequencing gene profiles. **Result:** The patients were 47 men (median age, 78yr) and 22 women (median age, 75yr). Tobacco history was present in 22 (30%) patients. Lymph node and brain metastases were observed respectively in 28 (37%) and 8 (10%) patients, and all the patients with brain metastases also presented lymph node metastases. Twenty-three (31%) of patients received adjuvant therapy. The percentage of MCs-PD-L1+ was < 1% (40%), 1-10% (40%) and > 10% (20%). The density of immune cells/mm2 was CD3+ (330), CD3CD8+ (110), CD3-PD1+ (85), CD68+ (58), CD68-PD-L1+ (2.5), CD3CD45RO+ (260), CD3CD45FOXP3+ (260) and CD20+ (46). The frequency of genotypes was: CTLA-4 (AA=40%; AG=25%; GG=10%), CD274 (AA=32%, GA=26%, GG=17%), PDCDL1LG2 (CC=100%), LAG3 (TC=32%, CC=31%, TT=12%) and VTCN1 (AA=57%, GA=13%, GG=5%). A significant association was found between CTLA-4 and CD20+ lymphocytes (R=-0.32; p=0.02), PD-L1and VTCN1 (R=0.26; p=0.02) and PD-L1 polymorphism and MCs-PD-L1 (R=0.26; p=0.04). Different models to predict risk of death were constructed by Cox Regression analysis. Initially, the model was constructed with patient age, histologic type, N stage, brain metastases and adjuvant treatment (p<0.05). Thus CTLA-4, CD274, PDCDL1LG2, LAG3 and VTCN1 genes were included in the model (p<0.05). The second model excluded PDCDL1LG2, VTCN1 genes and introduced MCs-PD-L1 and CD3CD8+, (p<0.05). The final model, controlled for age, histologic types and adjuvant treatment, reliably predicted low risk of brain metastases and death for patients in N1 stage (β coefficient=3.24; p=0.01), CTLA-4 rs231775 AG genotype (β coefficient=-3.71; p=0.04); CD274 rs2297136 GA genotype (β coefficient= -8.55; p=0.03), LAG3 rs870849 TC genotype (β coefficient=2.16; p=0.04), low density of MCs-PD-L1 (β coefficient=6.43, p=0.04) and high density of CD3+CD8+ lymphocytes (B coefficient=-3.06; p=0.04). **Conclusion:** Incorporating immune checkpoints genes polymorphisms into immunoprofiling score improves prediction of brain metastases and death in Brazilian NSCLC and may be promise as combining target therapy.

P1.06 MESOTHELIOMA
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.06-01 COMBINING IMMUNOPROFILE, IMMUNOGENIC COLLAGEN AND MISMATCH REPAIR PROTEINS PREDICTS RISK OF DEATH AND TARGET THERAPY IN MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) is a devastating disease characterized by aggressive growth and local invasion, poor outcome and limited therapeutic options. The immunogenic Type V collagen (Col V) has been identified as a significant risk factor for invasion in lung cancer, but the role of this collagen in MM is unknown. Although mismatch repair (MMR) proteins in malignancies function as genomic gatekeeper is not attained, these proteins may indirectly reinforce a high tumor mutation burden. We hypothesized that the cross-talk between Col V, MRR proteins and immune environment may elicit a paradoxal immunogenic response, promoting "cold-hot" switching while acting as a barrier, isolating and protecting neoplastic cells against cytotoxicity, chemotherapy and checkpoint inhibitors. **Method:** Ninety MM patients were enrolled, located in pleural and peritoneal serosae. We quantified through image analysis and employed immunofluorescence to evaluated Col V and immunohistochemistry to detect programmed death ligand 1 (PD-L1) expression in malignant cells (MCs), cells expressing the immune markers CD4, CD8 and CD20, BAP1, and MMR proteins (MLH1, PMS2, MSH2, MSH6). **Result:** 52 patients were men (median age, 61) and 25 women (median age, 60). Malignant mesothelioma involved the pleura (N=57), peritoneum (N=17) and testis (N=4). Histologic types included epithelioid (N=85) and non-epithelioid (N=7) and subtypes were solid (N=58), (N=13), papillary (N=11), micropapillary (N=4) and sarcomatoid (N=1). MCs-PD-L1 expression was 7/mm2, inflammatory cells expressing PD-L1 2.94/mm2, immune markers CD4+ 60/mm2, CD8+ 301/mm2 and CD20+ 186/mm2. Loss of BAP1 occurred in 61 (59%) cases. Col V fibers mean density were 2.67/mm3. The mean MMR protein expression in tumor cells was MLH1 (713/mm2), PMS2 (957/mm2), MSH2 (1306/ mm2) and MSH6 (855/mm2). We found significant association between expression of MLH1 with necrosis (R=-0.23;p=0.02), CD4+ (R=-0.32, p=0.002) and Col V (R=0.40, p=0.0001); PMS2 with necrosis (R=-0.30, p=0.02), BAP1 (R=0.22, p=0.03), MCs-PD-L1+ (R-0.27, p=0.009), inflammatory cells expressing PD-L1 (R=0.30, p=0.008) and Col V (R=0.54, p=0.0001); MSH2 with necrosis (R=-0.23, p=0.02) and CD4+ (R=-0.26, p=0.01), and MSH6 with MCs-PD-L1 (R=0.23, p=0.03), CD20+ (R=-0.24, p=0.01) and Col V (R=0.44, p=0.0001). Compared to non-epithelioid MPM, epithelioid MPM presented a significant association with MCs-PD-L1 (p=0.04), inflammatory cells expressing PD-L1 (p=0.002) CD8+ (p=0.005), MLH1 (p=0.001), PMS2 (p=0.01), MSH2 (p=0.04), MSH6 (p=0.02) and Col V (p=0.04). Different models to predict risk of death were constructed by Cox Regression analysis. The final model reliably predicted high risk of death for MM with necrosis (ß coefficient = -9.92, p=0.01), high nuclear grade (ß coefficient = 7.34, p=0.003), low MCs-PD-L1 (ß coefficient = -0.20, p=0.002), and inflammatory cells expressing PD-L1 (ß coefficient = -0.32, p=0.006), loss of BAP1 expression ((ß coefficient = 8.25, p=0.005), low CD4+ (ß coefficient = -1.70, p=0.008), increased expression of MLH1 (ß coefficient = 0.003, p=0.002), and MSH2 (ß coefficient = -0.04, p=0.01), and high Col V fibers (ß coefficient = 1.07, p=0.004). There was no significant difference between pleural and non-pleural disease. **Conclusion:** PD-L1 depends on the cross-talk between Col V and tumor mutation burden to promote cold-hot immunogenic switching and to predict death and target therapy in MM in pleural and non-pleural MM.

Keywords: malignant mesothelioma, Type V collagen, Mismatch repair protein

POSTERS

P1.06-02 NATIONAL TRENDS IN OUTCOMES IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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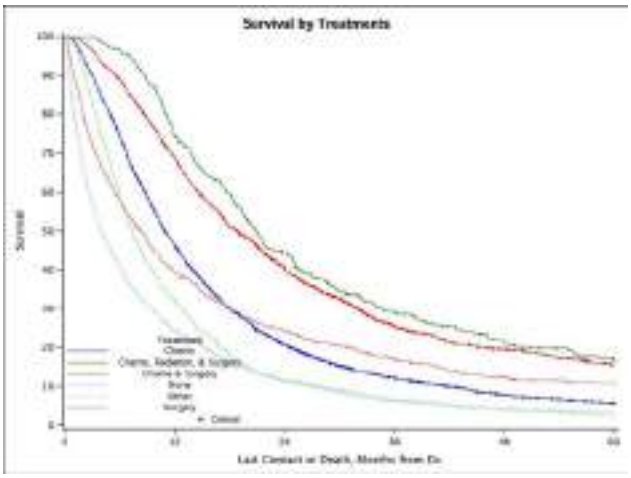
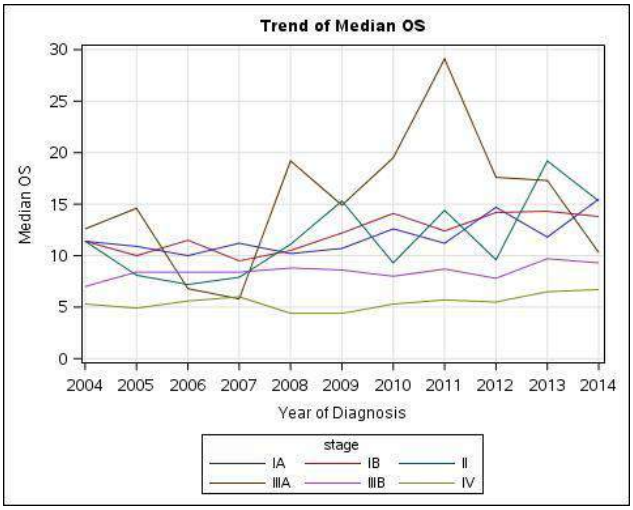
Background: Malignant pleural mesothelioma is an aggressive tumor and is often incurable. We aim to identify national practice patterns and trends in survival in patients with mesothelioma. **Method:** We queried National Cancer Database from years 2004-2014 to identify adult mesothelioma cases. We collected baseline characteristics were collected and analyzed treatment patterns and survival trends. Multivariable Cox regression models were applied to identify factors associated with survival. **Result:** Of 11,372 patients 4354 (38%) had epithelioid histology, 1431 (12%) sarcomatoid, 880 (0.7%) biphasic, and 4707 (41%) unspecified. 20% were stage IA, 22% stage IB, 2% stage II, 1% stage IIIA, 31% stage IIIV, and 23% were stage IV. Sarcomatoid histology was associated with worst overall survival (HR 2.2) while epithelioid histology had best survival (referent). Chemotherapy alone was the most common treatment modality (36%). Combined treatment with surgery, radiation, and chemotherapy was associated with best overall survival (HR 0.45) followed by chemotherapy combined with surgery. However, 1 year and 5-year OS remain low at 41.2% and 6.5% respectively. There has been no clinically significant improvement in overall survival from 2004 to 2014.

Multivariate Cox Regression		
Variable	**Level**	**HR (95% CI)**
Age	Unit=1	1.018 (1.015-1.020)
Academic	No vs Yes	1.171 (1.124-1.221)
Charlson Score	1 vs 0	1.104 (1.053-1.158)
	2 vs 0	1.201 (1.109-1.300)
	>=3 vs 0	1.460 (1.279-1.666)
Histology	Biphasic vs Sarcomatoid	0.737 (0.675-0.805)
	Epithelioid vs Sarcomatoid	0.460 (0.432-0.491)
	NOS vs Sarcomatoid	0.552 (0.518-0.587)
Sex	Female vs Male	0.817 (0.779-0.857)
Year	Unit=1	0.984 (0.977-0.990)
Insurance	Medicaid vs Private	1.193 (1.043-1.364)
	Medicare vs Private	0.993 (0.940-1.048)
	Other/None/Unknown vs Private	1.038 (0.938-1.148)
Stage	IB vs IA	1.156 (1.088-1.228)
	II vs IA	1.229 (1.056-1.431)
	IIIA vs IA	1.442 (1.164-1.788)
	IIIB vs IA	1.459 (1.379-1.544)
	IV vs IA	1.801 (1.695-1.913)
Treatment	Chemo vs None	0.613 (0.584-0.643)
	Chemo, Radiation, & Surgery vs None	0.450 (0.396-0.512)
	Chome & Surgery vs None	0.468 (0.436-0.504)
	Other vs None	0.737 (0.682-0.796)
	Surgery vs None	0.694 (0.638-0.756)





Conclusion: Survival outcomes in mesothelioma remain poor. There is a need for more clinical trials using combinatorial approaches to improve outcomes in mesothelioma.

Keywords: mesothelioma ncdb, mesothelioma national cancer database

P1.06-03 SELECTIVE DEPLETION OF FOXP3⁺ REGULATORY T CELLS AFTER LOCAL RADIOTHERAPY INDUCES ABSCOPAL EFFECTS IN MURINE MALIGNANT MESOTHELIOMA

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Background: Increasing evidence indicates that local radiotherapy (LRT) can invoke both local and systemic immune responses. Combining blockade of radiation-induced immunosuppressive responses with LRT may augment antitumor effects. Mice expressing a diphtheria toxin (DT) receptor under control of the *Foxp3* locus (DEREG mice) allow conditional and efficient depletion of Foxp3⁺ regulatory T cell (Treg) by DT injection. This study aimed to elucidate the antitumor effect of selective depletion of Tregs combined with LRT in a murine malignant mesothelioma model. **Method:** The infiltration of CD8⁺ T cells and Tregs was examined by flow cytometry at different time points after nonablative hypofractionated radiation (5 Gy x 3 days) in a murine mesothelioma model. AB12 murine mesothelioma cells were injected s.c. into syngeneic DEREG mice at two separate sites, defined as a "primary" site that was irradiated and a "secondary" site outside the radiation field. These mice were treated with LRT alone, DT injection alone, or a combination of LRT and DT injection. **Result:**

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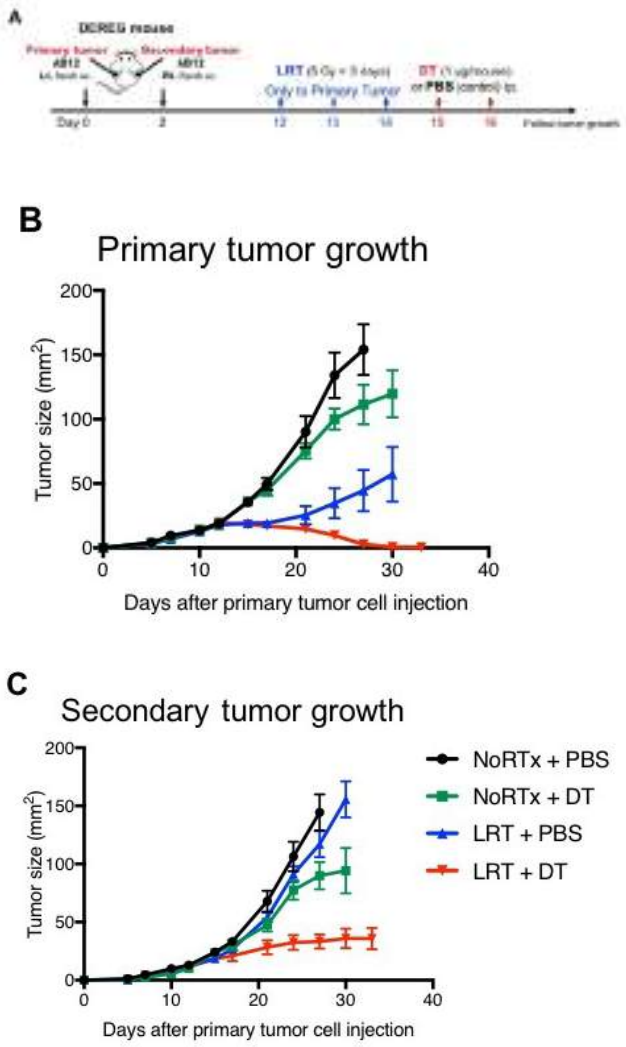

The proportion of CD8⁺ T cells and Tregs of total CD45⁺ cells in tumors were not different between radiated and untreated mice on day 2 and 5 after LRT. However, on day 7 and 12, both CD8⁺ T cells and Tregs in tumors significantly increased in mice treated with LRT compared with those without LRT. Selective Treg depletion by DT injection after LRT showed the best tumor growth delay in both primary and secondary tumor sites compared with LRT alone and DT injection alone. CD8⁺ T cells in spleen showed increased intracellular IFN-γ and Granzyme B production in mice treated with a combination of LRT and DT injection. **Conclusion:** Selective Treg depletion after LRT has the potential to evoke efficient local and systemic antitumor responses in murine mesothelioma. Our findings might have implications for future therapeutic strategies in mesothelioma patients.

Keywords: DEREG, Abscopal effect, Regulatory T cells

P1.06-04 DEEP LEARNING-BASED SEGMENTATION OF MESOTHELIOMA ON CT SCANS: APPLICATION TO PATIENT SCANS EXHIBITING PLEURAL EFFUSION

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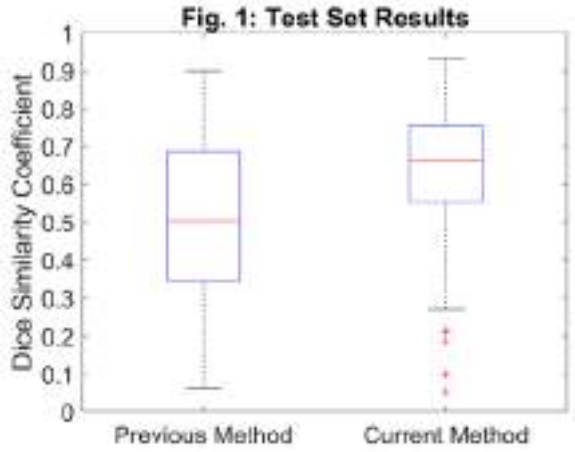
Background: Tumor volume has been a topic of interest in the evaluation of treatment response, staging and prognosis of malignant pleural mesothelioma patients. Many mesothelioma patients present with or develop pleural fluid, the presence of which may complicate tumor segmentation on CT scans. We implemented a method for the automated segmentation of mesothelioma tumor on CT that explicitly excludes pleural effusion, which, if included in the segmentation of tumor, could confound the assessment of tumor volume. **Method:** Deep convolutional neural networks (CNNs) were trained for the segmentation of mesothelioma tumor in each hemithorax. A database was collected of 180 CT scans of 160 mesothelioma patients who exhibited tumor and pleural effusion. 6026 axial sections containing segmented tumor (1243 sections exhibiting pleural effusion) from 134 chest CT scans were used to train deep CNNs for segmentation of mesothelioma tumor. A radiologist contoured tumor on a test set of 94 axial sections that exhibited both tumor and pleural effusion; these sections were randomly selected from 46 CT scans of 34 patients not included in the training set. Performance was evaluated on the test set by calculating the Dice Similarity Coefficient (DSC) between computer-generated and reference segmentations; DSC is a measure of overlap between a pair of segmentations (a value of 0 indicating no overlap, 1 indicating complete overlap). We compared the performance of the present method to a previously published deep learning-based method for the automated segmentation of mesothelioma tumor on CT scans; differences in DSC values achieved on the test set by the two methods were assessed through a two-tailed paired Wilcoxon signed-rank test. **Result:** A boxplot of DSC values achieved on the test set by the current method and the previously published method is shown in Fig. 1. The median DSC on the test set achieved by the current method was 0.66 (inter-quartile range 0.20); the median DSC on the test set achieved by the previously published method was 0.51 (inter-quartile range 0.34). The difference in DSC between the two methods was statistically significant ($p < 0.0001$).



Conclusion: A deep CNN was implemented for the task of automated segmentation of mesothelioma tumor on CT scans of patients who also exhibit pleural effusion. The present method achieved a statistically higher overlap ($p < 0.0001$) with radiologist-provided reference contours than a previously published method on a test set of 94 axial CT sections of mesothelioma patients exhibiting both tumor and pleural effusion.

Keywords: tumor segmentation, Computed tomography, malignant pleural mesothelioma

P1.06-05 CLINICAL FEATURES AND OUTCOMES OF RECURRENCE AFTER PLEURECTOMY/DECORTICATION FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor while most patients experience recurrence after multimodality treatment. However, few clinical studies have been conducted to evaluate the recurrence pattern and survival after Pleurectomy/decortication (P/D) for MPM. **Method:** We reviewed the patients who registered in the prospective MPM database of our hospital surgery program between September 2012 and December 2017. Eligibility criteria were age ≤80 years, histological subtype on pleural biopsy was epithelioid, clinical stage T1-3N0-1M0 (8th edition), an Eastern Cooperative Oncology Group performance status of 0-1, no major comorbidity. Neoadjuvant chemotherapy (NAC) consisted of pemetrexed followed by cisplatin was performed in all patients who met previously mentioned inclusion criteria. After NAC for three cycles, curative-intent surgery was planned in patients who showed no apparent tumor progression. In our hospital, P/D

was introduced in September 2012, and since then P/D was main operative method for MPM. After P/D, If the patients keep good general condition, the patients underwent adjuvant chemotherapy consisted of pemetreced follow by cisplatin. The subjects were 90 patients who underwent NAC followed by P/D from September 2012 to December 2017. Survival and recurrence were calculated by the Kaplan-Meier method using the log rank test. Clinical factors related to survival after recurrence was assed by a multivariable analysis using Cox proportional hazards model. **Result:** Between September 2012 and December 2017, 140 consecutive patients were eligible for multimodality treatment. All patients completed neoadjuvant chemotherapy. Of these, 112 patients proceeded to surgery, and the remaining 28 patients didn't because of progressive disease (N= 20) or because they refused to provide consent (N= 8). Of 112 patients who proceeded to surgery, 12 patients underwent Extrapleural pneumonectomy, 10 patients underwent exploratory thoracotomy. Finally, 90 patients underwent P/D. Of 90 patients, 65 patients (72.2%) completed multimodality treatment. The 1-year and 3-year overall survival rates after diagnosis were 93.3% and 65.3%, respectively. A recurrence developed in 57 (63.3%). The median time to recurrence was 19.0 months. 1-year and 3-year recurrence free survival were 69.7% and 34.0%, respectively. In the initial recurrence, local recurrence only was developed in 39 patients (68.4%), distant recurrence only in 6 patients (10.5%), and both local and distant recurrence in 12 patients (21.1%). 1-year survival rates after recurrence was 59.5%. 43 patients (75.4%) received a treatment for recurrence. On multivariable analysis, treatment for recurrence (hazard ratio, 0.16; 95% confidence interval, 0.06–0.41: P < 0.0001) and disease-free interval greater than 12 months (hazard ratio, 0.34; 95% confidence interval, 0.14 –0.79; P = 0.01) were identified as independently significant prognostic factors of survival after recurrence. **Conclusion:** The local recurrence remain the most frequent pattern of recurrence after P/D. Most of patients who had recurrence after P/D enabled treatment for recurrence. Treatment for recurrence and disease-free interval greater than 12 months are important prognostic factors of survival after recurrence.

Keywords: Mesothelioma, pleurectomy/decortication, Recurrence

P1.06-06 EORTC 1205: RANDOMIZED STUDY OF PLEURECTOMY/DECORTICATION (P/D) PRECEDED OR FOLLOWED BY CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: P/D is considered a valid surgical approach in selected pts with resectable MPM with less morbidity than extrapleural pneumonectomy. The procedure is however, poorly standardized and never radical, and is hence preferably preceded or followed by systemic chemotherapy. EORTC 1205 aims at comparing the optimal sequencing of chemotherapy with P/D with regard to overall treatment time and feasibility. **Method:** Functionally operable treatment-naïve pts with T1-3 N0-2 epithelial or biphasic mesothelioma and PS 0-1 are randomized between adjuvant (arm A) and neo-adjuvant chemotherapy (arm B). Chemotherapy in both arms consists of 3 cycles of cisplatin and pemetrexed at standard dosage and with premedication. P/D is performed by experienced thoracic surgeons in credentialed centers. Strict timelines between both procedures apply and surgical quality is audited with intra-operative mapping and imaging and comprehensive registration of complications. Primary endpoint in the intention-to-treat population is successful completion of the multimodality treatment within 20 weeks of randomisation and being alive with no signs of PD and/or persistent grade III-IV toxicity. **Result:** As of April 10, 2019, 30 pts of the required sample size of 64 have been randomized and 17 operated. Baseline patient and tumor characteristics appear well balanced sofar (table).

Characteristics and treatment results as per 1/04/2019

Table	Arm A	Arm B	All
N	16	14	30
Male gender (%)	56	71	63
Median age (y)	62	66	64
WHO PS 0/1	10/6	7/7	17/13
TNM Stage 1/2/3 at presentation	6/6/4	9/2/3	15/8/7
% administered 3 cycles of chemotherapy	88	100	94
N operated	9	8	17
Median time between randomization and 1st treatment modality (weeks)	2.9	1.6	2.0
Median time between 1st and 2nd treatment modality	5.7	11.0	10.1
N completed treatment	9	8	17
Median overall treatment time in those completing treatment	23.7	18.7	21.3

Conclusion: Trial accrual proceeds on schedule and last patient will be included in 2020. A protocol amendment will allow carboplatin/pemetrexed as induction regimen. An updated analysis on all included patients as per 1/08/2019 will be presented at the meeting.

Keyword: mesothelioma pleurectomy/decortication chemotherapy

P1.06-07 TARGETING PHOTO-THERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA; NEAR INFRARED PHOTOIMMUNOTHERAPY TARGETING PODOPLANIN

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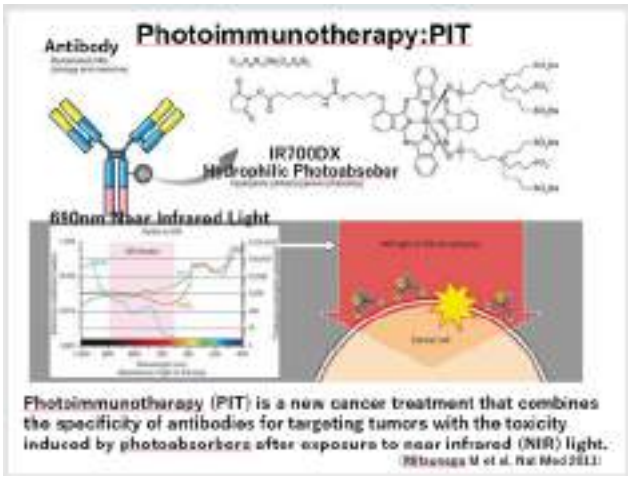
Background:



Malignant pleural mesothelioma (MPM) has a poor prognosis, and the number of patients is thought to increase in the future over the world. However, the therapy for MPM is very limited with few regimens. Thus, development of new therapies for unresectable MPM is highly desirable. Podoplanin is a transmembrane glycoprotein that has been reported to be specifically up-regulated in MPM, and the antibody(D2-40) has been used as a marker to decide MPM in pathological diagnosis. This time, we successfully established a new anti-podoplanin antibody, NZ-1. Near infrared photoimmunotherapy (NIR-PIT) is a recent-developed cancer therapy that combines the specificity of intravenously injected antibodies for targeting tumors with the toxicity induced by photosensitizers after exposure to near infrared (NIR) light. It is now in international Phase III clinical trial against locoregional, recurrent head and neck squamous cell cancer

(LUZERA-301), and expected to be clinically licensed in near future. In this preclinical study, we develop new photo-targeting therapy against MPM, with the combination of NIR-PIT and NZ-1. **Method:** An antibody-photosensitizer conjugate consisting of NZ-1 and a phthalocyanine dye, IRDye-700DX, was synthesized and evaluated its specificity. *In vitro* and *in vivo* experiments were conducted with a podoplanin, luciferase expressing mesothelioma cell line(MSTO-211H/PDPN-luc-GFP). *In vitro* NIR-PIT cytotoxicity was assessed with dead staining and luciferase activity. In vivo NIR-PIT was examined in mice with tumors implanted in the flank or in the thoracic cavity, by in vivo real-time imaging with luciferase activities. **Result:** *In vitro* NIR-PIT-induced cytotoxicity was in a light dose dependent. *In vivo* NIR-PIT led significant reductions in both tumor volume ($p<0.05$ vs. APC) and luciferase activity ($p<0.05$ vs. APC) in a flank model. Bioluminescence indicated that NIR-PIT lead to reduction in pleural dissemination mice model. **Conclusion:** This study suggested that podoplanin-targeting-NIR-PIT with NZ-1 could be a new promising treatment for MPM.

Keywords: podoplanin, Mesothelioma, Photoimmunotherapy

P1.06-08 WDPM-LIKE BUT NOT CRIBRIFORM AS SECONDARY GROWTH PATTERNS MODIFY SURVIVAL IN EPITHELIOID MALIGNANT PLEURAL MESOTHELIOMA

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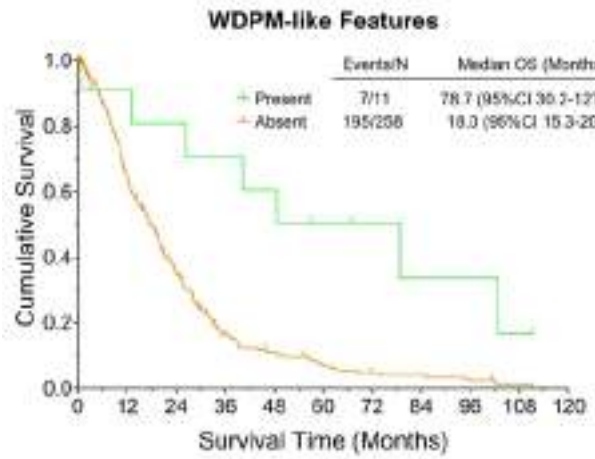
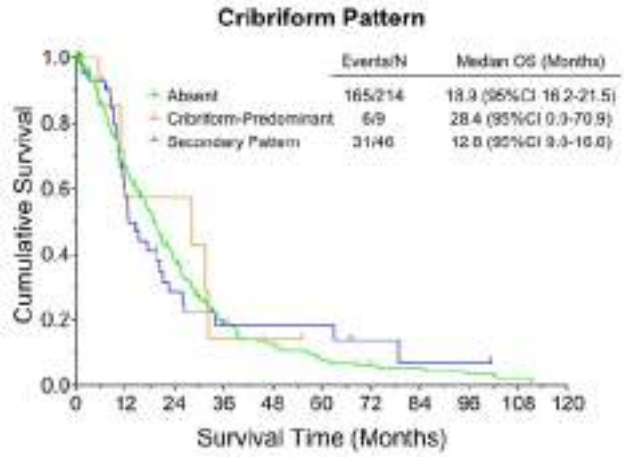
Background: The presence of well differentiated papillary mesothelioma (WDPM)- like and cribriform growth patterns in otherwise unequivocally invasive, tubulo-papillary-predominant epithelioid malignant pleural mesothelioma (MPM) is recognised in clinical practice, but their prognostic impact is largely uncertain. We hypothesise they modify prognosis as secondary patterns. **Method:** We retrospectively reviewed the tubulo-papillary-predominant, invasive epithelioid MPM (n=269) as a subset of 614 consecutive epithelioid MPM diagnosed at our institution over a 15-year period. The diagnostic criteria for WDPM-like and cribriform patterns were inferred from those of canonical WDPM and lung adenocarcinoma. Survival analysis was performed using Kaplan-Meier method. **Result:** We identified 10 cases of tubulo-papillary-predominant epithelioid exhibiting WDPM-like pattern, and one case being predominantly WDPM-like (Estimated incidence 4.1%). They are associated with significantly prolonged median overall survival (78.7 months vs. 18.0 months, p=0.001). On the other hand cribriform neither as predominant (n=9, 3.3%, p=0.672) or secondary growth patterns (n=46, 17.1%, p=0.952) achieved statistical significance in univariate setting compared with tubulo-papillary epithelioid MPM without such pattern.





Conclusion: We propose tubulo-papillary-predominant epithelioid MPM with WDPM-like features as a rare and favourable prognostic group. Further molecular analysis is planned. Cribriform pattern does not appear to be prognostically relevant. We recommend external validation of our findings for both growth patterns.

Keywords: well differentiated papillary mesothelioma, cribriform, malignant pleural mesothelioma

P1.06-09 PROPHYLACTIC IRRADIATION OF TRACTS IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The role of prophylactic irradiation of tracts (PIT) to prevent tumour seeding at the site of a diagnostic or therapeutic intervention in patients with malignant pleural mesothelioma (MPM) is controversial. This study aimed to determine the efficacy of PITs in preventing procedure tract metastases (PTM) after a procedure in MPM. **Method:** We searched biomedical literature databases and conference proceedings for randomized trials (RCTs) comparing PIT with no PIT in patients who had a chest wall procedure for MPM. We assessed the methodologic quality of individual RCT using the Cochrane Risk of Bias Tool. Meta-analysis was performed using a random effects model. Heterogeneity was assessed using the I^2 values. We used the GRADE approach to assess the quality of the overall evidence. The outcomes of interest were incidence of PTM and time to PTM. **Result:** We found five RCTs including 737 patients. All RCTs have low to unclear risk of bias in their methodologic quality. PIT was associated with a statistically non-significant reduction in the risk of PTM development (risk ratio (RR) 0.67, 95% confidence interval (CI) 0.35 to 1.28, P value (P) = 0.23, I^2 = 43%, GRADE: Moderate quality) and delay in the time to PTM development (hazard ratio (HR) 0.67, 95% CI 0.42 to 1.03, P = 0.07, I^2 = 0%, GRADE: Moderate quality). Limiting the meta-analysis to the two largest contemporary trials demonstrated that PIT significantly reduced the risk of PTM development (RR 0.58, 95% CI 0.37 to 0.92, I^2 = 0%, GRADE: High quality) and delay the time of PTM development (HR 0.60, 95%CI 0.37 to 0.99, I^2 = 0%, GRADE: High quality). **Conclusion:** Summation of contemporary evidence suggests that prophylactic irradiation of tracts can prevent or delay procedure tract metastases, and should be considered in patients with malignant pleural mesothelioma.

Keywords: Mesothelioma, Radiation therapy

POSTERS

P1.06-10 18F-FDG PET/CT IN MALIGNANT PLEURAL MESOTHELIOMA: DIAGNOSTIC/PROGNOSTIC PERFORMANCE AND CORRELATION WITH PATHOLOGICAL RESULTS

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Background: While the role of [18]F-FDG-PET/CT-scan in the staging of malignant pleural mesothelioma (MPM) is almost validated, the diagnostic and prognostic performance of this tool is not clearly established. The aims of this study were: 1) to evaluate the detection rate of [18]F-FDG PET/CT-scan and identify possible factors causing false-negative (FN) results 2) to explore the relationship between radiometabolic findings, pathological features and survival results. **Method:** From 01/09 to 07/18, among all 210 MPM-patients observed and treated in 2 high-volume Institutions, we retrieved the clinical, radiometabolic and pathological aspects of 141 cases who underwent [18]F-FDG PET/CT-scan during the diagnostic work-up examination. The Fisher-test was used to test dissimilarities in the prevalence of categorical variables and Cox-model to evaluate overall survivals differences. **Result:** Mean age and male/female ratio were 70.5±7.8 and 3:1, respectively. The mean FDG-SUVmax was 8.1 (SD±5.1); the overall detection rate was 88.3% with 16 patients (11.6%) presented with SUVmax<2.5 ("PET-negative"). The distribution of clinic-pathological variables according to PET-status was reported in Figure 1. PET-negative cases are more frequently observed in older patients (p=0.027) and early stage tumors (FN at 33.3% in Stage I and FN at 40.0% in T1-tumors, both p=0.014). SUVmax values were higher in sarcomatoid (11.8±4.6) and biphasic (mean 9.3±7.0) than in epitheliod (6.9±3.8) tumors (p<0.001). Concerning long-term survivals, we found that among with Stage (p=0.032) and histology (p=0.014), the FDG metabolic uptake (SUVmax values both as continuos and cathegorical variable) was a prognostic factor as confirmed at multivariable analysis (H.R.:2.65,C.I.:1.23-5.70,p<0.001; see Figure 2).

	PET-negative		PET-positive		
					p Value
Gender					1
M	12	11,9%	89	88,1%	
F	4	10,0%	36	90,0%	
Age of Diagnosis					0,027
Mean	73.6+/-4.6		68.2+/-9.6		
Pleural Effusion					1
N	2	8,3%	22	91,7%	
Y	14	11,4%	109	88,6%	
Side					0,719
Both	0	0,0%	3	100,0%	
Left	5	9,4%	48	90,6%	
Right	11	12,9%	74	87,1%	
T					0,014
T1	6	40,0%	9	60,0%	
T2 + T3 + T4	10	7,9%	116	92,1%	
N^					0,081
N0	10	11,6%	76	88,4%	
N1 + N2 + N3	6	11,3%	47	88,7%	
M					1
M0	16	11,9%	118	88,1%	
M1	0	0,0%	7	100,0%	
Stage					0,014
I	5	33,3%	10	66,7%	
II	8	14,3%	48	85,7%	
III	3	5,3%	54	94,7%	
IV	0	0,0%	13	100,0%	
Surgery					0,402
N	9	9,6%	85	90,4%	
Y	7	14,9%	40	85,1%	
Histology					0,267
Epithelial	13	14,6%	76	85,4%	
Biphasic	3	8,3%	33	91,7%	
Sarcomatoid	0	0,0%	16	100,0%	
Histology (grouped)					0,168
Epithelial	13	14,6%	76	85,4%	
Non-Epithelial	3	5,8%	49	94,2%	

Multivariate Cox Analysis (Model 1)			
	Hazard Ratio	**P value**	**(C.I. 95%)**
Age	0,92	0,06	0.84-1.00
Gender (M)	0,82	0,767	0.20-2.79
T-Factor	2,39	0,022	1.16-5.20
Histology (Grouped)	2,77	0,143	0.79-13.1
Multivariate Cox Analysis (Model 2)			
	Hazard Ratio	**P value**	**(C.I. 95%)**
Age	0,90	0,028	0.82-0.98
Gender (M)	0,82	0,766	0.20-2.84
Stage	2,94	0,004	1.47-6.43
Histology (Grouped)	2,46	0,205	0.67-12.0

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	# patients	# events	median	Hazard Ratio	P-value	(C.I. 95%)
Gender^						
M	99	78	17			
F	39	23	23	0,73	0,196	0.46-1.17
Age of Diagnosis						
				1	0,842	0.98-1.03
Smoking Habits^						
Non smokers	45	32	25			
(Former) Smokers	65	52	18	0,96	0,866	0.58-1.59
Asbestum^						
N	26	20	22,5			
Y	87	66	18	1,28	0,273	0.82-2.01
Pleural Effusion						
N	24	20	21			
Y	114	81	17	1,34	0,256	0.81-2.21
Side						
Both	3	1	28			
Left	51	34	21	2,26	0,424	0.31-16.56
Right	84	66	17	3,34	0,232	0.46-24.12
PS						
0	90	63	22			
1	36	28	13	1,51	0,072	0.96-2.37
2	9	7	12,5	1,64	0,219	0.75-3.60
3	3	3	18	1,51	0,484	0.47-4.84
PET Status						
Negative (SUXmax <2.5)	16	8	35			
Positive (SUXmax >2.5)	122	93	17	2,65	**0,009**	1.28-5.48
SUVmax (continuos)						
				1,07	**<0.0001**	1.04-1.11
T						
1	15	8	28			
2-3-4	123	95	17	1,99	**0,046**	0.94-4.03
N^						
0	87	61	22			
1-2-3	49	38	12	1,91	**0,002**	1.26-2.88
M						
0	131	95	18			
1	7	6	14	1,99	0,104	0.87-4.57
Stage						
I	15	10	24,5			
II	54	39	22	1,36	0,389	0.68-2.73
III	56	42	13	2,14	**0,032**	1.07-4.29
IV	13	10	14	1,93	0,144	0.80-4.64
Surgery						
N	91	69	17			
Y	47	32	19	0,77	0,230	0.51-1.18
Histology						
Epithelial	87	59	22			
Biphasic	35	27	16	1,30	0,268	0.82-2.05
Sarcomatoid	16	15	10	3,24	**<0.0001**	1.82-5.77
Histology (grouped)						
Epithelial	87	59	22			
Non epithelial	51	42	13	1,65	**0,014**	1.11-2.46

Multivariate Cox Analysis (Model 1)			
SUV	1,07	**0,0005**	1.03-1.10
Stage	1,31	**0,019**	1.05-1.65
Histology (grouped)	1,47	0,078	0.96-2.26
Multivariate Cox Analysis (Model 2)			
	Hazard Ratio	**P value**	**(C.I. 95%)**
Age	1,02	0,182	0.99-1.04
Gender (M)	1,48	0,105	0.92-2.38
PET Status	2,65	**0,013**	1.23-5.70
Stage	1,21	0,122	0.95-1.54
Histology (grouped)	1,75	**0,007**	1.16-2.63

Conclusion: Despite MPMs have an aggressive biological behavior, a low metabolic uptake at ^{18}F-FDG PET/CT-scan may be observed in part of them (about 12% in our cohort), especially in early-stage tumors occurring in elderly patients. High SUVmax value correlates with locally-advanced stage and non-epitheliod MPMs and is associated with a worse prognosis.

Keywords: malignant pleural mesothelioma, PET, SUVmax

P1.06-11 OVERLAPPING IMMUNOPHENOTYPES BETWEEN MESOTHELIOMA AND ANGIOSARCOMA: USEFULNESS OF CLAUDIN-5 IN THE DIFFERENTIAL DIAGNOSIS

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Background: Differential diagnosis between mesothelioma and angiosarcoma remains challenging because of their overlapping morphological and immunohistochemical phenotypes. Angiosarcoma may show both epithelioid and sarcomatoid morphology and is occasionally a cytokeratin-expressing tumor as with mesothelioma. Generally, endothelial markers are always expressed by angiosarcoma but not by mesothelioma; however, a subset of mesothelioma expresses endothelial markers, making the usefulness of these markers limited. Currently, little information is available about the immunoreactivity of mesothelioma to endothelial markers. Therefore, we investigated immunoreactivities of mesothelioma and angiosarcoma to endothelial markers and sought to identify a useful marker in their differential diagnosis. **Method:** We enrolled 147 cases of pleural mesothelioma, comprising 93 epithelioid, 25 biphasic, and 29 sarcomatoid subtypes. For comparison, we used 41 cases of angiosarcoma occurring in various organs. Using a tissue block showing the representative morphology, the expressions of endothelial (CD31, CD34, factor-VIII, ERG, and claudin-5) and of mesothelial markers (calretinin, WT-1, CK5/6, and EMA) were evaluated by immunohistochemistry. **Result:** Calretinin and WT1 were expressed in 82.2% (120/146) and 82.9% (116/140) cases of mesothelioma, respectively. Among the three subtypes of mesothelioma, the immunoreactivity of sarcomatoid mesothelioma to calretinin was relatively low with the positivity of 48.3% (14/29). Calretinin was expressed in none of the angiosarcoma cases (0/41), whereas WT-1 was expressed in 4.9% (2/41) cases of angiosarcoma. Conventional endothelial marker (CD31, CD34, factor VIII, and ERG) were expressed in 10.3% (15/146), 3.5% (5/142), 3.4% (5/146), and 29.1% (39/134) cases of mesothelioma, respectively. The immunoreactivities of sarcomatoid mesothelioma to conventional endothelial markers were relatively high with the positivity of 31.0% (9/29) for CD31, 7.1% (2/28) for CD34, 10.7% (3/28) for factor VIII, and 56.0% (14/25) for ERG. Claudin-5 expression was observed in all the angiosarcoma cases (36/36), but in none of the mesothelioma cases (0/138). **Conclusion:** We showed overlapping immunophenotypes between mesothelioma and angiosarcoma. Endothelial markers, except for claudin-5, were more frequently expressed than expected by mesothelioma, especially by sarcomatoid mesothelioma. High sensitivity and specificity of claudin-5 in the distinguishment of angiosarcoma from mesothelioma suggest the usefulness of this marker, indicating that claudin-5 should be included in a panel of immunohistochemical markers in the differential diagnosis between mesothelioma and angiosarcoma.

Keywords: Mesothelioma, Claudin-5, Angiosarcoma

P1.06-12 DEFECTS IN HOMOLOGOUS RECOMBINATION REPAIR INDICATES SUSCEPTIBILITY FOR OLAPARIB TREATMENT IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a tumour with dismal prognosis. Chemotherapeutic treatment with pemetrexed combined with cisplatin shows unsatisfying response-rates of 40%. The reasons for the rather poor efficacy remain largely unknown. However, it is conceivable that DNA repair mechanisms lead to an impaired therapy response. We hypothesize a major role of homologous recombination (HR) for genome stability and survival of this tumour. Therefore, we analysed expression levels of genes compiled under the term "BRCAness". An inhibition of this pathway with olaparib might abrogate this effect and induce apoptosis. **Method:** We evaluated the response of three MPM cell lines and lung fibroblasts, serving as a control to treatment, with pemetrexed, cisplatin and olaparib. Furthermore, we aimed to find correlations between response and gene expression patterns associated with BRCAness phenotype. Therefore, 91 clinical MPM samples were digitally screened for gene expression patterns of HR members. **Result:** We observed a BRCAness-dependent increase of apoptosis and senescence during olaparib-based treatment of BRCA-associated-protein 1 (*BAP1*)-mutated cell lines. The gene expression pattern identified could be found in approx. 10% of patient samples. Against this background, patients could be grouped according to their defects in the HR system. Gene expression levels of Aurora Kinase A (*AURKA*), *RAD50* as well as DNA damage-binding protein 2 (*DDB2*) could be identified as prognostic markers in MPM. **Conclusion:** Defects in HR compiled under the term BRCAness are a common event in MPM. The present data may improve the understanding of underlaying cellular mechanisms and open new possibilities for modern therapeutic approaches for this severe disease. Response to *Poly (ADP-ribose)-Polymerase* (*PARP*)-Inhibition could be demonstrated in the *BAP1*-mutated NCI-H2452 cells, especially when combined with cisplatin. This combination therapy might be effective for up to 2/3 of patients, promising to enhance patients' clinical management and outcome.

Keywords: malignant pleural mesothelioma, BAP1, PARP1

P1.06-13 TREATMENT PATTERNS AND OUTCOMES IN ADVANCED MALIGNANT PLEURAL MESOTHELIOMA: SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATA

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Background: Malignant pleural mesothelioma (MPM) is a rare neoplasm with poor prognosis. With only one approved systemic treatment (Tx) for advanced disease in first-line (1L), pemetrexed with a platinum agent, the objective of this study is to understand patterns of care and overall survival (OS). **Method:** This retrospective cohort study using Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims included patients aged ≥ 66 years with a primary diagnosis (Dx) of MPM between 2007–2013 (followed through 2014). Treated patients who received chemotherapy as 1L within 90 days of Dx, second-line (2L), or third-line (3L) therapy were identified. We used Kaplan-Meier product limit estimator for OS. **Result:** Of 1556 patients with MPM, 666 had advanced MPM. Of patients with advanced MPM, 82% were male, 87% white, 78% had AJCC Stage IV, and 70% had no mobility limitation indicators (eg oxygen tank use) at Dx. Chemotherapy for advanced MPM was received by 262 (39%) patients in 1L, 106 (16%) in 2L, and 29 (4%) in 3L. Of 1L patients, 209 (80%) received standard of care (SOC) pemetrexed with platinum (other 1L regimens included pemetrexed monotherapy; gemcitabine and vinorelbine). Of the 209 patients, 41% (n = 86) initiated 2L therapy, of whom 26% (n = 22) initiated 3L. Within 90 days of Dx, 52% of patients visited an emergency department, 78% were hospitalized, and 21% had hospice care. Common 2L therapies were gemcitabine and pemetrexed (alone or in combination); 3L regimens included vinorelbine and gemcitabine. Median OS for all patients was 7.2 months and 10.7 months for 1L (table). Unadjusted OS and Tx Duration

Cohort*	N	Median OS (months; 95% CI)	1-Year Survival (95% CI)	2-Year Survival (95% CI)	Median Tx Duration (days; IQR)
Dx	666	7.2 (6.6–8.2)	0.34 (0.30–0.38)	0.14 (0.11–0.17)	NR
1L	209	10.7 (9.6–12.0)	0.43 (0.36–0.50)	0.15 (0.11–0.22)	84 (42–136)
2L	86	5.3 (4.0–7.0)	0.22 (0.14–0.33)	0.04 (0.01–0.13)	55 (33–102)
3L	22	4.9 (3.8–7.3)	NR	NR	52 (24–77)

*1L, 2L, 3L include only 1L pemetrexed + platinum

Conclusion: This study highlights the significant unmet need in advanced MPM. Low Tx rates and poor overall survival were observed for all patient groups, suggesting patients may benefit from additional tx options.

Keywords: Survival, treatment patterns, Mesothelioma

P1.06-14 POSTERIOR INTERCOSTAL LYMPH NODE POSITIVITY AS A PROGNOSTIC INDICATOR OF OVERALL SURVIVAL IN RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA

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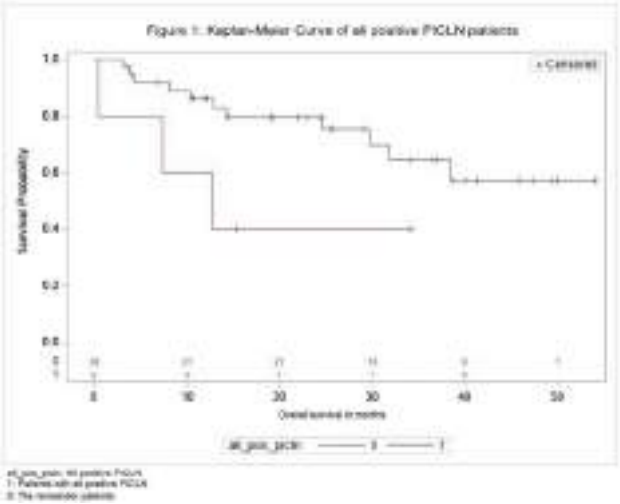
Background: Posterior intercostal lymph nodes (PICLN), located between posterior ribs and near the spine, are characterized as N1 disease and not typically sampled in resectable malignant pleural mesothelioma (MPM). It has been noted that positive PICLN were associated with decreased overall survival (OS), suggesting their proposed characterization as N2 disease. We seek to validate their significance in an independent patient cohort. **Method:** This single institution retrospective study included 43 MPM patients who underwent surgery, largely extended pleurectomy/decortication, from March 2015 to February 2019. During surgery, accessible PICLN were sampled for pathologic testing. Patients' demographic information, clinical history, and surgical pathology were collected via review of medical records after IRB approval. To examine associations between OS and number of PICLN, Pearson correlation coefficients were performed. Survival analysis was performed using log-rank test and Cox regression model. **Result:** Patient demographics and clinical characteristics are described in Table 1. Pathologic positivity of PICLN was significantly associated with stage (Fisher exact P=0.006). 11.6% of patients demonstrated disease in all sampled PICLN (all positive PICLN) and 4.6% of patients presented with solely PICLN involvement. Compared to patients with no nodal involvement, patients with all positive PICLN were associated with a shorter overall survival (p=0.08). In a Cox regression model that adjusted for stage, all positive PICLN were associated with an increased risk of death (HR=3.13, P=.048), while the presence of any positive PICLN was not significant (HR=2.03, p=0.23).

Table 1: Characteristics of Mesothelioma Surgical Patients (N=43)

Age (group)			
	<60 years old	9	20.93
	>=60 years old	34	79.07
Gender			
	Male	34	79.07
	Female	9	20.93
Smoking history			
	Never	26	60.47
	Former	14	32.56
	Active	3	6.98
Asbestos exposure			
	Yes	24	55.81
	No	19	44.19
Histology			
	Biphasic	7	16.28
	Desmoplastic	1	2.33
	Epithelial	34	79.07
	Sarcomatoid	1	2.33
Positive Thoracic Lymph Node (TLN)			
	Yes	21	48.84
	No	22	51.16
All positive TLN			
	Yes	1	2.33
	No	42	97.67
Any Positive Posterior Intercostal Lymph Node (PICLN)			
	Yes	9	20.93
	No	34	79.07
Solely PICLN involvement			
	Yes	2	0.05
	No	41	0.95
All positive PICLN			
	Yes	5	11.63
	No	38	88.37
Clinical stage*			
	Stage 1	19	44.19
	Stage 2	4	9.30
	Stage 3	20	46.51
	Stage 4	0	0.00
Surgery type			
	EPD	42	97.67
	Partial Pleurectomy	1	2.33
Pericardial resection			
	Yes	16	37.21
	No	27	62.79
Diaphragm resection			
	Yes	32	74.42
	No	11	25.58
Chemotherapy[1]			
	Yes	39	90.70
	No	4	9.30
Pre-operation chemotherapy			
	Yes	10	23.26
	No	33	76.74
Post-operation chemotherapy			
	Yes	31	72.09
	No	12	27.91
Additional chemotherapy[2]			
	Yes	10	23.26
	No	33	76.74
Radiation therapy[3]			
	Yes	12	27.91
	No	31	72.09
X-ray radiation therapy			
	Yes	10	23.26
	No	33	76.74
Status of patients at the last follow up		**N**	**%**
	Alive with disease	26	60.47
	Dead of disease	15	34.88
	No evidence of disease	2	4.65
Overall survival		**Mean**	**SD**
		23	15
		N	**%**
	<6 months	6	13.95
	6-12 months	8	18.60
	1-2 years	10	23.26
	2-3 years	8	18.60
	3-4 years	8	18.60
	4-5 years	3	6.98
	>=5 years	0	0.00

1. Chemotherapy: patient had any pre-surgery, post-surgery, or additional therap
2. Additional chemotherapy: After the post-surgery chemotherapy, some patients chemotherapy. Generally, it is a 2nd or 3rd line therapy, immunotherapy, or targ
3. Radiation therapy: Patient had either X-ray radiation therapy, proton therapy,

* Clinical staging is based on International Association for the Study of Lung Cancer the TNM classification for malignant pleural mesothelioma



Conclusion: In addition to validating the negative prognostic impact of PICN, our analysis suggests that survival may be more so dependent on the degree of PICLN involvement than positivity itself. However, given the limited number of patients with solely PICLN positive lymph nodes, the role of PICLN as an independent prognosticator cannot be confidently determined and larger studies are needed.

Keywords: pleural mesothelioma, posterior intercostal lymph nodes

POSTERS

P1.06-15 SAFETY OF IRRADIATION COMBINED WITH INTRACAVITARY CISPLATIN-FIBRIN AFTER LUNG-SPARING SURGERY IN A RAT MODEL OF MESOTHELIOMA

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Background: To investigate feasibility and toxicity of new localized therapeutic treatment combinations for malignant pleural mesothelioma (MPM), we performed lung-sparing surgery followed by cisplatin-fibrin application and hemithoracic irradiation in an orthotopic immunocompetent rat model of MPM. **Method:** Male F344 rats (n=9) were implanted sub-pleurally (parietal pleura) with 1 million rat mesothelioma cells (IL45-luciferase). Formed tumor nodules confirmed by IVIS bioluminescence imaging (BLI) were resected on day 9 after implantation. Following resection, animals were treated with local-intracavitary cisplatin-fibrin or placebo (NaCl-fibrin). Three days later, CT guided local irradiation of the former tumor region, resembling IMRT in human patients, was performed. Irradiation was given in a single high dose application using the image-guided stereotactic small animal irradiation X-RAD SmART (small animal radiotherapy) and image guided biological irradiator PXi (precision X-Ray) with precise localization. Treatment schemes after tumor resection were as followed: i) Intracavitary cisplatin-fibrin application (n=2) ii) Irradiation with 10 Gy (n=2) iii) Irradiation with 20 Gy (n=1) iv) Intracavitary cisplatin-fibrin plus 10 Gy radiotherapy (n=2) v) Intracavitary cisplatin-fibrin plus 20 Gy radiotherapy (n=2) Wellbeing of the animals was monitored daily until the predefined termination criteria were reached. Particular attention was given to possible irradiation toxicity related pulmonary side effects and weight loss. **Result:** We successfully treated 1-2 animals per group according to the methods above. The irradiation was performed after visualization of the tumor with BLI- and CT-imaging to ensure an individual treatment plan. None of the animals, whether with radiotherapy alone or in combination with cisplatin-fibrin application, showed any signs of pulmonary side effects. In addition, none had reduced pulmonary functions, measured by increased breathing or the appearance of blue or white colored ear/extremities/eyes assuming desaturation. Furthermore, neither significant body weight loss of ≥ 15%, deterioration of body conditioning score nor of the activity score were observed in the immediate post-interventional phase. In all animals, termination endpoint was reached because of tumor relapse. **Conclusion:** In this pilot study, we have shown that irradiation alone and in combination with local intracavitary cisplatin-fibrin application in rats is safe and feasible up to a dosage of 20 Gy. The efficacy of the various treatment schemes and a possible radio-sensitizing effect by intracavitary cisplatin is currently being evaluated in the same animal model.

Keywords: malignant pleural mesothelioma, intracavitary therapy, irradiation

P1.06-16 MOLECULAR SIGNATURE IN MALIGNANT PLEURAL MESOTHELIOMA (MPM). PRELIMINARY DATA OF RAMES STUDY

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Background: MPM is an uncommon cancer with limited therapeutic options and poor clinical outcomes. The relative rarity of these tumor has limited the identification of MPM-driver molecular as well as the development of specific drugs **Method:** RAMES study evaluated the second-line efficacy of gemcitabine/ramucirumab treatment vs. gemcitabine/placebo. From December 2016 to July 2018 (end of enrolment), 164 patients (pts) were admitted to this study. We evaluated by NGS the mutational profile of a panel of 34 genes (ACTB, ACTG1, ACTG2, ACTR1A, BAP1,CDH8, CDK4, CDKN2A, CDKN2B, COL3A1, COL5A2, CUL1, DHFR, GOT1, KDR, KIT, MXRA5, NF2, NFRKB, NKX6,-2, NOD2, PCBD2, PDZK1IP1, PIK3CA, PIK3CB, PSMD13, RAPGEF6, RDX, SETDB1, TAOK1, TP53,TXNRD1, UQCRC1, XRCC6). We reported the results of the first 87 pts (54%): hystotype was epithelioid in 70 pts (80%), biphasic in 14 pts (16%) and sarcomatoid in 3 pts (4%). Median age was 63 years (range 45-81). 70 pts were male (80%) and 17 pts were female (20%). In the present analysis, we included 55 pts in stage III (63%), 26 pts in stage IV (30%) and 6 pts whose stage was unknown. Median first-line PFS platinum/pemetrexed therapy was for 5.75 months (I.C. 95% 4.75-6.76). PFS was ≤6 months for 40 pts (49%), and 6 months for 41 pts (51%). **Result:** 187 functional somatic mutations were identified. Genomic alterations/patient were 1 gene in 29 pts (33%), 3 genes in 18 pts (21%) and ≥5 genes in 2 pts (2%). The most frequent somatic mutations were *RDX in 35 pts (40%), MXRA5 in 20 pts (23%), BAP1 in 13 pts (15%) and ACTG 1 in 9 pts (11%). When patients were collated by stage, the most frequent mutations were*: MXRA5 in 16 pts in stage III (29%), BAP1 in 5 pts in stage IV (19%) and RDX in 16 pts in stage IV (62%). The percentage of somatic mutations in patients with PFS as first-line chemotherapy for ≤6 and >6 months was 2.2 and 1.6 (p=0.032), respectively. The most frequent mutations/patient for ≤6 and >6 months PFS were: RDX in 14 pts (35%) with PFS ≤ 6, RDX in 19 pts (46%) with PFS >6 and MXRA5 in 11 pts (27%) with PFS >6. **Conclusion:** This preliminary data suggests a possible role that a genetic signature may play in distinguishing MPM with different clinical-pathological features. *The results are expected to be clarified further in the second step of the study, which is ongoing.*

P1.06-17 TUMOR TREATING FIELDS (150 KHZ) COMBINED WITH CISPLATIN OR PEMETREXED INHIBITS MESOTHELIOMA CELLS IN VITRO AND IN VIVO

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Background: Malignant pleural mesothelioma (MPM) is an aggressive thoracic cancer mostly linked to asbestos exposure. The standard of care (SOC) therapy for unresectable MPM is cisplatin plus pemetrexed. Tumor Treating Fields (TTFields) therapy is an effective anti-neoplastic treatment modality delivered via noninvasive application of low intensity, intermediate frequency, alternating electric fields. We explored the potential use of TTFields alone and in combination with SOC as a treatment for MPM. **Method:** NCI-H2052 and MSTO-211H cells were treated at various TTFields frequencies for 72 hours using the inovitro system. The combined treatment of TTFields and cisplatin or pemetrexed was tested by applying TTFields at the optimal frequency together with various drug concentrations. Cell counts, clonogenic potential and induction of apoptosis were determined. TTFields (1.2 V/cm, 150 kHz) were applied for 8 days to rats injected to the intrapleural cavity with IL-45 cells, and overall survival was tested. TTFields (2-3 V/cm) were applied to the torsos of Sprague-Dawley rats at 150 kHz for 2 weeks and all major internal organs were histologically compared. **Result:** TTFields optimal frequency was 150 kHz for both human cell lines. TTFields application (1.1 V/cm, 72 hours) at 150 kHz led to 45%-51% reduction in cell counts and 46%-64% additional reduction in clonogenic potential. The combined treatment of TTFields and cisplatin or pemetrexed led to a significant reduction in cell count, induction of apoptosis, and reduced clonogenic potential as compared to each modality alone (p<0.0001(. TTFields significantly prolonged the survival of rats compared to control group. Histological analysis did not reveal any increase in pathological findings with 150 kHz TTFields applied to the rat torso. **Conclusion:** These results demonstrate that TTFields are a potentially effective and safe treatment for mesothelioma. The combination of TTFields with cisplatin or pemetrexed further enhances treatment efficacy. These preclinical data are consistent with those reported in a recent MPM phase 2 study (STELLAR; EF-23 trial, NCT02397928), which showed improved overall survival for combined treatment with TTFields plus pemetrexed and a platinum agent compared with historical control data, with no increase in systemic toxicity. The combination of TTFields with pemetrexed or cisplatin may further enhance treatment efficacy in mesothelioma.

Keywords: Tumor Treating Fields, *in vitro*, In Vivo

P1.06-18 MICRORNA EXPRESSION IS LINKED TO RESPONSE OF MALIGNANT PLEURAL MESOTHELIOMA TO CISPLATIN-PEMETREXED CHEMOTHERAPY

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Background: Treatment of malignant pleural mesothelioma is difficult due to a high intrinsic drug resistance of these tumors. Currently, platinum-based chemotherapy represents the backbone of MPM treatment. However, only approximately 40% of patients respond to this therapy, and true predictors for response have yet to be identified. Towards this end, we here investigate the expression of microRNAs in responders and non-responders to chemotherapy. **Method:** FFPE tumour samples were available from 32 MPM patients, who showed either partial response (PR, N=21) or progressive disease (PD, N=11) following 3-4 cycles of cisplatin-pemetrexed chemotherapy. RT-qPCR based microRNA profiling was performed on chemo-naïve tissue of 5 PD and 5 PR patients using TaqMan Low Density Arrays (TLDAs, Thermo Fisher), which cover the expression of 754 microRNAs. Candidate microRNAs with differential expression ($P \leq 0.05$ Mann-Whitney Test) were then measured in the remaining samples using microRNA-specific RT-qPCR. Expression of these microRNAs was also assessed in post-chemotherapy specimens (obtained during extrapleural pneumonectomy) and compared to that in chemo-naïve samples. In addition, for two candidates, preliminary *in vitro* experiments investigating the effect of microRNA overexpression (transfection with microRNA mimics) on cell growth were performed. **Result:** TLDA-based profiling identified 35 microRNA with differential expression between patients with PD and PR following cisplatin-pemetrexed chemotherapy. The majority of these microRNAs showed higher expression in patients who showed no reponse to therapy. In an initial step, 8 candidates identified from the profiling (miR-145, miR-193a-3p, miR-30a-3p, miR-24, miR-380-5p, miR-494, miR-625-3p, miR-221-3p) were further evaluated in additional 16 PR and 6 PD samples. This confirmed a trend towards differential expression for miR-145 (p=0.08). Interestingly, when comparing expression pre- and post-chemotherapy, levels of miR-145 significantly decreased in patients with PD, while they remained stable in PR. Lack of validation of other microRNAs could be the result of the low number of cases with PD in this preliminary validation set, and additional samples will included. For miR-221-3p and miR-380-5p, preliminary analysis *in vitro* showed that overexpression in established MPM cell lines results in an increased sensitivity towards cisplatin. **Conclusion:** Taken together, our data show that several microRNAs show trends towards differential expression between responders and non-responders to chemotherapy. Overall, higher expression appears to be linked to PD under cisplatin-pemetrexed, however further in-depth investigations are required. Furthermore, preliminary *in vitro* data suggest that altering expression of specific microRNAs has the potential to increase sensitivity of MPM to chemotherapy.

Keywords: malignant pleural mesothelioma, microRNAs, chemotherapy resistance

P1.06-19 REGIONAL MESOTHELIOMA MULTIDISCIPLINARY TEAM MEETINGS: PERSPECTIVES FROM A UK CARDIOTHORACIC TERTIARY CENTRE

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Background: The 2018 British Thoracic Society Guideline for the Management of Pleural Mesothelioma recommend that discussion at Specialist Mesothelioma Multidisciplinary Team (MDT) Meeting 'may improve diagnostic accuracy and recruitment to clinical trials', and that all cases of mesothelioma should be 'referred to a regional mesothelioma MDT'. Royal Papworth Hospital is a tertiary centre situated in Cambridgeshire and is home of the Mesothelioma Centre for the East of England. February 2018 saw the emergence of the weekly Regional Mesothelioma MDT. **Method:** Data from MDT minutes, recorded on an electronic database, from the first year (01.02.2018-31.01.2019) was compared with the targets set by the 2018 National Mesothelioma Audit. Information collected included clinical trials consideration, TNM stage, ECOG performance status, referring hospital, age, histological subtype, asbestos exposure and gender. **Result:** 160 discussions took place concerning 93 patients. Median age 71yrs (range 45-92). 84(90%) had documented occupational asbestos exposure. 9(10%) female. Referrals from distant district general hospitals were more evident. Histological subtype was recorded for all patients who had a biopsy. Second opinion histology was reviewed; no diagnosis overturned. 9(10%) patients had a clinical radiological diagnosis of mesothelioma confirmed. Patients were referred for discussion for various reasons including confirmation of diagnosis, suggested disease management, consideration of trials, and for second/'specialist' opinion.

	National Mesothelioma Audit Standard %	Royal Papworth Regional Mesothelioma MDT %
Performance status	90	92
Staging score (TNM for pleural mesothelioma)	90	100
Discussion at MDT	95	100
Confirmed pathology	95	100
PS 0/1 patients considered for clinical trials		100

Conclusion: Prior to the Regional Mesothelioma MDT, patients were discussed within the lung cancer MDT. The Regional Mesothelioma MDT provides opportunity for discussion among experts who see more than 30 mesothelioma patients each year. More patients are being referred from the local and distant district general hospitals. The hope is that this offers equitable care, treatment and access to clinical trials for all patients with mesothelioma. Future work will look at short and long term outcomes for these patients. *Thank you to the Royal Papworth Hospital Mesothelioma MDT for their support with this abstract.*

Keywords: Mesothelioma, MDT, Audit

P1.06-20 MALIGNANT PLEURAL MESOTHELIOMA: SURVIVAL META-ANALYSIS FROM 15 YEARS OF A STANDARD SYSTEMIC THERAPY

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Background: Malignant pleural mesothelioma is a rare malignancy with an annual incidence of 3,000 cases in the US and is still considered incurable. The standard of care for this cancer, a combination of pemetrexed and a platinum drug, was established in 2003 as the result of a landmark study that reported a median overall survival of 12.1 months for this combination in patients not eligible for surgery. The aim of the current analysis was to determine if there has been a change in the outcome for this population in the past 15 years. **Method:** A PubMed search was performed and 9 prospective, randomized or single arm (minimum n=50), trials were selected. All studies included patients treated using pemetrexed in combination with platimun as front line therapy in unresectable mesothelioma patients. Average and weighted average OS were calculated and also corrected per the reported odds ratio for survival between the epithelioid and non-epithelioid histologies. **Result:** The average OS was 12.9 months and the weighted average OS was 13.3 months (range: 8.5 – 16.1 months). The two studies showing the highest median OS (MAPS and LUME-meso) had a higher percentage of tumors with epithelioid histology, which could explain their favorable outcome. Adjusting the average OS using the reported odds ratios for survival between epithelioid and non-epithelioid histologies eliminated the superior outcome in these studies. Furthermore, correcting average survival per the original ratio between tumor histologies for all studies included in the meta-analysis showed an average and weighted average OS lower than 13 months. **Conclusion:** This analysis strongly supports the contention that survival results for nonoperative patients with mesothelioma should be stratified by histology, epithelioid versus nonepithelioid, similar to the trend in the surgical mesothelioma literature. When factoring in histology, it appears that overall advances in patient care and additional treatments have not significantly changed the overall survival for nonoperative mesothelioma patients in the last 15 years. This meta-analysis underscores the desperate need for new and innovative treatments for this cancer.

Keywords: Survival Meta-analysis in Malignant Pleural Mesothelioma, Survival of Standard Systemic Therapy in Mesothelioma

P1.06-21 SAFETY META-ANALYSIS OF CLINICAL TRIALS DELIVERING TUMOR TREATING FIELDS TO THE UPPER TORSO

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Background: Tumor Treating Fields (TTFields), a non-invasive, loco-regional, antimitotic treatment approved for glioblastoma (GBM), are delivered via transducer arrays to tumor region. Localized dermatitis underneath the arrays were main adverse events (AEs) reported in phase 3 GBM trials. The safety of TTFields was analyzed in phase I and II studies in non-small-cell lung cancer (NSCLC) [EF-15, NCT00749346] and malignant pleural mesothelioma (MPM) [STELLAR, NCT02397928]. **Method:** TTFields studies in this pooled analysis were EF-15 (n=41, advanced NSCLC; plus pemetrexed) and STELLAR (n=80, MPM; plus platinum and pemetrexed). TTFields were applied 12 - 18 hours/day at a frequency of 150 kHz. All patients received standard of care systemic chemotherapy for their disease in addition to TTFields. Severity and frequency of AEs, and association with TTFields treatment were evaluated (CTCAE criteria version 4.0). **Result:** Patients were aged 27-78 years: STELLAR: 67 (27-78) and EF-15: 63 (44-78), ECOG 0-1; 7 patients in EF-15 had ECOG 2. The incidence of grade 1-2 gastrointestinal (GI) toxicities was 35%. The most common low grade GI toxicities were: nausea (17%), vomiting (6%), constipation (10%) and diarrhea (6%). Grade 1-2 general disorders (16% fatigue and 11% asthenia) were common. Dyspnea Grade 1-2 (12%) and Grade 3-4 (5%) were considered related to standard chemotherapy or underlying disease. Grade 1-2 cardiovascular AEs were 7%; one case of severe arrhythmia (atrial flutter) was unrelated to TTFields. The only common TTFields-related adverse event was dermatitis below the transducer arrays. 59% patients had dermatological AEs: 53% Grade 1-2 dermatitis, 4% grade 3 dermatitis and 11% Grade 1-2 pruritus. **Conclusion:** Treatment of solid tumors with TTFields 150 kHz to the thorax did not result in serious AEs or treatment-related pulmonary, cardiac, hematological or gastrointestinal toxicities. Expected dermatological toxicity beneath the device transducer arrays was seen in 59% patients, and resolved after a short treatment break or termination of treatment. These safety results and encouraging survival outcomes support the potential use of TTFields therapy in NSCLC and mesothelioma.

Keywords: Safety meta-analysis of Tumor Treating Fields, Safety Tumor Treating Fields in NSCLC and Mesothelioma, TTFields in lung cancer

P1.06-22 PATHOLOGIC AND IMAGING RESPONSE CORRELATIONS IN PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY FOR MESOTHELIOMA

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Background: In light of the emergence of neoadjuvant immunotherapy for the treatment of non-small cell lung cancer, there has been interest in developing neoadjuvant therapies with immune-checkpoint inhibitors for mesothelioma. Neoadjuvant trials allow the incorporation of pathologic responses as endpoints which have not been validated for mesothelioma. We sought to assess the correlation between pathologic and imaging responses in the neoadjuvant setting in patients with mesothelioma. **Method:** We identified patients with mesothelioma who were treated with neoadjuvant chemotherapy and underwent subsequent resection at Mayo Clinic Rochester, MN from 2000-2017. We used modified Response Evaluation Criteria in Solid Tumors (RECIST) to determine radiographic responses. Imaging response was defined utilizing modified-RECIST criteria, with response defined as either complete (disappearance of all pleural and non-pleural disease) or partial (>30% decrease) response and imaging non-response was defined as either progressive (increase in size by 20% and 5 mm from nadir) or stable (meeting criteria for neither) disease. All cases were reviewed by a thoracic pathologist (ACR) to confirm the diagnosis and to define the pathologic response, which was performed blinded to the imaging response. For the purpose of this exploratory study we defined pathologic response as percent viable tumor 50% or less and non-response as >50%. **Result:** We identified 22 patients with sufficient data and tissue available for inclusion in our study. The median age was 65 (range 48-74). There were 20 patients with epithelioid, 2 with biphasic and 0 with sarcomatoid subtypes of mesothelioma. There were 12 (55%) patients with radiographic responses and 9 (41%) with pathologic responses. Five patients had both a pathologic and imaging responses, 7 patients did not have a pathologic response but had an imaging response, 4 patients had a pathologic response without an imaging response, and 6 patients had neither a pathologic nor imaging response (χ^2= 0.0063, p=0.937). **Conclusion:** Since neoadjuvant trials have the potential to improve survival, and may be used to assess drug efficacy and accelerate drug approvals, it is important to have a unified and effective strategy to determine responsiveness of drug therapy. In our single institution, retrospective series we did not identify a significant correlation between imaging and pathologic responses which might be, at least in part, to the fact that mesotheliomas often have large areas of necrosis even without neoadjuvant therapy. Larger studies will be needed to define appropriate pathologic response endpoints in neoadjuvant trials for mesothelioma.

Keywords: Mesothelioma, neoadjuvant

P1.07 NURSING AND ALLIED PROFESSIONALS
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.07-01 LUNG CANCER SUPPORT GROUPS: STILL RELEVANT IN A DIGITAL WORLD?

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Background: People diagnosed with lung cancer experience high levels of distress and have greater unmet emotional needs than those with other types of cancer. Historically, an important way to meet unmet social support needs has been through in-person groups, the benefits of which extend beyond psychosocial support and may include increased feelings of control and confidence and decreased depression and distress. Thirty years after the value of in-person support groups was first study documented, in a world where we can instantaneously connect with others from all over the world through a tap or swipe, are support groups still relevant? This study sought to examine overall satisfaction with and impact of in-person lung cancer support group participation on distress, loneliness, self-efficacy and overall quality of life. **Method:** Lung cancer patients, survivors and loved ones enrolled in seven in-person lung cancer-specific support groups and completed baseline questionnaires at their first group with follow-up surveys administered after six months. Validated measures assessed cancer-related distress (15-item CSS, CancerSupportSource®); loneliness (UCLA Three-Item Loneliness Scale); and group satisfaction (Helpful Group Experiences Questionnaire). Three self-efficacy questions were also included and developed specifically for this study. Qualitative data was gathered through focus groups. Statistical comparisons of baseline vs. six-month levels of cancer-related distress, loneliness and positive affect were conducted using paired-samples t-tests. **Result:** Eighty-six participants completed baseline questionnaires with 29 completing/partially completing follow-up surveys. Univariate Analyses demonstrated statistically significant decreases in total cancer-related distress but not loneliness or positive affect. Responses to self-efficacy questions showed high confidence in making treatment decisions (86%). Confidence was also high in communicating with healthcare teams and the ability to access information and resources (both 90%). Group satisfaction was high with 100% (n=27) indicating they would recommend their group to others. The highest rated group experiences included sense of belonging and receiving support and encouragement. The lowest rated experiences included feeling they had helped others and having talked about recurrence fears. **Conclusion:** These results indicate in-person support groups serve an important role in relieving distress and providing connection for people with lung cancer and their loved ones. Convenient digital support platforms like online communities and apps may help to meet the emotional needs of people some people with lung cancer and their loved ones but perhaps are not a replacement for the in-person experience of community.

Keywords: Support groups, survivorship, Distress

P1.07-02 IMPLEMENTATION OF A HEALTH AND WELLBEING PROGRAMME IN CONJUNCTION WITH PULMONARY REHABILIATATION

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Background: Pulmonary rehabilitation is currently provided for people who have had surgery, radical radiotherapy, SABR and/or chemotherapy in a dedicated unit called BreathingSpace. A programme has been developed to encompass all aspects of health and well being, including physical, psychological and social support to patients and carers to enhance their recovery,to improve quality of life and offer ongoing support to patients and carers living with and beyond lung cancer. A variety of social events including a choir, yoga, Tai Chi and craft courses have been developed as well as education and infomative sessions on diet, relaxation and benefits advice. Continuous smoking cessation support and advice is also available. **Method:** Patients and carers are invited to participate in the social activities provided in a stimulating environment following completion of the rehabilitation programme. Health and well being initiatives are also offered to all people following a diagnosis of lung cancer or mesothelioma if they require more support with improving breathlessness and excercise. In adddition to this, an analysis of all the local support groups and networks were identified to encourage further support and social integration for people which were not just focused on cancer. A wealth of support mechanisms were identified including Rotherham Get Active, Rotherham Carers Forum, the local football club association and numerous other social groups. **Result:** The implementation of the health and wellbeing programme is ongoing and the trial is still in progress. **Conclusion:** Following completion of the programme, participants will be offered the opportunity to become involved in other social activities dependant on their ability and performance status. Qualitative feedback and evaluations from patients and carers will be utiliised to develop the programme further.

Keyword: health and wellbeing, pulmonary rehabilitation, patient and carer support groups

P1.07-03 IMPROVING NON-ONCOLOGY PROVIDER KNOWLEDGE OF UNIQUE IMMUNOTHERAPY ADVERSE EVENTS

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Background: Immunotherapy use is increasing in frequency among oncology patients as a single treatment or in combination with other modalities. Immunotherapy related adverse events (IrAE) have unique presentations that are often overlooked or misdiagnosed outside of oncology. This IRB approved study sought to evaluate the effectiveness of microteaching on non-oncology providers' identification of IrAEs and timely initiation of definitive therapy. A second aim was to review result on patient outcomes through review of EHR. **Method:** Microteaching sessions of 10 minutes in length were scheduled. Sessions occurred before or after staff meetings, at change of shift huddles, and at the monthly ER physician meeting. The six item test pretest/posttest evaluated familiarity with immunotherapy, and identification of and appropriateness of treatment for patients with IrAEs. A paper version of the pretest was given prior to the education which was delivered to nursing in small groups consisting of 2 to10 participants. All physician participants received education at the same time. Immediately following the teaching participants completed the posttest. A retrospective review of electronic health records was conducted to determine timeliness of identification of IrAEs and appropriateness of treatment. **Result:**

All Nurses

	Pre N=129		Post N=125		
	Yes	No	Yes	No	P
Are you familiar with immunotherapy as a treatment for cancer?	53.9% (67)	46.1% (62)	96.8% (121)	3.2% (4)	<.0001
Are you familiar with national guidelines for the management of immunotherapy adverse events?	8.5% (11)	91.5% (118)	90.4% (113)	8% (10)	<.0001
Are you familiar with the intervention(s) needed to start reversing most immunotherapy adverse events?	14% (18)	86% (111)	96% (120)	3.2% (4)	<.0001

	Pre N=129		Post N=167		
	True	False	True	False	P
Immunotherapy and chemotherapy may be administered simultaneously.	52.7% (68)	45% (58)	89.6 % (112)	9.6% (12)	<.0001
Neutropenic patients who are receiving chemotherapy can be treated with steroids.	49.6 % (64)	48.1% (62)	95.2% (119)	4.% (5)	<.0001

A Phi coefficient was calculated to measure the association between pretest and posttest scores on five questions. For all RNs, all items demonstrated an increase in knowledge (p <.0001). Similarly, ER nurses demonstrated an increase in knowledge in all items (p < .0001). Conversely, oncology nurses had better baseline knowledge compared to "all" nurses. This supports the premise that within the oncology specialty, information about irAEs is better known and understood. Although oncology nurses are more prepared to identify and manage these issues, these nurses are not involved in patient care during an ER visit or admission to an ICU. Physicians also had higher baseline scores compared to all nurses, however, to the question 'are you familiar with the intervention (s) needed to start reversing most immunotherapy adverse events?' had a significant increase in knowledge following the micro-teaching in-service (p < .0001). **Conclusion:** Immunotherapy is increasing in use in oncology, as a result, non-oncology providers will progressively encounter patients receiving these agents in non-oncology settings throughout the hospital such as emergency department or ICU. Brief educational sessions were found effective in increasing non-oncology providers knowledge of these immunotherapy agents and their AEs management .

Keyword: Adverse Events, Immunotherapy, Non-Oncology Providers

P1.07-04 EARLY LUNG CANCER TEAM INTERVENTION IN EMERGENCY ADMISSIONS

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Background: The Liverpool Lung Cancer Unit is a unique diagnostic service diagnosing approximately 430 patients per year. Although the majority of cases of suspected lung cancer can be managed as outpatients where the diagnostic pathway is well developed, a proportion still present unwell via the emergency department where their subsequent journey is less certain. Along with same-day reporting for emergency scans, we have developed a rapid review service for such individuals and were interested in assessing its performance. **Method:** We looked at all patients with suspected lung cancer who presented through our emergency department at The Royal Liverpool University Hospital in 2018, focussing on outcome, time to be seen following admission, and the histological diagnosis rate. **Result:** Of the 561 referrals to our lung cancer unit, 196 (35%) presented through the emergency department: 73 (37%) were discharged to outpatient cancer investigation. The remaining 123 (63%) were admitted to 26 different locations (8 medical specialities, surgical, vascular and orthopaedic wards). Of these, 72% were seen by the lung CNS within one working day and appropriate management initiated. This was aided by our live CT scan database,

where 69/79 (87%) were coded on the same day. Daily CNS checks of the database ensure early inpatient identification and review by the lung clinician and CNS, often before formal referral from the responsible clinical team is made. Overall 103 patients (84%) who presented as emergencies subsequently were diagnosed with a malignancy. 96 were diagnosed with a primary lung cancer of which 56 (58%) had histological confirmation. **Conclusion:** Our results show that, by coordinating care between the emergency and radiology departments and the lung cancer team, patients presenting unwell can be managed rapidly even if they remain in hospital. In addition, by actively seeking them out we can not only provide them with timely and appropriate investigations but also early CNS intervention, facilitating symptom management, the opportunity to maximise their performance status and offer psychological support to not only the patient but to their families as well. This approach also ensures that the managing medical teams are given the right information from a specialist team. The Lung Cancer Team resource is therefore focussed on looking after lung cancer patients and those patients that do not have cancer but are referred to the team are informed at the earliest opportunity and treatment decisions made accordingly by the team responsible for their care.

Keywords: emergency presentation, Lung cancer nurse

P1.07-05 DEVELOPING A NURSING TRIAGE TOOL TO ASSESS PATIENT SUPPORT NEEDS THROUGH TREATMENT FOR LUNG CANCER

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The Christie Hospital Foundation Trust, BX/United Kingdom

Background: Improvements in treatments and outcomes within lung cancer has resulted in an increasing number of patients requiring access to appropriate support. Within a tertiary specialised centre for the treatment of lung cancer, stratification of support is required in order to target the patients with the greatest needs and identify services to sign post them to. The Lung cancer Clinical Nurse Specialists (LCNS) are developing a triage tool which uses a red, amber, green approach to stratifying need. It assesses 10 areas of patient vulnerability. On completion of the assessment, those with particular needs will be triggered by an amber or red flag. The tool will proactively identify patient need, whilst helping the LCNSs to work towards a manageble caseload. **Method:** The LCNS team had been assessing patient need through intuition, using their own criteria. The aim of the tool was to create a consistent approach to this assessment and led to the identification of key areas of patient vulnerability. Already validated tools for these key areas were incorporated into the design. A scoring system was developed against each key area and the tool was piloted on a number of patients in order to identify the boundaries of stratification. However, due to the variability in scores and inconsistent outcomes, scores were replaced with red, amber or green for each category. Any category resulting in an amber or red outcome, led to a more complex intervention. All Green Outcomes: Information pack, LCNS contact details, referral back to local CNS Any Amber Outcomes: *In addition to the 'Green' interventions*, a day 8 (of treatment) telephone consultation in nurse led clinic, Community referrals Any Red Outcomes: *In addition to the 'Green and Amber' interventions*, follow up call post initial consultation, specialist service referrals **Result:** The tool will be further piloted by the LCNSs and interventions implemented in line with the outcomes. The aim is to roll the tool out across the Greater Manchester area so that it can be used by CNSs in the District General Hospitals and will be continually used throughout the patient pathway as their needs change. The resulting assessment will be recorded on the electronic patient record and therefore will be auditable across the patient population to ensure that LCNS patient interventions are at the appropriate level to the support need. Outcome measures: - Reduced hospital admissions - Improved outcomes for patients - Patient Satisfaction through service user feedback **Conclusion:** Identifying patient need through their cancer pathway has until now been a process of intuition and individual preference by each LCNS. This triage tool, whilst not replacing clnical judgement, is designed to remove the inconsistency of assessment and create a stratified approach to patient need. This will enable appropriate allocation of resources and provide auditable data to allow service improvement and ultimately enhance the patient experience.

Keywords: Assessment Tool, Lung cancer, Clinical Nurse Specialist

P1.07-06 USE OF THE NUTRITIONAL RISK INDEX AS SCREENING FOR MALNUTRITION IN PATIENTS WITH LUNG CANCER

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Background: Introduction: Malnutrition is a critical condition for patients with lung cancer (LC). High turnover clinics require an easy, fast and good sensitivity screening instrument. Objective: To compare Buzby's Nutritional Risk Index (NRI) tool and to correlate it with nutritional status assessment from anthropometric parameters. **Method:** ology: This is a cross-sectional study, with patients with clinical stage IV lung adenocarcinoma, followed at a reference oncology clinic in Rio de Janeiro. During the first visit, data on age, sex, current weight, usual weight, height, arm circumference (AC), triceps skinfold thickness (TST) and serum albumin were collected. To assess the nutritional status, calculations of NRI (Busby et al., 1998), body mass index (BMI), AC adequacy and arm muscle circumference (AMC) adequacy were used. Patients were classified as undernourished or undernourished. The data were analyzed through the SPSS program, version 13.0. **Result:** 23 patients participated in the study, with a mean age of 66.4 ± 11.3 years, of which 52.2% were female. The percentage of patients considered malnourished by IRN was 52.2% for IRN, 21.7% for BMI, 39.1% for CB adequacy and 26.1% for WBC adequacy. The BMI was the index that most classified individuals as without malnutrition (78.3%). When the INR was crossed with the other evaluation methods used, it was found that there was a very low degree of agreement regarding BMI (Kappa = 0,1), p <0.06. **Conclusion:** in this study IRN was more sensitive to identify inadequacy in nutritional status when compared to BMI, CB and CMB. The use of IRN in patients with lung cancer helps to identify the nutritional diagnosis early, favoring nutritional intervention and consequently the quality of life of the patient.

Keywords: Lung cancer, nutritional status, nutritional risk index

P1.07-07 AN INTERDISCIPLINARY COLLABORATIVE APPROACH TO DISCHARGE READINESS ON A THORACIC SURGERY SPECIALTY UNIT

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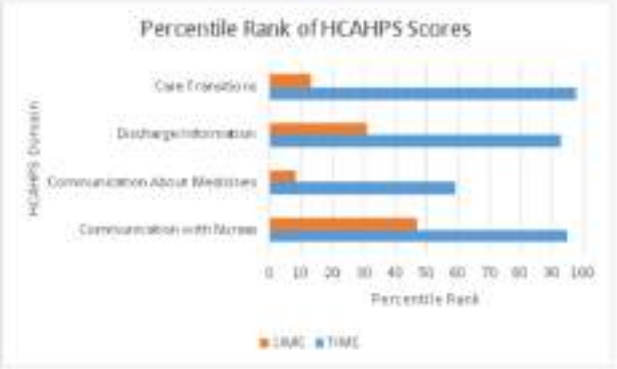
Background: This six month process improvement pilot aims to address the U.S. Centers for Medicare & Medicaid Services' mandate that hospitals improve quality of care through improving outcomes such as length of stay (LOS), 30 day readmission, and patient satisfaction. **Method:** A collective of Thoracic Surgery staff established a multidisciplinary process that included daily interdisciplinary rounds to discuss patients' progress and discharge readiness. An interactive discharge readiness tool that looks like a board game, based on an evidence-based concept that is effective in the pediatric patient population, was created to engage the patient and family in discharge readiness. A patient education guide and documenting mechanism were built into the electronic medical record to aid and que staff in educating the patient and allow the multidisciplinary team to view the patients' progress. **Result:** Patient satisfaction scores, measured using the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS), in the domains of Communication with Nurses, Communication About Medicines, Discharge Readiness, and Care Transitions each improved. The Thoracic Intermediate Care Unit (TIMC) ranked above the 90th percentile in three of the four measured domains and significantly outperformed its sister unit, the Surgical Intermediate Care Unit (TIMC), in all categories. Surprisingly, LOS and 30 day readmission increased during the first quarter of the six month pilot.



Conclusion: The improvement in patient satisfaction in all measured domains highlights the positive impact of this initiative. The increase in HCAHPS scores after implementing the Journey Board imparts the benefit of using an interdisciplinary tool to engage the patient and family in discharge readiness. The Care Transitions domain, which examines the patient's perception of their ability to manage their health and understanding of their medication, connects directly to the purpose of the Journey Board. Prior to this pilot the TIMC was underperforming in the Care Transitions domain at 54.6%. During the first quarter of the pilot the HCAHPS score jumped to 80.3% and although it dipped to 72.2% in the second quarter if the pilot this is still a meaningful increase from the pre-pilot period. The improvements in HCAHPS scores are especially notable when comparing the percentile ranks of the TIMC and SIMC, sister units with the same nursing staff. It appears that the having a formal process in place provides the interdisciplinary team with a structure to engage the patients and families in preparation for going home. Although unimproved, the inability to decrease LOS and 30 day readmission can be explained by the concurrent increase in case mix index, a measurement of acuity, of the patients on the TIMC.

Keywords: Interdisciplinary, Discharge Readiness, Patient Education

P1.07-08 SCREENING FOR FEAR OF CANCER RECURRENCE IN OPERABLE LUNG CANCER PATIENTS-SCALE VALIDATION AND CURRENT STATUS

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Background: Fear of cancer recurrence (FCR) is one of the most distressing concerns for cancer patients. A brief scale to screen FCR is important for use in busy clinical oncology settings. The purposes of the study are to (1) translate the 7-item fear of cancer recurrence scale (FCR7) into Chinese and validate the psychometrics of the 7-item Chinese version (FCR7-C), and (2) explore the level of FCR in a cohort of early-stage lung cancer patients after tumor resection surgery in Taiwan. **Method:** Eligible subjects were recruited from chest surgery outpatient department in a medical center in Taiwan. The FCR7 was first translated and back translated between English and Chinese. The translated FCR7-C was evaluated for content validity and internal consistency reliability (Cronbach's alpha). Construct validity was determined by evaluating correlations between FCR7-C theoretical assumptions and confirmatory factor analysis (CFA). **Result:** In our cohort of 160 patients, the FCR7-C was shown to have satisfactory content validity and internal consistency reliability (Cronbach's α = 0.9). The uni-dimensional structure was confirmed by CFA that showed a good fit for the model. The FCR7-C score correlates positively with the degree of physical symptoms, anxiety, and depression, but correlates negatively with patient age, performance status, and quality of life. We found that 81.9% of patients reported at least some FCR, with a mean FCR severity of 15.2 (SD= 7.8). **Conclusion:** FCR7-C is a brief assessment with good psychometrics. For operable lung cancer patients, FCR is still a concern for most of the early stage lung cancer patients though it is not very severe. We strongly suggest its use for screening cancer patients for FCR to allow for appropriate interventions in lung cancer patients.

Keywords: fear of cancer recurrence, Early Stage Lung Cancer, psychometrics

P1.07-09 IMPLEMENTATION OF A NURSING PROGRAM FOR CANCER PATIENTS TREATED WITH IMMUNOTHERAPY BY AN IMMUNOTHERAPY NURSE SPECIALIST

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Background: Immunotherapy is one of the fastest-evolving areas of oncology to date including non-small cell lung cancer. Due to their mechanism of action they can produce immune related adverse effects (irAES), in which a coordinated multidisciplinary approach is essential for their management, and immunotherapy nurse practice is rapidly changing achieving an important role as a case manager. To describe the implementation of a nursing program for cancer patients treated with immunotherapy by an immunotherapy nurse specialist. We present preliminary data that will be updated for the presentation. **Method:** Before starting immunotherapy, patients receive health education that includes an explanation of the mechanism of action, prohibited medications, possible side effects and the emergency workup that must be followed in case of occurrence. Additionally, all baseline necessary procedures are revised and concomitant medication is registered. An educational booklet specifically made by the nurse is also given, which also includes the contact information of the nursing consult. In the follow-up visits, toxicities are identified and graded according to CTCAE v4.0 and the patient's health changes are also summarized. In case of toxicity, the nurse starts the process of referral to the specialist and a close follow-up is carried out. Additionally, virtual follow-up visits and doubts and questions about immunotherapy are also answered. **Result:** From August 2018 to April 2019 a total of 703 visits and 270 virtual visits have been done by the immunotherapy nurse specialist. 176 cancer patients have been visited and 100 of them had lung cancer. During this period, it has been necessary to refer patients to the specialist on 71 occasions, mostly to endocrinology, rheumatology, dermatology and pulmonology department. **Conclusion:** The implementation of the immunotherapy nursing program has contributed to an improvement of early detection and management of irAEs in cancer patients receiving immunotherapy as well as a greater patient satisfaction along with a reduction of waiting time for the visit with the specialist.

Keywords: Multidisciplinary, immunotherapy nurse specialist, nursing program

P1.07-10 INVESTIGATION ON NUTRITIONAL STATUS AND QUALITY OF LIFE OF PATIENTS WITH LUNG CANCER TREATED BY RADIOTHERAPY IN DIFFERENT SEXES

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Background: Malnutrition is the most common complication of lung cancer patients. The purpose of this study was to investigate the nutritional indicators and quality of life of patients with locally advanced non-small cell lung cancer (NSCLC) who received definitive radiotherapy, to compare the nutritional status and quality of life of male and female patients, and to explore the relationship between them. **Method:** Patients with locally advanced NSCLC who received definitive radiotherapy in our hospital were enrolled. The quality of

life of patients was assessed by the Cancer Therapeutic Function Scale. Height, weight and body composition were collected by Inbody 230. Nutritional indicators such as albumin and hemoglobin were recorded within a week. **Result:** Between January 2018 and March 2018, ninety-six male patients and 32 female patients were enrolled. The BMI of 7.3% of male patients was lower than 18.5 kg/m^2, and that of all female patients was more than 18.5 kg/m^2. The proportion of male patients with hypoalbuminemia was equal to that of female patients, accounting for 65.6% of the total number. 6.3% of male patients with hypoalbuminemia and BMI were lower than 18.5 kg/m^2 at the same time. The proportion of male patients with anemia was higher than that of female patients (χ^2 = 7.626, P = 0.006), and the skeletal muscle and water content were higher than those of female patients (T = 5.653, P = 0.000; T = 8.184, P = 0.000). Body mass index, fat content, skeletal muscle content and water content in male patients were positively correlated with quality of life (β = 0.225, P = 0.046; β= 0.232, P = 0.042; β = 0.291, P = 0.009; β= 0.328, P = 0.004), while there was no significant correlation between nutritional indicators and quality of life score in female patients. **Conclusion:** Protein malnutrition is the main type of malnutrition in lung cancer patients,the manifestation is that body weight is maintained in normal range or even overweight, but serum albumin, lymphocyte count and other indicators are abnormal. However, some male patients are suffer from mixed malnutrition, the consumption of weight and decrease of serum nutritional indicators both occurre, which is a serious life-threatening malnutrition. So, male patients with lung cancer are more likely to suffer from serious malnutrition than female patients, and malnutrition has a greater impact on the quality of life of male patients.

Keywords: Lung cancer, Nutrition, Quality of life

P1.07-11 AN EVALUATION OF THE PATIENT'S EXPERIENCE AND EXPECTATIONS DURING THE IMPLEMENTATION OF NHS ENGLAND, NATIONAL OPTIMAL LUNG CANCER PATHWAY

K. Clayton[1], A. Mciver[2], A. Bougler[3], C. Buckle[4], C. Butler[5], J. Draffen[6], S. Earl[7], Y. Jeffs[8], S. Jones[9], C. Jordan[10], J. Morley[11], H. Neal[12], S. Newbold[13], J. Roberts[14], P. Rose[15], P. Shepherd[16], B. Smith[2]

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Background: The NLCFN workshop group were keen to explore the impact on patient experience of the National Optimal Lung Cancer Pathway (NOLCP). Evaluation of patient experience to collect data on their corresponding pathways. Hospital based lung cancer diagnostic services across the UK at 18 Trusts. **Method:** Newly diagnosed lung cancer patients referred on the 62 day pathway during October 2017 to July 2018 were eligible. 135 patient pathway and questionnaire data were analysed from 15 Trusts. Data Collection Data collection was in two parts: A patient survey and a data collection tool to reflect key points along the patient pathway. All data was anonymised. Data Analysis Data was submitted by 15 Trusts and analysed by the workshop participants **Result:** Overall, patients were satisfied with their experience of the pathway. Data collection demonstrated significant variation across pathways. Service evaluation and development is a key part of the LCNS role, however there were variations in Trust governance processes which caused delays and non submissions. **Conclusion:** Overall, patients were satisfied with their experience of the pathway. Data collection demonstrated significant variation across pathways. Service evaluation and development is a key part of the LCNS role, however there were variations in Trust governance processes which caused delays and non submissions.

Keyword: Patient, experience, lung cancer

P1.07-12 ESSENTIAL PSYCHOSOCIAL REQUIREMENTS FOR QUALITY LUNG CANCER CARE

C. Degi

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Background: In 2016 ECCO's board - European CanCer Organization - approved a project on essential requirements for quality cancer care (ERQCC). Available clinical guidelines on cancer care define the medical content of optimal treatment of a given type of cancer but do not give indications on how to organize this treatment and how to measure its outcome. Thus, there is a need for defining organizational criteria on how to deliver this essential care to each patient and subsequently a quality measurement system. **Method:** The ERQCC project aims at: a). improving outcomes for cancer patients in Europe through the adoption and the implementation in Europe of essential requirements for quality cancer care; b). complementing existing clinical guidelines and improving their efficacy; c). shaping the policy environment at European and national levels to improve the quality of cancer care across Europe and decrease inequalities in outcomes; and d). positioning ECCO as the multidisciplinary cancer organization able to reach a consensus on essential requirements for quality cancer care. **Result:** ECCO Essential Requirements for Quality Cancer Care (ERQCC) are checklists and explanations of organization and actions that are necessary to give high-quality care to cancer patients. They are written by European experts representing all disciplines involved in cancer care. Due to its multidisciplinary nature, in this presentation, the essential psychosocial requirements for quality lung cancer care will be presented in two parts. In the first part, the psychosocial challenges in lung cancer are listed in details then in the second part, we expand on the role of psycho-oncology in lung cancer care. Results disseminated at the Congress are part of the ERQCC Lung Cancer Working Group Meetings from Brussels in 2018. **Conclusion:** The information presented here is a description of the requirements to consider essential psychosocial requirements for quality lung cancer care, especially in the European region. More information here: https://www.ecco-org.eu/ERQCC.

Keywords: essential requirements, psychosocial care, Lung cancer

P1.07-13 THE APPLICATION OF INTRACAVITARY ELECTROCARDIOGRAM IN THE FEMORAL VEIN CATHETER TIP LOCATION IN CHEMOTHERAPY PATIENTS WITH LUNG CANCER

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Background: For lung cancer patients with superior vena cava obstruction (SVCO), femoral vein PICC catheter at mid-thigh can be used to achieve chemotherapy. The X-ray, as the gold standard for catheter location, has some limitations such as long time-consuming and delayed in judgment. The intracavitary ECG location has been applied to the superior vena cava(SVC) catheter, which can make up for the shortcomings of X-ray. However, it is not clear whether it is suitable for inferior vena cava(IVC) catheter. Our research aim is to explore the clinical application value of intracavitary ECG location on femoral vein PICC at the mid-thigh . **Method:** From January 2017 to December 2018, a total of 91 patients with SVCO, who were placed femoral vein PICC at the mid-thigh, were in enrolled. In the self-controlled study, catheter tip at the eighth to tenth thoracic vertebrae by X-ray location as the gold standard positive, and catheter tip at the position where the intracavity ECG occurred the first biphasic P wave and then receding 2 cm as the positive for the screening test. The study calculated the authenticity, reliability and practicality indicators of intracavitary ECG location. **Result:** This study found the relationship between the position of the catheter tip and the P wave. When the tip of the catheter was in the IVC, most patients has negative P wave, and some patients has a low flat positive P wave. When the tip of the catheter entered the right atrium(RA), patients has biphasic P wave, and when the tip of the catheter entered the top of the RA, patients has huge biphasic P wave. In the study, the screening test was used to evaluate the accuracy and clinical application potential of intracavitary ECG in femoral vein PICC catheter tip location. In the authenticity index, the sensitivity was 98.73%, and the specificity was 91.67%. Yoden index was 0.90, the accuracy was 97.80%, the false positive rate was 8.33%, the false negative rate was 1.27%, the positive likelihood ratio was 11.85, and the negative likelihood ratio was 0.01. In the

reliability index, the Kappa index value was 0.90. In the practical index, the positive predictive value was 98.73%, and the negative predictive value was 91.67%. **Conclusion:** Intracavitary ECG location can accurately locate the tip of the femoral vein PICC catheter at the mid-thigh. It has higher reliability and practicability, and has more great clinical application potential. It is worthy to clinical application.

Keywords: Femoral vein catheter, Catheter tip location, Intracavitary electrocardiogram

P1.07-14 FRAILTY AND TREATMENT DECISION MAKING IN OLDER PEOPLE WITH LUNG CANCER

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Background: Currently there is little research exploring patient or clinician treatment decisions among older lung cancer patients. Existing research has confirmed that variation in treatment preferences exist between patients, and between patients and clinicians, that could be influenced by perceptions of age and frailty. Clinician's concerns about providing certain treatments to patients deemed to be frail may influence an older person's decisions regarding treatment. This was reported in a recent systematic review [1] identifying the most common factor influencing older adult's decision to accept or decline cancer treatment was physician recommendation. **Method:** A prospective qualitative exploratory study was undertaken. Semi-structured interviews conducted with older patients with lung cancer (n=12); and a range of health care professionals (n=12), including respiratory physicians, clinical nurse specialists, oncologists. Data were audio-recorded, transcribed verbatim and analysed using Framework Analysis. **Result:** Three themes illuminated factors influencing treatment decision making in older people with lung cancer. *Perceptions of frailty* illustrates how older people were able to recognise dimensions of frailty but did not consider themselves to be frail. For the healthcare professionals, frailty was not universally considered in treatment decision-making. *Decision making conversations* details the multiple factors that facilitate or hinder the process. *Aspects of service delivery* consider the wider context in which treatment decisions are made. **Conclusion:** There is merit on drawing on the concept of frailty to inform treatment decision making. In the current climate where the use of standardised tools to assess frailty is being promoted [2,3], we propose incorporating a series of trigger questions to be used alongside existing assessment tools. In so doing there is potential to capture a clearer impression of an older person's fitness for treatment.

Keyword: lung cancer, frailty, treatment decisions

P1.07-15 SCREENING FOR LONG TERM OTOTOXICITY IN LUNG AND UPPER AERODIGESTIVE CANCER SURVIVORS TREATED WITH PLATINUM CHEMOTHERAPY

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Background: Platinum-induced ototoxicity (PIO) is the hearing disorder that results from the temporary or permanent inner ear dysfunction after treatment with platinum based chemotherapy. Debilitating symptoms can include hearing loss, tinnitus and ear pain, affecting 40-80% of adults treated with platinum chemotherapies (up to 50% of lung cancer patients). There is no cure for PIO and the focus should be on early detection and lifestyle management. Ototoxicity negatively impacts quality of life in survivorship impacted by difficulty in speech recognition, safety concerns, social isolation and depression. At most cancer centres, hearing tests are not routinely performed in adults receiving cisplatin. This study aims to implement screening audiometry initially through formal audiometry testing, and later through a mobile electronic tablet-based platform. Our study goals are: i) to confirm the high prevalence of ototoxicity; and ii) the feasibility of implementing an in-clinic tablet based hearing test as part of routine care for lung cancer patients. **Method:** Using the CIHR Knowledge-to-Action framework, we formally assessed the clinic readiness, barriers to implementation, identification of facilitators, and initiated a pilot outpatient clinic-based study in our lung and head and neck cancer patients to determine viability and sustainability within the clinic. **Result:** Prevalence of hearing loss ranged between 22-58% of cisplatin-treated patients. Barriers to implementation included: (i) difficulty contacting some survivors; (ii) coordinating testing across broad geographic areas; (iii) missing test results; (iv) allocation of physician versus nursing responsibilities in a multidisciplinary setting; (v) health care provider education; and (vii) long-term transition plan to primary care follow-up. Nursing/clinic champions improved uptake substantially. New procedures were necessary to ensure that tests are performed, results checked, and patients were triaged accordingly. **Conclusion:** Substantial barriers were identified for clinical implementation of the routine post-platinum audiometry screening for ototoxicity in lung cancer survivors, but a list of potential solutions has led to good uptake of this process in the clinic. In a future follow-up pilot, we will test the potential benefits (time- and labour-savings; more efficient use of resources) of an in-clinic, portable, brief, tablet-based hearing test screening program, in place of formal audiometry testing.

Keywords: Audiometry, Ototoxicity, Chemotherapy

P1.07-16 TRAINING PROGRAM FOR UNIVERSITY NURSING STUDENTS TO REDUCE LUNG CANCER PATIENT EMOTIONAL DISTRESS

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Background: Communication skills are the cornerstone of the patient provider relationship in cancer care. Lack of these skills can diminish disclosure, increase patient anxiety. Nurses play an important role in providing emotional care and support to lung cancer patients and their families. Unfortunately, few nurses receive sufficient training to ensure they are proficient in key communication tasks. This study was carried out to determine the impact of communication skills training program on reduce lung cancer patient emotional distress. **Method:** A quasi experimental design with pre-post assessment was utilized in this study with sample size of 86 participants from internship year nursing students. The study was conducted in Training Unite and Oncology Units at Suez Canal University Hospitals. Internship year nursing students went through the problem-based learning process and role-playing exercises with regular feedback on basic communication skills, breaking bad news, effectively providing information and how to deal with patient's emotions during the training program. In the training program of the Internship year nursing students,the content was presented utilizing various techniques and approaches including: went through the problem-based learning process and role-playing exercises, group discussion, phrase filling, using media and videos, all of this with regular feedback on basic communication skills. Finally after one week of completing the program, the Communication Skills Observation Form was completed at the lung cancer patients ward of oncology units at Suez Canal University Hospitals **Result:** The training improved internship year nursing students' empathic tendency, empathic and communication skills. "Respect to patients, giving constructive feedback, using effective body language, using continuing and leading reactions" showed gradual improvement during observations while self-disclosure and "ineffective communication techniques" were lower Table 1. Pre- and post-Tests of Empathic Tendencies Scale & Communication Skills Evaluation Scale. (n=36)

P-value	t-test	SD	Mean	Scales
0.000 0.018	5.37 2.48	9.57 7.63 8.65 6.31	68.53 76.83 80.08 83.36	*Empathic Tendency Scale* Pre-test Post-test *Communi-cation Skills Evaluation Scale* Pre-test Post-test

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Conclusion: Communication skills training programs have effectively improved the empathic tendencies and communication skills of internship year nursing students,. Therefore, although empathy is an innate quality it can be developed through training. It is vital to give importance to give importance to communication in the professions worked with human beings and to develop/proceed empathy which is among the key elements of communication. It can be advised to give a place to the subject in theories and practices before graduation, support with continuous and adequate in-service trainings in professional life, to give priority to the ones working in hospitals with lung cancer patients with special needs such as cancer patients in order to develop empathetic skill of the nurses.

Keyword: Lung cancer patient, Nursing student, Communication program

P1.07-17 TRANSFER OF CARE: EFFECTIVE COMMUNICATION TO PROMOTE IMPROVED PATIENT EXPERIENCE

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University Health Network - Princess Margaret Cancer Centre, Toronto/ Canada

Background: As the world of cancer research continues to evolve, clinical trials remain a vital component to discover new treatment modalities in the fight against cancer. Across Canada, this percentage is closer to 5%. As cancer treatment evolves, it is imperative that our nursing care and culture does as well in order to support our patients appropriately. There remains a dichotomy of care between patients participating in a clinical trials and patients who are on standard therapies. Nursing practice and processes can be different for each and ultimately the patient is affected by this. Reflecting on our practice, there has not been a formal way of transitioning patients between different types of treatment and care. **Method:** As clinical trial nurses, we have designed a standardized worksheet for nurses to effectively provide more effective transition of care. Over a 6 week period from March 19th to April 30th, 2018, 13 ambulatory and trial nurses completed the worksheet for 29 patients in two GYNE and Thoracic clinics at Princess Margaret Cancer Centre. The worksheet is straight forward, quick and easy to complete. **Result:** Feedback from nurses was evaluated through a multiple choice questionnaire (Likert scales). Clinical trial and Ambulatory Nurses strongly agreed that the worksheet was helpful in streamlining important aspects of care for our patients, improvement in the flow of busy clinics, alerting nurses to important tests, procedures, treatments and toxicities . With the increased awareness of nurses in both trial and ambulatory setting and improved communication amongst the interprofessional team, the team was more efficient and proactive. **Conclusion:** The form facilitates effective communication and collaboration between clinical trial nurses and ambulatory nurses in clinic. Our initiative is grounded in improving continuity of care for the patients and they transition between the two modalities. We will discuss the worksheet component, feasibility amongst disease sites, feedback received and other positive implications of the hand over standardization process.

Keywords: Effective communication, patient experience, Transfer of care

P1.07-18 THE EFFECT OF LUNG CANCER ON PATIENT SEXUAL FUNCTIONING: NURSING VIEW

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Background: Lung Cancer (LC) is a major cause of chronic morbidity and mortality; it is currently the fourth highest cause of death in the world, and is predicted to be the third leading cause of mortality worldwide by the year 2020. Therefor this study aims to assess the effect of Lung Cancer (LC) on sexual functioning of the affected patients compared with healthy group. **Method:** This is a correlational exploratory study design to examine the relationship between LC and patients' sexual functioning. Data were collected from December 2016 to the end of May 2017, at Suez Canal University Hospital, Ismailia, Egypt. The study was approved by the institutional ethics committees and an oral approval from participants was obtained. An accidental convenient sample of one hundred patients were recruited according to the inclusion criteria. **Result:** Table 1. Frequency and percentage distribution of subjects' in relation to socio-demographic characteristics.

Variables N 86	Study		Comparison group		X2	p
	%	N 86	%			
Age						
⩽30 Years	12	14.0	14	16.2		
31–40 years	36	41.9	41	47.6	1.71	NS
41–50 years	32	37.1	28	32.5		
51 years	6	7.0	3	3.4		
Education						
Not reading/writing	32	37.2	10	11.62		
Primary	22	25.58	18	20.9		
Secondary	15	17.44	30	34.88	4.7	NS
University	17	19.77	28	32.56		

Table 5. negative effects of COPD on sexual functions of the study group as compared to the comparison.

Variables N 86	Study group		Comparison group		X2	P
	%	N 86	%			
Difficult breathing not interrupting sexual intercourse						
Sever	44	50.4	12	14	7.4	<0.05
Moderate	35	41.5	19	22.1		
Mild	7	81	55	64		
Breathing difficulties interrupt sexual intercourse						
Not concerned	23	26.7	69	80.2		
Yes	53	62	8	9.3	8.6	<0.05
No	10	11.7	9	10.5		
Fatigue interrupts intercourse						
Not concerned	28	32.5	69	80.2		
Yes	46	54	11	12.8	12.9	<0.05
No effect	12	13.9	6	7.0		
Difficult breathing in particular sex positions						
Yes	59	70.2	3	3.5		
Sometimes	23	27.4	9	10.5	7.9	<0.05
No	2	2.4	74	86.5		
Difficult breathing affects physical sexual performance						
Yes	55	65.5	5	5.8		
Sometimes	27	31.4	14	16.3	22.6	<0.001
No	4	3.6	67	77.9		

Figure 2

Conclusion: A negative impact on the quality of sexual functions of Lung Cancer patients attend the oncology unite at Suez Canal University Hospital leading to a disordered sexual life as compared to healthy .

Keyword: Sexual Dysfunction, Lung Cancer, Egyptian Patients

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P1.07-19 PALLIATIVE CARE SOCIAL WORKERS MULTI-DIMENSIONAL ROLES: A NAMIBIAN PERSPECTIVE

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University of Namibia, Windhoek/Namibia

Background: Background and Context This article provides insight on multi-dimensional roles of twenty social workers providing palliative to patients with life-limiting illnesses (e.g. cancer, cardiovascular diseases, diabetes, etc.) in six hospitals in primary care in Namibia. **Method:** Constructive grounded theory as a qualitative research approach was utilized and an ethnographic study was carried out through in-depth interviews with twenty practicing social workers at six public hospitals in Namibia using an audio-tape recorder to explore how social workers perceive their role in providing palliative care to patients with life-limiting illnesses.Purposive, non-probability sampling through qualitative in-depth face-to-face and open-ended interviews. Data were gathered using a narrative approach. Memoranda through field notes, memos assisted in data analysis, applying traditional grounded theory coding techniques applied. Data collection and analysis were conducted interchangeably. **Result:** Social workers perform multi-dimensional roles in the provision of palliative care such as advocate, assessor, broker, counsellor, educator, facilitator, patient liaison, mediator, discharge planner and manager of in-country referrals. Understanding the importance of the multi-dimensional roles of social workers in the provision of palliative care to patients with life-limiting illnesses is critical. **Conclusion:** National palliative care policy guidelines and further research are needed in strengthening social workers' role in the provision of the field of palliative care. This can be achieved through effective training and capacity building of social workers through continuous education in palliative care.

Keywords: Life-limiting illnesses, Namibia, Role of Social workers

P1.07-20 EVALUATION OF THE EFFICACY OF CONTINUING NURSING EDUCATION SESSIONS FOR ONCOLOGY NURSES AT PRINCESS MARGARET CANCER CENTRE

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Background: The evolving health care systems and ongoing advances in cancer treatments require continual education. Continuing Education (CE) is one of the most common methods that healthcare professions use to keep their members aware of new information issues, and trends in healthcare. Advocates for continuing education state that CE serves to sustain the effectiveness of healthcare professionals by ensuring Clinical competence, thereby enhancing the quality of healthcare[1,2] and reducing malpractice issues[3]. To advance the quality of healthcare, it is expected that participants of CE programs acquire and retain information so that it may be transferred into professional practice[4]. Adult learning theory [5,6,7] and research suggest that effective CE programs should progress from the traditional lecture-based approach and seek new avenues of effective presentation for the adult learner. Nursing education has been said to be effective when it leads to improvement in practice and patient care. The current landscape in oncology nursing is ever evolving which leads nurses to adapt rapidly to the changing practices and therapies to update and improve their knowledge and skills. In February 2018 the Nursing Unit Council at Princess Margaret Cancer Centre recognized a need and developed a plan to implement education sessions for clinical trial, ambulatory, chemo-daycare and student nurses. **Method:** 10 educational sessions lasting 1 hour on various oncologic topics presented by staff oncologists (radiation, medical & pathologists) were held from March 9th 2018 to Mar 29, 2019 for nurses. A questionnaire, which contained 11 sections was created specifically for this project to assess the effectiveness of these sessions. These were completed anonymously by 41 participants (19 trial nurses, 8 ambulatory nurses, 4 student nurses & 10 staff nurses). **Result:** Feedback from nurses was evaluated through a multiple choice survey questionnaire (Likert scales). The information provided contributed to the understanding of the effectiveness of continuing education. The 1 hour format was feasible and liked among the nurses as it generally occurred during the lunch hour. The RN respondents reported collecting 10 hours total continuing education hours, with 84% related to current work. 65% of respondents indicated they learned new skills/information that they will apply to nursing practice. 30 % indicated the CE sessions validated their current practice and 100% of respondents indicated the content of each session fit with their experience level. **Conclusion:** Nurses perceived that learning new skills and information was a strong contributor to their professional development. Furthermore, participating in these sessions enhanced their learning needs. Collecting CE hours and session content were other contributing factors that impacted their decision to attend these sessions. Nursing Educational sessions were deemed valuable and well received by nurses in the various departments at Princess Margaret to improving clinical practice and guiding the future of oncology nursing. References 1. Boissoneau R. 1977;71:35-50. 2. Thurston HI. 1992;23:6-14. 3. Little CD. *J Contin Educ Health Prof*. 1993;13:159-167. 4. Oliver SK. *J Contin Educ Nurs*. 1984;15:130-134. 5. Knowles MS. Associated Press; 1975. 6. Cross KP. San Francisco, CA: Jossey-Bass; 1981. 7. Jerin JM, Rea TD. *Emerg Care*. 2005;9:333-337.

Keywords: Nursing, Efficacy, Continuing Education

P1.09 PATHOLOGY
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.09-01 IMMUNOPROFILING DEPENDS ON MOLECULAR DETERMINANTS TO PREDICT METASTASES AND TARGET THERAPY IN NON-SMALL CELL LUNG CARCINOMAS

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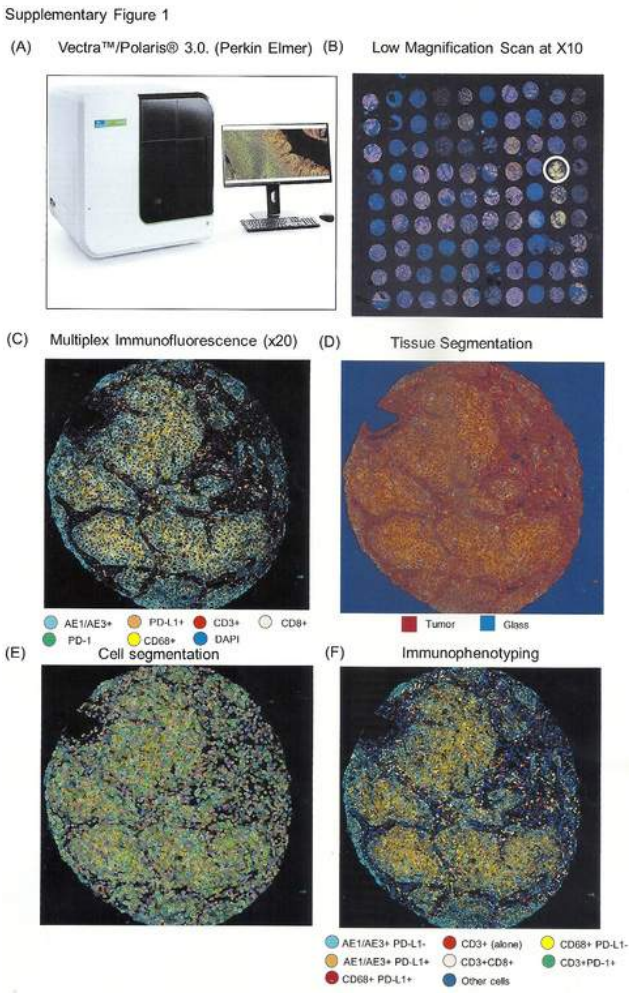
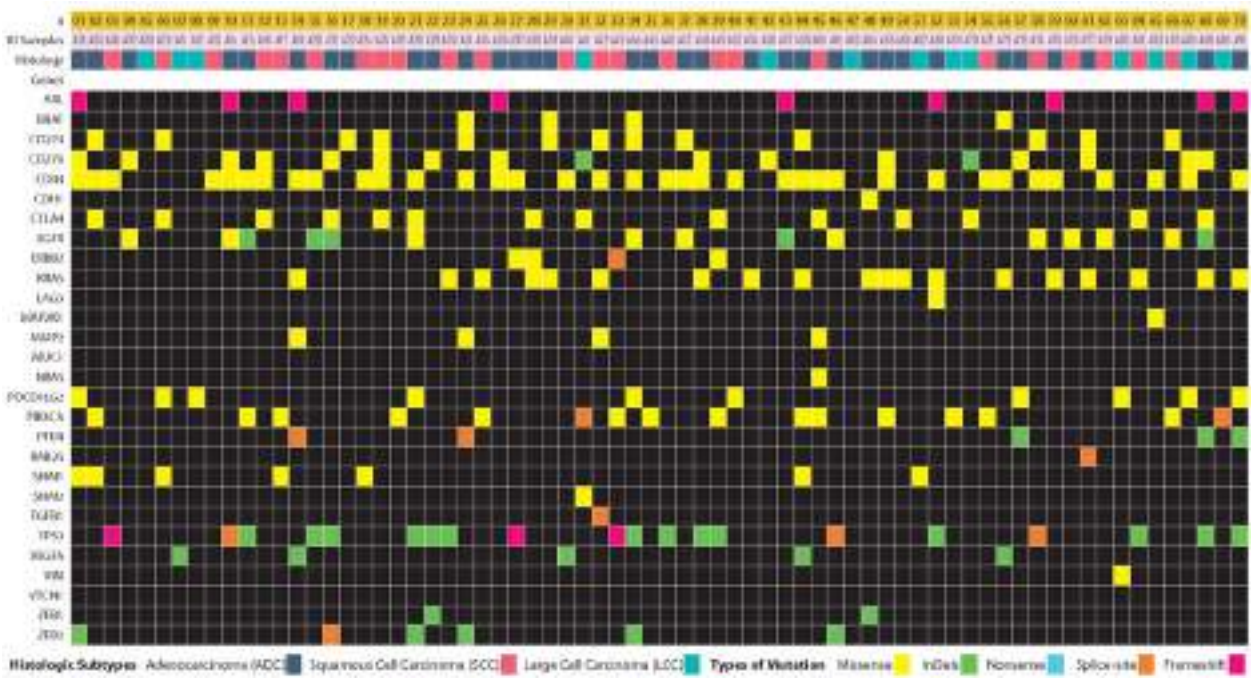
Background: To gain insight into the pathogenesis and progression of non-small cell lung carcinomas (NSCLCs) by 1) characterizing the tumor microenvironment using multiplex immunofluorescence (mIF), image analysis, and genetic mutation analysis and 2) correlating findings with clinicopathologic characteristics and data on tumor progression and prognosis. **Method:** Tissue microarrays from 164 primary tumors from patients with stage I–III NSCLC were examined. The specimens included 94 adenocarcinomas, 51 squamous cell carcinomas, and 19 large cell carcinomas. Using mIF and image analysis, we evaluated programmed death ligand 1 (PD-L1) expression in malignant cells (MCs), CD68+ macrophages, and cells expressing the immune markers CD3, CD8, CD57, CD45RO, FOXP3, PD-1, and CD20 (Figure 1). Cell phenotype data were then integrated with clinicopathologic characteristic and next-generation sequencing gene profiles.



Result: PD-L1 expression by MCs and other cells was associated with specific clinicopathologic characteristics and next-generation sequencing profiles (Figure 2). In addition, higher densities of antigen-experienced T-cells were associated with brain metastases. The most frequent microenvironments in the NSCLC tissues were type II (immunologic ignorance) and type IV (tolerance). Multivariate analysis showed that tumors with 1) brain metastasis, 2) lower densities of T-cells, memory T-cells, and natural killer T-cells, and 3) CD276, CTLA4, MMP-2, and TP53 mutations had worse overall survival compared with tumors without 1) brain metastasis, 2) higher densities of T-cells, memory T-cells, and natural killer T-cells, and 3) tumors without CD276, CTLA4, MMP-2, and TP53 mutations.

Conclusion: We detected cell phenotypes and gene mutations associated with tumor metastases in NSCLC.

Keyword: Immunoprofiling; lung cancer; multiplex immunofluorescence; image analysis; next-generation sequencing



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P1.09-02 COMPREHENSIVE GENOMIC PROFILING OF NON-SMALL CELL LUNG CANCER IN BRAZIL (GBOT 0118/ LACOG 0418)

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Background: Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide. Cancer driver mutations have been examined extensively and are the basis for modern precision therapy. The access of genomic tests in Brazil and, therefore, the prevalence of driver mutations of NSCLC in the country is not well described. The objective of this study is to carry out an epidemiological analysis of the somatic genetic profile of Brazilian NSCLC samples tested with FoundationOne®. **Method:** GBOT 0118/ LACOG 0418 is a retrospective cross-sectional study with patients diagnosed with NSCLC in Brazil and who performed comprehensive genomic profiling (CGP) using FoundationOne® or FoundationACT®. Raw data containing anonymous clinical-pathological characteristics and the results of CGP was analyzed. We described the molecular profile of patients using descriptive statistics. Categorical variables are presented as frequency and compared using the Chi-square test. **Result:** We obtained a total of 513 CGP results, 457 (89.0%) from Foundation One® and 56 (10.9%) from FoundationACT®. Adenocarcinoma was the most common histological subtype (83.8%) followed by NSCLC NOS (16.1%). Median age at testing date was 64 years, and 51.27% were male. *EGFR* activating mutations were detected in 23.39% patients, *ALK* rearrangements in 5.65%, *ROS1* rearrangements in 2.34%, *RET* alterations in 2.53%, *BRAF* mutations in 5.46%, *KRAS* mutations in 25,15% and NTRK fusions in 0,58% . Tumor mutational burden (TMB) analysis was available for 80.51% of samples tested and was measured in mutation per megabase. TMB were divided into three groups based on the Foundation Medicine reports: low (1-5 mutations/mb), intermediate (6-19 mutations/mb) and high (≥ 20 mutations/mb). The of tumors had low (42.69%) or intermediate (32.36%) TMB, and only 5.46% had high TMB. Table 1. Frequency of somatic genetic alterations in tumors tested with FoundationOne® and availability of targeted therapies in Brazil.

GENE	Frequency in NSCLC (%)	Availability in Brazil
EGFR	23.39	Approved
ALK	5.65	Approved
ROS1	2.43	Approved
BRAF	5.46	Approved
KRAS	25.15	No drugs available
RET	2,53	Drugs available but not approved
NTRK	0,58	Drugs available but not approved

Conclusion: This is the most comprehensive study describing CGP of NSCLC in Brazil using FoundationOne® or ACT. Our study shows rates of *EGFR* mutations and *ALK* rearrangements similar to those previously described. The knowledge of the molecular patterns of NSCLC in Brazil may help to improve health policies and access to targeted agents in the country.

Keywords: NGS, drive mutation, TMB

P1.09-03 CLINICOPATHOLOGICAL CHARACTERISTICS FOR NSCLC HARBORING EGFR EXON 20 INSERTION

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Background: For the majority of EGFR-mutant NSCLC patients harboring exon 19 deletion or exon 21 L858R, EGFR-TKIs are key therapies for outstanding anti-tumor effects. However, for the population harboring minor mutations, clinical benefit of EGFR-TKIs are controversial. Specifically, exon 20 insertion is acknowledged as a poor prognostic mutation type compared to other minor mutations. There are few reports describing clinicopathological characteristics harboring exon 20 insertion NCSLC. **Method:** We retrospectively analyzed patients harboring EGFR exon 20 insertion at our institution over 3 years. Clinical testing for the detection of EGFR mutations was cobas® EGFR Mutation Test v2. We evaluated pathological features for diagnostic specimens or re-biopsy samples, CT or PET images for the detection of primary lesions or metastatic locations. **Result:** A total of 213 EGFR-mutant adenocarcinomas were reviewed for the study and screened. Of these, 19 were positive for exon 20 insertion (8.9%). Of 19 cases, 13 displayed advanced stage while 6 cases were classified as early stage. Compound major mutation was detected in 26.3% (3 cases were exon 19 deletion; 2 cases were exon 21 L858R). In advanced cases, the location of primary lesions was found mainly in the subpleural domain (84.6%), and pleural dissemination was confirmed in 77%. The majority of cases included pleural effusion. Furthermore, 70% contained mucinous type pathologically in advanced cases. In total, more than half of the cases showed well-differentiated subtypes pathologically, which was contrary to a past report[1]). **Conclusion:** Contrary to a past report, EGFR exon 20 insertion in adenocarcinoma often showed pathologically mucinous and well-differentiated subtypes. For clinical characteristics, especially in advanced stage, pleural dissemination and effusion were observed with high frequency, which might be due to the primary lesion often located in the subpleural domain. 1) Mol Cancer Ther; 2012(2); 220–9

Keywords: EGFR-mutant NSCLC, Exon 20 insertion

P1.09-04 COMPREHENSIVE GENOMIC PROFILING IN A BRAZILIAN COHORT OF LUNG CANCER PATIENTS: REAL-WORLD IMPACT

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Background: The implementation of comprehensive genomic profiling (CGP) for every patient would ideally inform on all types of alterations, both frequent and rare events that might be useful for treatment. However, less than 50% of Brazilian lung cancer patients have access to any molecular testing. Giving the lack of literature data regarding CGP and clinical practice change, we aimed to evaluate how CGP changed patient treatment in a fully-annotated cohort of lung cancer in Brazil. **Method:** A retrospective study was conducted to review lung cancer patients for whom CGP was performed from October 2017 to February 2019 in a national, private oncology institution. Patients with all histological subtypes tested with Foundation One (F1) were included. Data regarding microsatellite instability (MSI), tumor mutational burden (TMB) and genomic findings were collected, as well as therapies/ clinical trials with possible clinical benefit. Demographic data were collected from chart review. **Result:** From 25 patients included in this cohort, 56% were male with a median age of 64-year-old. Tissue and blood sample were analyzed in 80% and 20%, respectively. The most common histological subtype was adenocarcinoma (68%) followed by squamous cell carcinoma (12%). CGP was ordered in 16% of treatment-naive patients; 52% in the first-line treatment and 8% and 12% after second and third line, respectively. None of them had MSI and 12% had high TMB. The most frequent genomic alterations were TP53 (64%); KRAS (32%); STK11 and ARID1A (16%); PIK3, CDKN2AB, and RB1 (12%); ATM, CTNNB1, ERBB2, MLL2, MSH2, PTPN11 and BRCA (8%). One patient was negative for EGFR mutation, tested by COBAS, but was found to have EGFR mutation by CGP. Although CGP showed up to 15 therapies and 37 clinical trials available for this cohort, none of the physicians have changed treatment after testing results due to limited access to clinical trials or one death before the beginning of anti-EGFR therapy. **Conclusion:** In our cohort, 25 patients with lung cancer had CGP tested during 16 months of follow-up, highlighting the limited access to the test. For most cases, CGP was ordered later during the treatment which could negatively impact on patient outcome. Furthermore, due to a paucity of available clinical trials and lack of access to new drugs in the country, the use of CGP had a limited impact in clinical decision making.

Keywords: Lung cancer, Comprehensive genomic profiling

P1.09-05 ALK TESTING IN CHINESE ADVANCED NSCLC PATIENTS: A NATIONAL-WIDE MULTICENTER PROSPECTIVE REAL-WORLD DATA STUDY (THE RATICAL STUDY)

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Background: ALK-tyrosine kinase inhibitors increase ORR and PFS times in ALK-fusion positive NSCLC patients. It is therefore crucial to assess the efficacy of different methods for detecting ALK rearrangement. At present, there are most testing methods approved by cFDA to detect ALK rearrangement in China. However, many issues regarding to the procedure and quality control (QC) data of ALK testing in the routine clinical practice is still to be studied. This study is to evaluate the ALK testing platforms, testing procedures, result interpretation quality control and clinicopathological characteristics of ALK positive patients in the real world for Chinese lung cancer patients, and achieve expert consensus on the clinical practice of ALK testing. **Method:** Top 31 hospitals with lung cancer patients in China will participate in the study. All advanced NSCLC subjects who received ALK gene test and all ALK positive NSCLC patients who received surgical treatment from Oct. 2018 to Dec. 2019 will be enrolled. The testing platforms include IHC-Ventana,FISH,RT-PCR and NGS. It is expected to enroll a total of 30,000 cases, and the clinicopathological information of the patients will be collected. Ring study and interpretation training will be conducted before the study initiated. When 2,000 and 10,000 cases are enrolled, the interim summary and quality control will be conducted respectively. The results were the interim summary and quality control results of 2,000 cases. **Result:** The 2263 enrollees (mean age, 63 years) included 1365 males (60.32%) and 907 females (39.68%). 205 (of 2263, 9.06%) cases were ALK positive. The ALK positive rate of females (11.10%) was significantly higher than that of males (7.74%). The ALK positive rate of non-smoking patients (11.54%) was significantly higher than that of smoking patients (5.70%). In addition to ALK, the positive rate of EGFR, KRAS, ROS1, HER2, MET, RET and BRAF gene alterations was 46.05%, 9.52%, 3.13%, 3.09%, 2.98%, 2.12% and 0.94%, respectively. Total rate of all driver gene mutation was 60.37% in males, while it was 91.71% in female. Total rate of all driver gene mutation was 59.77% in smoking patients and 90.44% in non-smoking patients. Concurrent mutation of ALK with EGFR, KRAS or ROS1 was 0.33%, 0.45% and 0.22%, respectively. The fusion of EML4-ALK accounted for 75%. The inconsistency rate of IHC-Ventana with FISH, RT-PCR, NGS was 95.07%, 91.30% and 95.45%, respectively. For ALK IHC quality control, 109 slides were used for ring study, and 31 pathologists participated in the interpretion. Among 60 negative cases, 25 cases (41.7%) were diagnosed as positive (false positive) by at least one pathologist. Among 49 positive cases, 12 cases (24.5%) were diagnosed as negative (false negative) by at least one pathologist; 34 cases (31.2%) were diagnosed as inconclusive by at least one pathologist. There were 3.5% and 1.1% of cases found to be misinterpreted during the internal QC and regional QC, respectively. **Conclusion:** NSCLC patients harboring ALK gene translocation have unique clinicopathological characteristics. Some problems will still be encountered in the real world clinical practice of ALK testing, which need to be guided by establishment of expert consensus.

Keywords: Lung cancer, Real world data, ALK testing

P1.09-06 EVALUATION OF MOLECULAR TESTING IN A DUTCH COHORT OF METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS FROM 2017

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Background: Adequate and timely testing for genetic alterations in non-small cell lung cancer (NSCLC) is necessary to consider targeted therapy when a certain genetic alteration is present. Previously, we demonstrated that in the Netherlands molecular testing was suboptimal in 2015, as 25% (EGFR/KRAS and ALK) to 50% (ROS1) of patients were not tested according to the guidelines, and notable variation between laboratories was present. Currently, by analyzing a cohort of metastatic NSCLC from 2017 we aim to assess whether the performance of molecular testing improved. **Method:** All fully registered stage IV non-squamous NSCLC with incidence year 2017 from the Netherlands Cancer Registry were matched to the Dutch pathology registry (PALGA). Using information extracted from pathology excerpts, proportions of tumors tested for EGFR and/or KRAS, BRAF, and HER2 mutation, and ALK, ROS1, and RET rearrangement within 3 months after diagnosis were determined, and reason for not testing were assessed. **Result:** Of 2596 identified patients, we have currently analyzed 511 (20%). Twenty-three patients were non-eligible after matching, leaving 488 patients. Of these patients, 262 (54%) were male and 413 (88%) had an adenocarcinoma. EGFR and/or KRAS testing was performed within 3 months after diagnosis in 412 patients (84.4%). Of the EGFR/KRAS wildtype tumors (n=184), 167 (90.8%) were tested for BRAF, 158 (85.9%) for HER2, 157 (85.3%) for ALK, 110 (59.8%) for ROS1, and 73 (39.7%) for RET. Insufficient tumor tissue and inappropriate specimen were the most stated reasons for not testing. **Conclusion:** These preliminary data show significantly higher testing proportions for EGFR and/or KRAS and ALK as compared to 2015. Further improvement remains possible to identify candidates for targeted therapy. At the WCLC meeting, we expect to present the variation between laboratories for the entire cohort.

Keywords: molecular pathology, variation in care, metastatic NSCLC

P1.09-07 THE CLINICAL UTILITY AND PERFORMANCE OF WHOLE-EXOME SEQUENCING FOR NSCLC PATIENT CARE: A COMPARISON TO STANDARD-OF-CARE

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Background: Next-generation sequencing (NGS) has provided the technology to rapidly profile individual tumours and measure the increasing number of biomarkers particularly relevant to the treatment of NSCLC. The Australian Translational Genomics Centre (ATGC) was established as collaboration between the healthcare sector (Metro South Hospital and Health Service), higher education sector (Queensland University of Technology) and a government-run pathology service (Pathology Queensland) to provide genomic profiling of NSCLC patients at the princess Alexandria Hospital. The program was developed to integrate the ordering, processing and interpretation of large scale NGS sequencing into clinical practice. **Method:** NSCLC samples derived from endobronchial ultrasound (EBUS) or from formalin-fixed, paraffin-embedded (FFPE) histological sections were used for molecular profiling with NGS technologies by the ATGC, providing the first NATA-accredited ISO15189 program for lung cancer in Australian public hospital. The genomic test utilized whole-exome sequencing (WES) in combination with a high-coverage spike-in panel of known cancer genes. The clinical reports included the calculation of tumour purity, tumour mutational burden, the assessment of copy number events and somatic mutations down to 3% allele frequency. In addition, the performance of the genomic profiling was compared to the current standard practice performed by Pathology Queensland, based on a gene panel (and back-up IHC for *EGFR* and *BRAF*) with reporting on Tier 1-2 variants in selcted exons of *EGFR*, *BRAF*, *KRAS* and *NRAS*, and immunohistochemistry on EGFR and ALK. For this purpose, patient biopsies were processed in parallel by ATGC and Pathology

Queensland. **Result:** We demonstrated that samples derived from EBUS and FFPE sections routinely provides high quality diagnostic material of sufficient quality and tumour purity suitable for molecular profiling with NGS technologies. Thirty-six lung cancer samples were tested by WES/panel, and an average of 1.5 clinically significant Tier 1- 2 mutations were detected in NSCLC samples by WES/panel testing, and that 11 out of 36 cases had a high tumour mutational burden (>10 mutations/megabase). Of the 36 cases, 17 were also tested by Pathology Queensland. In 7 of those 17 cases, WES/panel detected variants in genes other than *EGFR, KRAS, NRAS,* and *BRAF* not detected or reported by standard methods; and, based on the additional variants reported by WES/panel, an additional 7 of the 17 patients would be eligible for enrolment in a clinical trial in Australia (source: Molecular Match; www.molecularmatch.com).This did not include trials or medications based on the tumour mutational burden. **Conclusion:** We demonstrate that integration of WES/panel testing into clinical practice is practical and provides significant advantages over standard testing by providing multiplexed testing of current and emerging biomarkers. Furthermore, adoption of WES/panel testing for the care of NSCLC patients is superior to standard-of-care in the stratification of lung cancer patients into appropriate Australian clinical trials.

Keywords: NSCLC, Molecular profiling, Whole Exome Sequencing

P1.09-08 REGISTRATION OF PRE-OPERATIVE LUNG CANCER PET/CT SCANS WITH POST-OPERATIVE HISTOPATHOLOGY MAPS

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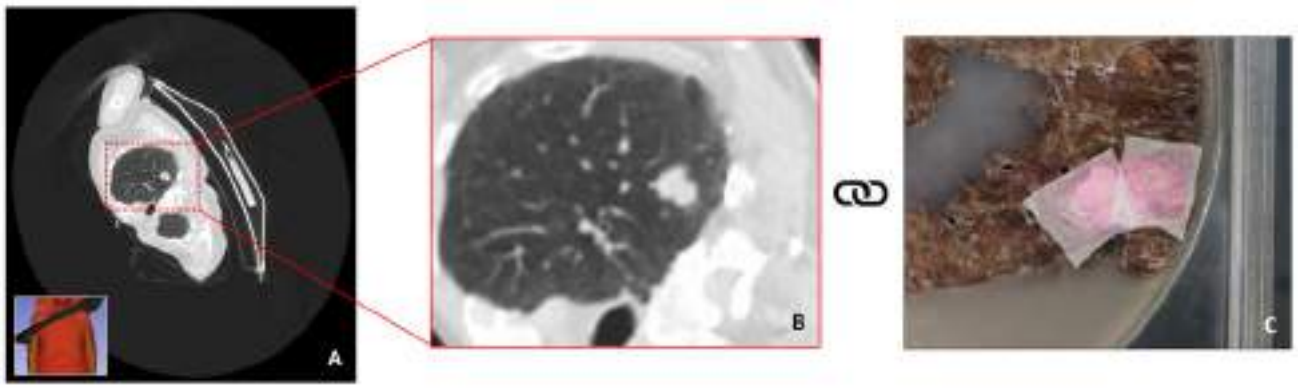
Background: Currently there is insufficient data describing the cellular make-up of a tumour in relation to its functional imaging. This research project focuses on registering pre-operative PET/CT scans from lung cancer patients to their post-operative histology slides, enabling clinicians to draw spatial correlations between the tumour's metabolic fingerprint and its actual histopathology map. **Method:** Between January and June 2018 the research team identified and recruited 9 patients diagnosed with primary NSCLC and referred for radical lobectomy, across NHS Greater Glasgow and Clyde sites. Each participant was scanned in a combined PET/CT scanner prior to surgery, as per standard of care. The resected lobe was fixed in formalin for a minimum of 48 hours and injected with a 4% agar solution through the airways to stiffen the tissue and facilitate slicing. Once solid, the whole lobe was placed in a purpose-built slicing rig and dissected at regular 5-millimetre intervals. Each slice was photographed using a digital camera, then processed using a microtome and stained using immunohistochemistry (IHC) methods. Virtual 3D tumour models were reconstructed from the CT and gross pathology images and registered using a linear affine transformation algorithm in Matlab 2017b (The MathWorks Inc, US). Real CT data was subsequently deformed using the same transformation matrix to match the gross pathology cutting planes. Histology slides were also aligned to the block-face photographs by applying a non-linear registration algorithm, constrained by one-to-one correspondences between common landmarks (i.e. edges, vessels, airways) identified on both image datasets. **Result:** An average Dice similarity coefficient of 83% was obtained for the CT-to-pathology tumour model registration. Due to the quasi-spherical shape of most tumours, the orientation was found to be wrong in 3 cases, despite high overlapping scores. Therefore, we introduced a weighted registration algorithm that considers fiducial markers located in and around the tumour (e.g. airways or vessels) to ensure correct orientation. The figure below shows a sample slice of a transformed CT volume (A,B) which is matched to its corresponding gross pathology photograph (C), with overlapped histopathology data.



Conclusion: Building on the preliminary results presented last year in IASLC WCLC 2018, this proof-of-concept study has managed to spatially match pre-operative CT tumour data with its actual histopathology map, and we are in the process of extrapolating these results to 4D FDG PET data. This acquired knowledge shall provide an informed targeted approach for future radiotherapy studies.

Keywords: Pathology, PET/CT, Image Registration

P1.09-09 MODEL TO PREDICT SMALL LYMPH NODES METASTASIS IN NON-SMALL CELL LUNG CANCER

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Background: Accuracy target volume delineation is a fundamental problem in radiotherapy in patients with non-small cell lung cancer(NSCLC). There is a lake of "golden standard" in gross tumor volume(GTV) delineation can be defined so far. Especially in the delineation for lymph node target volume (GTVn).The standard most widely used in NSCLC radiotherapy planning was lymph nodes have a short-axis diameter greater than or equal to 1.0cm was regarded as malignant.However,it is clearly that lymph node size isn't a reliable parameter for the evaluation of metastasis.The aim of this paper is to develop a nomogram model to predict small lymph nodes metastasis in patients with NSCLC,expecting provide guidance for lymph node target volume delineation. **Method:** We retrospectively evaluated patients with NSCLC who had underwent Multi-slice Spiral Computed Tomography (MSCT) before radical surgery between October 2015 and December 2016. The least absolute shrinkage and selection operator regression model (LASSO) was used to selecting features for predicting small lymph node metastasis.Binary logistic regression analysis was applied to build a predicting model based on LASSO regression.The nomogram model were assessed using the C-index, calibration plot, and decision curve analysis(DCA). Internal validation was tested using the bootstrapping validation. **Result:** 279 lymph node stations among 82 patients met with inclusion criteria were observed, 44(15.7%) of them were pathologically confirmed metastasis. Twelve features were reduced to seven potential predictors in the LASSO regression model, including primary tumor location(left lobe and right lob), pathological type (quamous carcinoma,adenocarcinoma and other types),T stage,vascular invasion ALK mutation, lymph nodes clustered and short-axis of the maximum lymph node. The model displayed good discrimination with a C-index of 0.895 and good calibration. High C-index value of 0.856 could still be reached in the internal validation. Decision curve analysis showed that the nomogram model was clinically useful. **Conclusion:** The nomogram model incorporating clinical,radiological and pathological features could be conveniently used to predict the risk of metastasis in small lymph nodes in patients with NSCLC,and contributed to the delineation of tumor target volume.

Keywords: Lymph nodes metastasis, Nomogram, Non-Small Cell Lung Cancer

P1.09-10 MOLECULAR IMMUNOCYTOCHEMISTRY IN VARIOUS NSCLC SAMPLES PREPARED AS NON-CELL BLOCK CYTOLOGY

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Background: Molecular prognostic-predictive immunocytochemistry is obligatory for therapy decision in NSCLC patients. Immunocytochemistry on cell blocks FFPE cytology is preferred because of some validation advantages, but is not always sufficient in terms of samples acquisition and cell number adequacy. Aim of the study is to compare molecular immunocytochemistry expression between cytology samples obtained with bronchoscopy (bronchial washing/brushings and transbronchial fine needle aspirations) and other cytology samples such as pleural effusion, FNA of peripheral lymph nodes and skin nodules and transthoracic FNA/biopsy; all prepared as non-cell block cytology. **Method:** We compared archive records of the 1109 immunocytochemistry (ICC) results of ALK, ROS1 and PD-L1 expression in carcinoma cells in relation to specimen type (bronchoscopic and non-bronchoscopic samples) prepared as smears and cytospins at our institution over a one-year period.

Air dried cytology smears and cytospins of NSCLC samples were stained with Anti-ALK Clone D5F3, Cell Signaling, appendix positive control; Anti-ROS1 Clone D4D6 Cell Signaling, HCC-78 cell line positive control and Anti-PD-L1, Clone 22C3, Dako, placenta imprint positive control; EnVision detection system on Immunocytochemistry Autostainer. PD-L1 protein expression was scored using Tumor Proportion Score (TPS) with positive cut-off of ≥1%, membrane staining. The slides were routinely examined and scored by two cytologists. Internal and external quality control were performed on FFPE cell blocks and histology slides with corresponding Ventana antibodies and staining systems. **Result:** Out of 1109 results, 440 were ALK ICC results, 111 ROS1 and 558 were PD-L1 ICC staining results. Among them 314/440 (71, 36%) ALK, 75/111 (67,57%) ROS1 and 392/558 PD-L1 ICC (70,25%) were in bronchoscopic samples and 126/440 (28,64%) ALK, 36/111 (32,43%) ROS1 and 166/558 (29,75%) PD-L1 ICC were in various non-bronchoscopic samples. Comparison in ALK, ROS1 and PD-L1 ICC distribution between two groups of samples showed no statistical significant difference among groups (X^2 test, df 2, p=0,730). Positive ALK and ROS1 numbers were in observed range, but insufficient for statistical analysis. PD-L1 ICC scored results were in total of 392 samples collected during bronchoscopy and 166 of various other non-bronchoscopic samples: 88 were obtained by FNA of peripheral lymph nodes and skin nodules, 38 by transthoracic FNA/biopsy and 40 pleural effusions. PD-L1 ICC scored negative in total of 281/558 (50,36%) samples, 191 bronchoscopic and 90 non-bronchoscopic. PD-L1 ICC scored positive in total of 277/558 (47,11%) samples of which 201 were obtained with bronchoscopy and 76 of samples collected with other methods. Among of total PD-L1 positive smears, 128 were PD-L1 positive ≥ 50%; 90/128 (70,31%) were bronchoscopical samples and 38/128 (29,7%) other samples. Comparison in PD-L1 expression between two groups of samples showed no statistical significant difference among groups (X^2 test, df 1, p=0,236). Comparison between two groups of PD-L1 positive ≥ 50% showed no statistical significant difference among sample groups (X^2 test, df 1, p=0,436). **Conclusion:** There were no statistical significant differences in molecular ALK, ROS1 and PD-L1 immunocytochemistry results between samples collected during bronchoscopy and non-bronchoscopic samples prepared as non-cell block cytology. PD-L1 scoring results were also independent of cytology sample type in our study.

Keywords: molecular immunocytochemistry, non-cell blocks cytology, NSCLC

P1.09-11 INFLUENCES OF SAMPLING METHOD TO MORPHOLOGICAL FEATURE MEASUREMENT OF LUNG CANCER CELL

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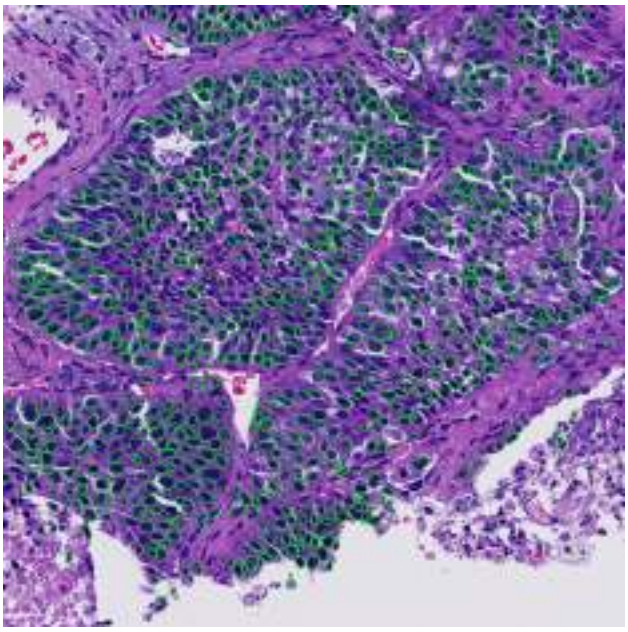
Background: Progress of imaging technologies in the field of histopathology enables us to exploit artificial intelligence (AI) techniques to detect cancer based on digital images for screening or quality assurance of diagnosis process. Nowadays, reports on the application of AI to cancer detection which claim 99-percent detection accuracy are found in every proceedings or journal of digital pathology. However, little attention has been paid to the influences of sampling method to AI-based histological diagnosis. **Method:** Whole slide images of hematoxylin and eosin (H&E) stained slides collected from 94 non-small cell lung cancer (NSCLC) cases were captured by a virtual slide scanner (NanoZoomer, Hamamatsu Photonics, Japan). Sampling methods were needle biopsy (59 cases), operation (12 cases) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (29 cases). Regions of interest (ROI) were selected by an experienced pathologist. After selecting tumor cells only by AI-based tumor cell detecter (Figure.1), following morphological features were calculated: nuclear area, perimeter (Peri), circularity (Circ) and five texture features, i.e., angular secondary moment (ASM), contrast(Cont), homogeneity (Hom) and entropy (Ent) of gray level co-occurrence matrix (GLCM), and contour complexity (CC).



Result: We found significant differences (p<0.05) in most of feature values except nuclear area and perimeter. **Conclusion:** Our results suggest that methods of sampling significantly affect morphological feature values of nucleus and this fact must be taken into consideration when applying AI-based techniques to tissue image classification.

P1.09-12 IN-SITU HYBRIDIZATION VISUAL SCORING OF EPIGENETIC IMPRINTING GENES IMPROVES EARLY DIAGNOSIS AND GRADING OF LUNG CANCERS

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Background: Pathologists rely on cellular morphology to determine cancer diagnosis. However earlier grades (dysplasia) and stages (Carcinoma-in-situ) of cancers which are most treatable have less obvious changes. Epigenetic changes occur at most stages of carcinogenesis, but the application of epigenetic testing in cancer diagnosis is limited. Imprinted genes are normally silenced in one of two parental alleles, but is reportedly reversed in carcinogenesis, with expression of biallelic (Loss of Imprinting-LOI) or multiallelic (Copy Number Variations-CNV) expression (Figure 1A). We present here a novel visual and quantitative approach targeting imprinted genes involved in lung cancer development and progression. **Method:** The Lisen in-situ hybridization(ISH) targets non-coding introns of imprinted genes to provide a visual and quantitative analysis of malignancy associated changes, unlike bisulfite reduction techniques. Formalin fixed lung cancer and benign lung samples are tested with an epigenetic panel (imprinted genes GNAS, GRB10 and SNRPN) stains. Diagnostic algorithm for a grading model based on LOI, CNV and summed "Total Expression (TE)" counts is developed comparing cancer samples in different stages and benign samples (Figure 1A).

Figure 1A

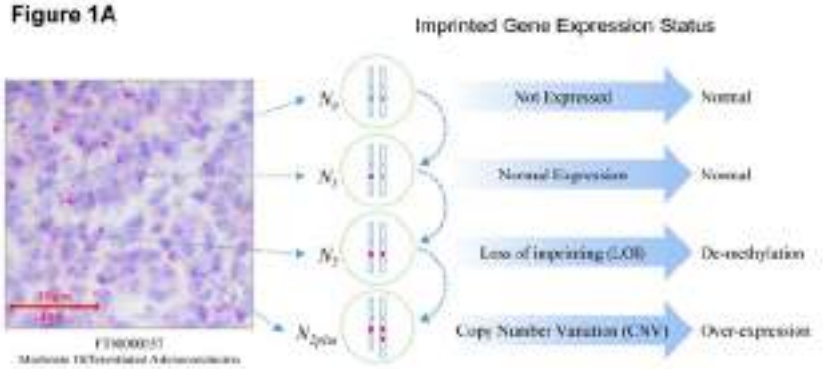
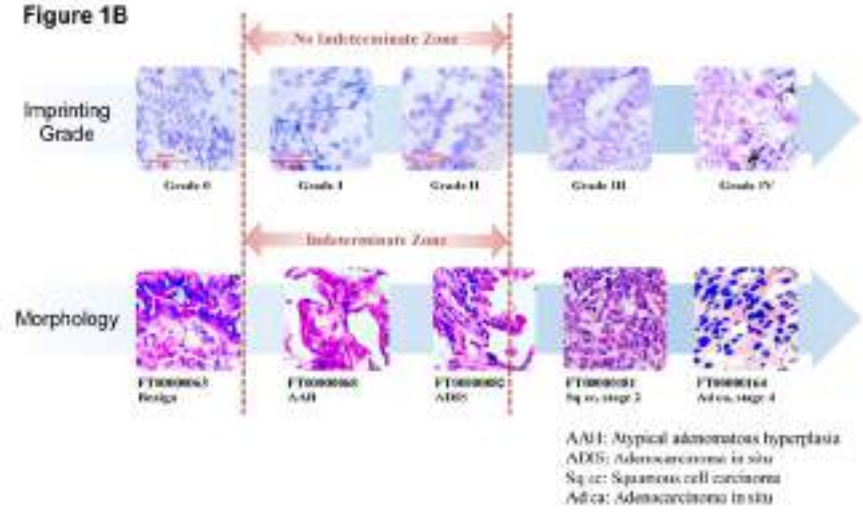


Figure 1B



Result: Technicians trained in counting LOI and CNV studied 198 cases of lung samples in a blinded fashion to score LOI, CNV and TE (Figure 1A). These included 29 benign, 20 with Atypical Adenomatous Hyperplasia (peripheral), 11 Adenocarcinoma-in-situ (ADIS), 138 invasive squamous and adenocarcinomas (64 stage 1, 20 stage 2, 54 stages 3&4). A grading model from Grade 0 (benign) to Grade IV (highly malignant) is developed based on the expression pattern of the three genes epigenetic panel to correlate with pathological staging. Grade 0 (benign) corresponds with benign normal, Grade I (malignant potential) corresponds with precancerous AAH, Grade II (limited disease) corresponds to ADIS, Grade III (more invasive) corresponds to stage 1 and 2, and Grade IV (highly invasive) corresponds to stages 3 and 4. (Figure 1B) **Conclusion:** Imprinted gene detection by ISH staining provides a novel way to visualize and quantify epigenetic changes occurring in earlier stages of lung cancer development. The quantitative grading model can reduce the subjective variation in diagnosis and provide a more precise tool to assist the pathologist. Inclusion of an expanded panel of imprinted genes, studying larger specimen sets and adaptation by automated image analysis hold promise of advancing standardization of early lung cancer diagnosis.

Keywords: Genomic Imprinting, epigenetic alterations, early diagnosis

POSTERS

P1.09-13 PROGNOSTIC VALUE OF TMPRSS4 EXPRESSION AND ITS ROLE AS DIAGNOSTIC BIOMARKER BY LIQUID BIOPSY IN EARLY STAGE NSCLC

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Background: Relapse rates in surgically-resected non-small cell lung cancer (NSCLC) patients are between 30-45% within 5 years of diagnosis, which reflects the clinical need to identify those patients at high risk of recurrence and death. TMPRSS4 is a serine protease that plays a role in lung cancer growth, development of metastasis and resistance to chemotherapy in NSCLC models. TMPRSS4 is overexpressed through promoter hypomethylation in NSCLC tumors. **Method:** Two cohorts of NSCLC patients (MD Anderson (MDA), n=489; and Clinica Universidad de Navarra (CUN), n=95) were used to investigate the prognostic value of TMPRSS4. The WHO 2004 classification and 8th TNM edition was used for tumor stratification. We have also developed a method to quantify he degree of TMPRSS4 and SHOX2 methylation status in liquid biopsy (plasma and bronchoalveolar lavages (BALS)) by digital droplet PCR (ddPCR), in tumor-free individuals and patients with NSCLC. **Result:** High levels of TMPRSS4 were significantly associated with reduced relapse-free survival (RFS, p<0.001) and overall survival (OS, p<0.001) in the MDA cohort, and with OS in the CUN cohort (p<0.049). In univariate Cox regression analysis using the MDA cohort, high TMPRSS4 levels were RFS (HR=2.09; 95% IC [1.53-2.87], p<0.001) and OS (HR=1.82; 95% IC [1.38-2.41], p<0.001). In multivariate analyses, TMPRSS4 was found as an independent prognostic factor for both RFS (HR=1.82, IC [1.28-2.60], p<0.001) and OS (HR=1.44, IC [1.07-1.94], p<0.014).

In our MDA cohort, stage IA and stage IB showed no statistical differences for RFS (p=0.27) or OS (p<0.001). However, when considering the protein expression of TMPRSS4 we were able to substratify stage IA patients in low and high risk patients, since those with high TMPRSS4 levels showed a significantly reduced RFS (p=0.002) and OS (p<0.001). Similar tendency was observed for stage IB, although statistical differences were not found.

After successful establishment of the ddPCR conditions for TMPRSS4 and SHOX2 methylation status, we analyzed plasmas and BALS in case-control studies. In BALS (79 NSCLC patients and 26 controls), significant hypomethylation (p<0.01) was found for TMPRSS4 in the case of patients with early stage NSCLC in comparison with controls, with an AUROC of 0.72 (95% IC, 0.57-0.87) (p=0.008). SHOX2 was significantly hypermethylated in BALS from early stage NSCLC compared to controls (p<0.01), with an AUROC of 0.71 (95% IC, 0.56-0.86) (p=0.01). In the case of plasmas (89 NSCLC patients and 25 controls): in early stages, a significant hypomethylation was found for TMPRSS4 (p<0.05), with an AUROC of 0.73 (95% IC, 0.54-0.90) (p=0.015). For SHOX2, only late stages NSCLC showed significant hypermethylation with respect to controls (p<0.05), with an AUROC of 0.68 (95% IC, 0.54-0.80) (p=0.025). **Conclusion:** High TMPRSS4 levels are associated with worse prognosis in NSCLC patients. TMPRSS4 expression significantly discriminates patients with higher risk of disease progression and poor survival outcome in early stage NSCLC. Methylation status of TMPRSS4 can be used in both plasma and BALS to identify patients with NSCLC.

Keywords: TMPRSS4, liquid biopsy, methylation

P1.09-14 COMPARISON BETWEEN LIQUID BIOPSY AND CONVENTIONAL TISSUE BIOPSY IN EGFR GENOTYPING OF NON-SMALL CELL LUNG CANCER

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Background: In lung cancer, tissue biopsy is usually invasive and could provoke a severe procedural complication depending on the location and size, while liquid biopsy is non-invasive, and novel emerging method in lung cancer. In this study, we investigated the sensitivity, specificity, and concordance rate of liquid biopsy (blood and bronchoalveolar lavage fluid (BALF)) comparing with tissue biopsy. **Method:** A total of 31 patients' tissue, blood, and BALF were available. The EGFR mutation status in blood, and BALF were investigated by ultrasensitive droplet-digital polymerase chain reaction (ddPCR) method. We applied two QC criteria for the results of ddPCR were used as previous study showed: 1) the droplet number must be greater than 9000; 2) the wild type levels to be greater than 100 copies/mL. **Result:** Female was 15 (48.4%) and mean age was 66.4 ± 9.6. Clinical sensitivity was 20.0% [2/10] for E19del and 36.4% [4/11] for L858R in plasma, while in BALF, those was 70.0% and 81.8%, respectively. The concordance rates of plasma with tissue-based results of EGFR mutations were 71.0% for E19del and 77.4% for L858R. In BALF, those were 83.9% for E19del, and 90.3% for L858R. The area under the curve (AUC) for E19del was 0.576 in blood and 0.802 in BALF. The AUC for L858R was 0.682 in blood and 0.884 in BALF. The values of AUC between blood and BAL did not show significant difference. **Conclusion:** BALF could be a substitute for biopsy in EGFR genotyping and BALF might be helpful in diagnosis of lung cancer in situations where it is difficult to perform biopsy or rebiopsy is needed. Further prospective large scaled studies are needed to investigate the utility of BAL in lung cancer.

Keywords: EGFR, droplet digital PCR, bronchoalveoloar lavage fluid

P1.09-15 HYBRID ORGANOID REVEALS THAT PODOPLANIN-POSITIVE CANCER-ASSOCIATED FIBROBLASTS ENHANCE PROLIFERATION OF LUNG CANCER CELL

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Background: Podoplanin-positive cancer-associated fibroblasts (CAFs) play an important role in tumor progression. The aim of this study was to evaluate the effect of podoplanin (+) CAFs on the proliferation of cancer cells using a three-dimensional (3D) organoid model. **Method:** We examined the success rate of organoid culture containing PC-9 cancer cells and CAFs. Thereafter, we compared the proliferating index (MIB-1 index) of PC-9 cells co-cultured with podoplanin-overexpressing CAFs and control CAFs using organoid specimens. Furthermore, we compared the MIB-1 labeling index of cancer cells in podoplanin (+) CAFs cases (n = 13) and podoplanin (-) CAFs cases (n = 14) using surgically resected adenocarcinoma specimens. **Result:** Without CAFs, PC-9 cells did not form any organoid (success rate: 0%). When PC-9 cells were mixed with CAFs (1:10), the mixed cells generated round and steric aggregates (hybrid cancer organoids, success rate: 100%). In three independent experiments, the MIB-1 index of PC-9 cells in hybrid cancer organoids containing podoplanin-overexpressing CAFs was significantly higher than that of PC-9 cells in organoids containing control CAFs (Exp. 1: 40.4% vs. 24.4%; Exp. 2: 40.0% vs. 24.5%; Exp. 3: 40.3% vs. 25.2%; p < 0.001). Surgically resected human tumors revealed that the MIB-1 index of adenocarcinoma cells was significantly higher in the case of podoplanin (+) CAFs than in the case of podoplanin (-) CAFs (34.8% vs. 16.2%; p < 0.01). **Conclusion:** Our data suggested that the hybrid cancer organoid model might reflect the growth-promoting effect of podoplanin (+) CAFs in cancer cells, and this new system can be a useful tool for evaluating the tumor microenvironment.

Keywords: podoplanin, cancer associated fibroblast, hybrid cancer organoid

P1.09-16 TUMOR PROLIFERATION IS ASSOCIATED WITH THE TUMOR IMMUNOLOGICAL STATUS: A STUDY ON NSCLC USING MULTIPLEX IMMUNOFLUORESCENCE

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Background: Several studies have been focused on the immunoprofiling of non-small cell lung carcinomas (NSCLC) trying to characterize its immunological microenvironment and its association with therapy, clinical outcome and mutational status, including tumor mutation burden (TMB), with special emphasis on the identification of potential predictive biomarkers. Tumor proliferation index (TPI) evaluated by the expression of Ki67 in the tumor cells had shown clinical relevance as a general prognostic and predictive marker in several tumor types such as breast cancer, although its clinical relevance in NSCLC is not fully clear. Therefore, our goal was to analyze the TPI in NSCLC and to correlate it with the tumor immune profile, including PD-L1 and tumor-associated lymphocytes. **Method:** Formalin fixed, paraffin embedded tissue sections from 48 NSCLC specimens (25 adenocarcinomas, 22 squamous cell carcinomas, 1 NSCLC NOS) were immunostained with a multiplex immunofluorescence (mIF) panel including keratins (AE1/AE3), PD-L1, PD1, CD8, CD68 and Ki67. All samples were obtained according the Declaration of Helsinki. The mIF slides were imaged in a multispectral scanner (Polaris, Akoya Biosciences) and analyzed by using Definiens Insights platform with custom algorithms at Definiens AG (Munich, Germany). The data was then analyzed by various parameters to generate Spearman's correlation coefficients. **Result:** Our preliminary analysis showed that TPI correlated with the percentage of malignant cells expressing PD-L1 (r = 0.63). TPI also correlated with the infiltration by proliferating cytotoxic T-cells (CD8+ Ki67+, r = 0.67). Cell density of proliferating cytotoxic T-cells also correlated with the percentage of PD-L1 expression by malignant cells (r = 0.75), percentage of PD-L1 positive macrophages (r = 0.79), and with the expression of PD-1 by cytotoxic T cells (r = 0.79). Interestingly, we noticed that higher histological tumor grades (but not TNM stage status) presented a trend to show higher readouts including TPI, percentage of PDL1 expression in tumor cells and macrophages, and CD8 cell densities. **Conclusion:** Our multiplex IF analysis on NSCLC including tumor proliferation index shows evidence suggesting a correlation between the tumor proliferative activity and the immune microenvironment, including PD-L1 expression in both, tumor cells and macrophages, as well as higher proliferative cytotoxic T-cells. We hypothesize that the tumor proliferative activity has a mechanistic association with the tumor immunological status; therefore, TPI evaluated by Ki67 expression in tumor cells could be a candidate as a potential biomarker in association with the immunoprofiling data.

Keywords: Tumor Proliferation Index, Tumor Immune Microenvironment, multiplex Immunoflourescence

P1.09-17 IN THE MINIMALLY INVASIVE ERA, WHAT IS THE ROLE OF INTRA-OPERATIVE FROZEN SECTION PRIOR TO LOBECTOMY: A SINGLE INSTITUTION PERSPECTIVE

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Background: Current guidelines recommend tissue diagnosis prior to radical surgical resection (lobectomy), especially as there are cases when the final histology may be benign. Regardless of anatomical, technical or patient specific factors, the availability of pre-operative CT guided biopsy and intra-operative frozen section (IOFS) is an important consideration, which likely contributes to variability between surgeons, hospitals, tumour boards and regional/national practice. With the widespread uptake of Robotic and Video-Assisted Thoracoscopic Surgery (RATS/VATS), there has become more of a trend towards 'exploration' with planned 'wedge biopsy', IOFS and then proceeding to anatomical resection if positive for malignancy. This has the potential to minimise delays in the patient cancer pathway. In the era of minimally invasive thoracic surgery, we sought to establish the role of IOFS in our institution. **Method:** A retrospective analysis was performed for 309 consecutive lobectomy pathology specimens from a single institution (six surgeons) between Jan 2016-Jun 2017. 78/309 cases identified without pre-operative tissue analysis (25%) and further interrogated. **Result:** Figure 1 shows management pathway followed for the patients who underwent lobectomy without pre-operative tissue diagnosis. 49% had positive IOFS and proceeded to lobectomy (final histology: all malignancy). There were 8 negative IOFS (10%), which proceeded; half were malignant on final histology (5.1%). 32/78 patients (41%) proceeded directly to lobectomy without diagnosis; 22% had CT-Biopsy attempted while 16% were not amenable. 53% (n=17) had IOFS attempted but not possible. In this cohort 5 cases were benign on final histology.

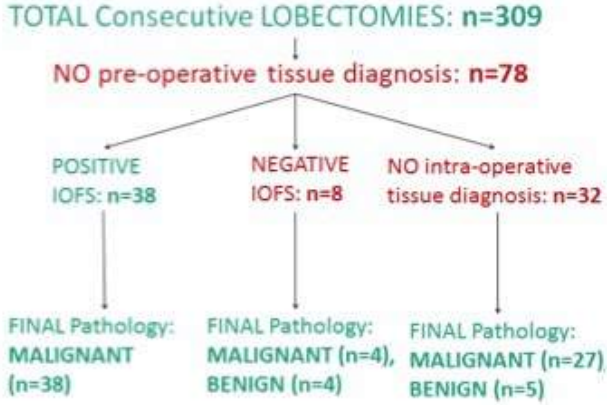

Figure 1: Flow Chart summarising key study findings

Conclusion: Efforts to obtain tissue diagnosis prior to surgical resection should be made, as up to 3% could be for benign pathology. In our tertiary thoracic centre, there was observed variability in CT-guided biopsy protocols between regional tumour boards, along with surgeon specific practice. Nevertheless more than half of patients without a pre-operative tissue diagnosis required IOFS, which was 100% accurate in confirming patients with lung cancer on final histology. Although direct resection is arguably merited based on history, imaging and current stratification (Brock/Herder) models, unnecessary procedures can cause patient morbidity and mortality. Therefore, IOFS still has a key role in thoracic surgical practice and close collaboration between surgeons and pathologists should be fostered in the future. Finally with the introduction of screening for patients deemed high risk for lung cancer likely to increase the case-load for tumour boards, we argue that availability of IOFS in institutions will continue to be necessary to help with optimising the patient cancer pathway.

Keyword: frozen-section, lobectomy, lung cancer

P1.09-18 SMALL-SIZED SPREAD THROUGH AIR SPACES (STAS) IN RESECTED PULMONARY ADENOCARCINOMA: IS IT NECESSARY TO RECORD IT AS A PROGNOSTIC FACTOR?

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Background: Spread through air spaces (STAS) is a recently recognized invasive pattern of lung cancer that is a prognostic factor in patients who have undergone resection. It is histologically defined as "micropapillary clusters, solid nests, or single cells extending beyond the edge of the tumor into air spaces" in the 2015 World Health Organization classification of lung tumor fascicles; however, the prognostic significance of each pattern has not been studied well. This study evaluated their prognostic significance through a histological review of 1043 resected pulmonary adenocarcinoma (P-ADC) specimens. **Method:** STAS was classified as follows: STAS 1, tumors with mainly small-sized clusters (1–3 tumor cells); STAS 2, tumors with mainly medium-sized clusters (4–20 typical micropapillary-pattern tumor cells); and STAS 3, tumors with large-sized clusters (>20 tumor cells). We recorded the STAS type of each specimen, analyzed its association with clinicopathological parameters, and assessed the prognostic significance of STAS in resected P-ADC specimens. **Result:** Overall, 366 tumors (35.6%) were STAS positive, which was associated with male gender (P = 0.005), larger tumor size (P < 0.001), node metastasis (P < 0.001), lymphovascular and pleural invasion (all, P < 0.001), and higher

stage (P < 0.001). The commonest type of STAS was STAS 2 (n = 262, 24.9% of all tumors), followed by STAS 3 (n = 69, 6.4% of all tumors) and STAS 1 (n = 28, 2.6% of all tumors). Patients with STAS-positive tumors had worse overall survival (OS) and disease-free survival (DFS) than patients with STAS-negative tumors (both P < 0.001). Patients with STAS 3 and STAS 2 tumors had worse prognosis than patients with STAS-negative tumors. However, there were prognostic differences between patients with STAS-negative tumors and those with STAS 1 tumors (log rank test, P = 0.764 for OS; P = 0.958 for DFS). **Conclusion:** STAS is a strong prognostic factor; however, tumors with small-sized STAS (STAS 1) do not differ from tumors without STAS with respect to recurrence and mortality in patients with P-ADCs. This result may indicate that it is not necessary to record or recognize small-sized STAS as STAS.

Keywords: lung adenocarcinoma, Pathology, spread through air spaces (STAS)

P1.09-19 HIGH-THROUGHPUT NEXT GENERATION SEQUENCING OF TREATMENT-NAÏVE NON-SQUAMOUS NSCLC: THE SINGAPORE NATIONAL LUNG PROFILING STUDY

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Background: Scaling traditional single biomarker assays are hampered by the need to evaluate an expanding list of therapeutically relevant biomarkers in small biopsies. We sought to compare the performance of targeted NGS panels with traditional assays, and correlate the mutational landscape with PD-L1 status in Singaporean lung cancer patients (pts). **Method:** We identified consecutive pts diagnosed between Jan 2016 to Sep 2017 with residual tissue after standard molecular testing (for EGFR, ALK, ROS1, MET, RET alterations). Tissue samples were tested using a targeted NGS panel (29 selected genes including BRAF, ERBB2, KRAS/NRAS, TP53) and an RNA fusion panel (ALK, ROS1, RET). PD-L1 immunohistochemistry (E1L3) was also performed (TPS: <1%, 1-49%, ≥50%). **Result:** A total of 174 samples were evaluated: PD-L1 (n=170), NGS DNA panel (n=161) and RNA fusion panel (n=118). Median age was 68 years, 53% were male, 58% were non-smokers, 85% were Chinese, 66% had metastatic disease and 95% had adenocarcinoma histology. In NGS DNA profiled pts, EGFR (55%), KRAS (16%), ERBB2 (4%) and BRAF (2%) alterations were found. RNA fusion testing revealed ALK (6%), RET (3%) and ROS1 (1%) fusions. The sensitivity and specificity for NGS versus standard molecular testing was >90% for all subtypes of EGFR mutation. Only 11% of the cohort had both no detectable actionable alteration on NGS (with targeted agents that are approved or in ongoing clinical trials) and PD-L1 <1%. Median turnaround time for NGS was 10 days (range 6-30). Cost-effectiveness analysis demonstrated that current standard testing was less effective and more costly than the other three testing strategies. Compared to sequential testing of NGS in EGFR negative pts only, upfront NGS testing resulted in an additional 1% of pts receiving targeted therapy for an additional SGD$110 and compared to upfront NGS testing, hotspot testing (NGS in EGFR, ALK/RET/ROS1 FISH negative pts only) resulted in an additional 4% of pts receiving targeted therapy for an additional SGD$1044. In the subset of pts with metastatic EGFR mutant NSCLC after first-line therapy with EGFR TKI (n=64), PFS was worse in patients with EGFR and TP53 co-mutation (n=32) compared to EGFR mutation alone (n=32; HR 0.54, 95%CI 0.30-0.98, p=0.042). **Conclusion:** We demonstrated that even in an EGFR mutant predominant population, upfront NGS and PD-L1 testing represents a feasible, cost-effective method of diagnostic molecular profiling. The additional information from NGS in characterizing the wider genomic profile may also have prognostic significance in EGFR mutant pts. More broadly, our results support the implementation of NGS in non-squamous NSCLC to allow pts access to the most appropriate personalized therapy.

Keywords: Molecular profiling, Targeted therapy, Next generation sequencing

P1.09-20 SIGNIFICANCE OF MAXIMAL DIAMETER MEASUREMENT IN SMALL-SIZED ADENOCARCINOMAS

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Background: 8th edition of the TNM classification for lung cancer has been available since Jan. 2017. The changes are based on a new database of about 90000 evaluable patients with lung cancer. The proposed changes primarily reflect stratification of patients with lung cancer into prognostically more-precise categories. The revision includes new tumor-size criteria and better-defined classification of additional tumor nodules, subclassifications of lymph node, and systemic metastases. However, invasive size measurement is difficult in some cases, so interobserver variability is inevitable. A maximal size measurement can reduce the interobserver variability to assess the small tumors. To clarify the significance of the maximal diameter measurement, small-sized tumors (10mm or less in maximal diameter) was also subclassified and prognosis after surgery was compared with conventional classification. In addition, we identified the characteristics of small-sized tumor with a worse prognosis. **Method:** Pulmonary adenocarcinoma treated surgically at our hospital between Jan. 2006 and Dec. 2011 were recruited. All the cases were evaluated according to the 8th TNM classification. Subsequently, the group with maximal diameter 10mm or less were subcategorized. The Kaplan-Meier method was used to calculate survival. Moreover, clinicopathological characteristics of recurrent cases were also reviewed. **Result:** Tumors with 10mm or less maximal diameter comprised 33.6% (94/288) of pTis, pT1mi and pT1a tumors. Average maximal diameter did not differ statistically between pT1mi and pT1a groups (*P*=0.38). Prolapse-free and disease-specific survivals of the cases with maximal diameter 10mm or less tumors without nodal metastasis were 98.8% and 100%, respectively. Only two cases with maximal diameter 10mm or less tumors recurred (2%, 2/94), both being solid type on CT image and one of the two cases exceptionally showed vascular and pleural invasion as well as nodal metastasis. The maximal diameter of recurrent cases clustered around the value of 10mm. **Conclusion:** Only a small fraction of tumors with maximal diameter 10mm or less recurred in our series. Since the recurrent cases clearly showed particular findings including vascular and pleural invasion and a solid image on CT, they can be differentiated from other tumors pathologically or by CT. The maximal diameter measurement is useful in tumors with 10mm diameter or less to estimate the tumor prognosis.

Keywords: prognosis, pulmonary adenocarcinoma, maximal diameter measurement

P1.09-21 TUMOR RESPONSES BASED ON TUMOR GROWTH RATE DURING PD-1 INHIBITOR THERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS

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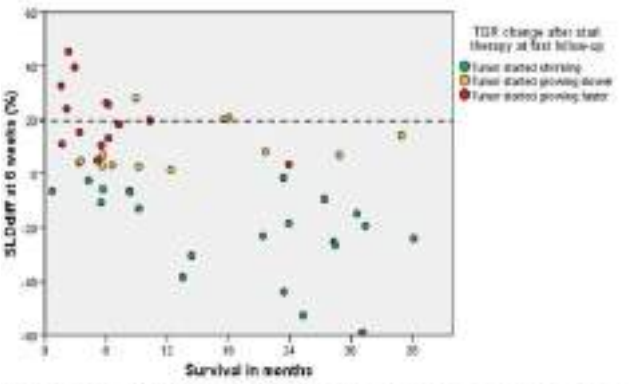
Background: Immune checkpoint inhibitors have emerged as a standard of care treatment for non-small cell lung cancer (NSCLC). However, there remains debate about the tumor growth kinetics during treatment, for instance the incidence of rapid disease progression, described as hyperprogressive disease (HPD). To get insight into variations in tumor growth kinetics and their potential predictive values for outcome we evaluated tumor growth rate (TGR) in patients receiving PD-1 checkpoint inhibitors. **Method:** An analysis and radiological review of all Nivolumab treated NSCLC patients (n=196) between 06-2015 and 09-2017 in an early access program and as standard of care was performed. Differences in TGR before and after the start of treatment were calculated by entering the sum of the longest diameters from CT-scans before and after the initiation of therapy into a formula that assumes a volumetric exponential tumor growth. TGR variations, possible predictors for TGR changes and its relationship to overall survival (OS) were studied. For comparison tumor response was assessed using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1).

Result: Among the 58 evaluable patients, 37 patients (64%) showed deceleration of TGR and 16 patients (27%) showed acceleration of TGR after initiation of therapy, with a significant difference in median OS of 18.0 versus 6.0 months (HR=0.35; 95%CI:0.18-0.71) between these groups. Four patients (7%) were defined as having HPD. In 5 patients (9%), the tumor growth remained stable. These TGR categories were not significantly different according to age, gender, histology, smoking or previous radiotherapy. Of the patients defined as having progressive disease by RECIST1.1 at first follow up 40% showed response to CPI by a decrease in tumor growth rate. (Figure 1) **Conclusion:** Tumor growth kinetics can be used as a clinically relevant predictor for OS in anti-PD1 treated NSCLC patients, and may provide additional information to RECIST measurements.



Keywords: PD-1 inhibitor, Tumor growth rate, Non-Small Cell Lung Cancer

P1.09-22 PROGRAMMED DEATH LIGAND-1 EXPRESSION IN NON-SMALL CELL LUNG CANCER IN MEXICAN POPULATION AND CORRELATION WITH CLINICOPATHOLOGIC FEATURES

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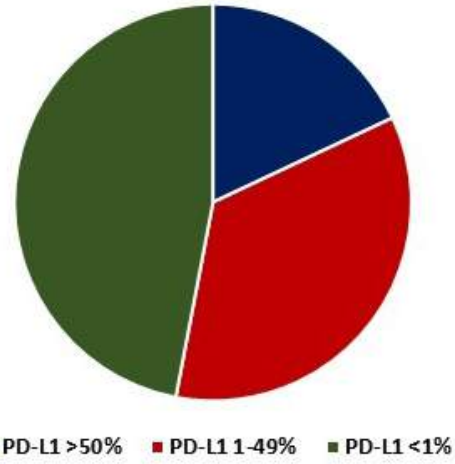
Background: Immune checkpoint inhibition is an important therapeutic option in patients with non-small cell lung cancer. Programmed cell death ligand-1 (PD-L1) expression may serve as a predictive and prognostic factor for anti-PD-1/PD-L1 therapies. We conducted a national, retrospective, observational study to determine PDL1 prevalence and correlation with clinicopathologic features. **Method:** Patients with histologic confirmed stage III/IV NSCLC and available tissue block were included. PDL1 tumor expression was performed with PDL1 IHC (SP263) assay on a Ventana Benchmark XT platform. Tumor cell PD-L1 expression was scored as Tumor Proportion Score (TPS) and classified as negative (<1%), 1-49% and ≥ 50% for correlation with clinicopathologic features. **Result:** Of a total of 948 patients included in the study, 170 (18%) were TPS >50%, 333 (35%) and 445 (47%) were TPS 1-49% and negative (<1%) respectively. The TPS was higher in squamous cell carcinomas (p=0.001) due to increased proportion of strong expression (>50%). Among the 778 non-squamous carcinomas, 187 (24%) had EGFR mutations and 31 (4%) showed ALK translocations. A TPS >50% was seen in 25% (47/187) and 21% (6/31) EGFR mutant and ALK translocated tumors, respectively.

Figure 1. Frequency PD-L1 Expression in Mexican population



Conclusion: The overall prevalence of TPS ≥ 50% is slightly lower than previously reported. TPS was significantly higher in squamous cell carcinomas and there was no correlation between PD-L1 expression and molecular abnormalities, or age, gender and smoking status.

Keywords: PD-L1, NSCLC PATHOLOGY, prognosis

P1.09-23 A33 AND SATB2 IMMUNOHISTOCHEMISTRY FOR DIFFERENTIATING METASTATIC COLORECTAL CARCINOMA FROM PULMONARY ENTERIC ADENOCARCINOMA

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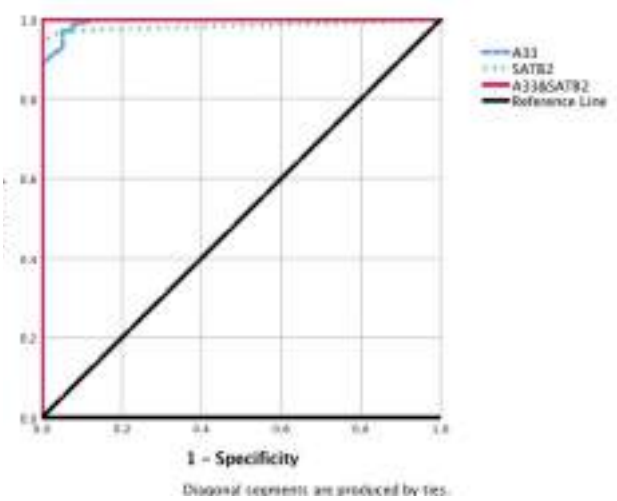
Background: Primary pulmonary enteric adenocarcinoma (PEAD) resemble morphology and immunohistochemistry with metastatic colorectal carcinoma(mCRC). it is sometimes difficult to differentiate PEAD from mCRC. Here, we evaluated the diagnostic value of A33 and SATB2 in discriminating between PEAD and mCRC. **Method:** Resected 39 PEAD and 69 mCRC cases were retrospectively recruited. PEAD patients were performed colonoscopy postoperatively and were followed more than 1 year to exclude mCRC. Patients with mCRC were diagnosed by colorectal carcinoma history before or after thoracic surgery. A panel of immuohistochemistry markers were analyzed including A33, SATB2, CK7, CK20, TTF-1, Napisn A, CDX2 and villin. Tumor staining was scored for positive percentage and intensity, with a maximum possible score of 300. **Result:** A33, SATB2 and CK20 showed specificity for PEAD: 94.9%, 92.3% and 88.9%, respectively; sensitivity for mCRC: 97.1%, 97.1% and 91.3%, respectively. CK7 expression was 91.4% sensitive and 90.9% specific for PEAD. A33 and SATB2 were slightly higher than CK20 for specificity in PEAD. The AUC for tumor staining of A33, SATB2 was 0.994 and 0.984, individually; In combination of them, the AUC was 1.000. The staining of TTF-1 was focal and weak in one mCRC case. No Napsin A expression was found in mCRC. The positive rate of TTF-1 and Naspin A expression in PEAD was 46.2% (18/39) and 25.6% (10/39). There was similar for CDX2 and villin expression between PEAD and mCRC.



Conclusion: Our results showed that a panel of A33 and SATB2 was potentially optimal markers for differentiating PEAD from metastatic colorectal carcinoma.

Keywords: Pulmonary enteric adenocarcinoma, differential diagnosis, A33 and SATB2

P1.09-24 TUMOR NECROSIS CORRELATES WITH PD-L1 AND PD-1 EXPRESSION IN LUNG ADENOCARCINOMA

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Background: Predictive biomarkers for immunotherapy in lung cancer are intensively investigated, however, correlations between PD-L1/PD-1 expressions and clinical features or histopathological tumor characteristics determined on hematoxylin and eosin stained sections have not extensively been studied. **Method:** We determined PD-L1 expression of tumor cells (TC) and immune cells (IC), and PD-1 expression of IC by immunohistochemistry in 268 lung adenocarcinoma (LADC) patients, and correlated the data with smoking, COPD, tumor grade, necrosis, lepidic growth pattern, vascular invasion, density of stromal IC, and *EGFR/KRAS* status of the tumors. **Result:** There was a positive correlation between PD-L1 expression of TC and IC, as well as PD-L1 and PD-1 expression of IC. Tumor necrosis was associated with higher PD-L1 expression of TC and PD-1 expression of IC. A negative correlation was observed between lepidic growth pattern and PD-L1 expression of TC and PD-L1/PD-1 expression of IC. *EGFR* mutation seemed to negatively correlate with PD-1 expression of IC, but this tendency could not be verified when applying corrections for multiple comparisons. No significant effect of the *KRAS* mutation on any of the studied variables could be established. **Conclusion:** Here we first demonstrate that the presence of necrosis correlates with higher PD-L1 expression of TC and PD-1 expression of IC in LADC. Further studies are required to determine the predictive value of this observation in LADC patients receiving immunotherapy.

Keywords: PD-L1, lepidic growth pattern, tumor necrosis

P1.09-25 THE USE OF IN-SITU RNA ANALYSIS IN THE DETECTION OF METASTATIC HPV MEDIATED SQUAMOUS CELL CARCINOMA TO THE LUNG WITH P16 CORRELATION

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Background: The distinction between metastatic squamous cell carcinoma and a pulmonary primary is often necessary to determine treatment recommendations and communicate prognosis to patients and their families. Human papillomavirus (HPV) is oncogenic mediator of oropharyngeal squamous cell carcinoma (SCC), cervical SCC, including SCC of cutaneous, and other genital sites. The incidence of distant metastases from HPV-mediated oropharyngeal carcinoma can be as high as 12% (Huang, et al Oral oncology 2013) and the lung is the most common site of metastasis. The significance of p16 immunohistochemistry (IHC) expression in primary lung SCC is unknown however; in the oropharynx and cervix, p16 IHC positivity has been established as a surrogate marker for high risk HPV infection. Our study will aim to examine the detection of HPV E6/E7 mRNA transcripts in infected tumor cells using RNAScope® in situ hybridization (ISH) on formalin fixed paraffin embedded tissue and its utility to help differentiate metastatic disease from a lung primary. **Method:** A retrospective review of institutional archives in pathology and laboratory medicine between September 2006 and September 2018 was conducted. Nineteen cases of lung SCC in patients with a history of head and neck, cervical, perianal and perineum squamous cell carcinoma were identified. Materials from the primary sites were allocated. As a control group, nineteen additional cases of pulmonary SCC without a prior history of malignancy were identified and included in the study. Immunohistochemistry for p16 (clone E6H4), HPV RNA ISH for high-risk and low-risk HPV subtypes were performed and evaluated. **Result:** Three of nineteen cases were excluded due to a lack of sufficient material. Ten of Sixteen presumed HPV mediated primaries were positive for p16. The remaining six were negative for p16 and negative for HPV RNA ISH. Seven of Sixteen (44%) cases with a presumed HPV mediated primary were from oropharyngeal sites and were positive for both p16 and high risk HPV RNA ISH while negative for low risk HPV RNA ISH. The remaining ten of sixteen cases (62.5%) were negative for p16, high-risk and low-risk HPV RNA ISH. Two primary cervical squamous cell carcinomas were positive for p16 however, one of two subsequent lung biopsies showed p16 positivity and both were negative for HPV RNA-ISH. In the control group, two of nineteen cases (10.5%) were reactive for p16, however all cases were negative for high and low-risk HPV RNA ISH. **Conclusion:** HPV RNA ISH is a rapid confirmatory assay allowing for detection and confirmation of metastatic disease in patients with HPV mediated malignancy, particularly from oropharyngeal origin. Immunohistochemistry for p16 alone is not specific in distinguishing between a lung primary and metastatic SCC and is not recommended as a surrogate marker for confirming metastatic disease. Detection of viral transcrips allows for successful treatment and prognostic stratification. These preliminary findings may be useful to assess on a larger scale.

Keyword: metastatic, oropharyngeal, HPV

P1.09-26 PREVALENCE OF PD-L1 EXPRESSION RATES IN DIFFERENT NSCLC SPECIMENS

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Background: Programmed death-ligand 1 (PD-L1) expression on tumor cells by immunohistochemistry (IHC) is a predictor of response to immune checkpoint inhibitors used to treat advanced non-small cell lung cancer (NSCLC). High PD-L1 expression (≥50% of tumor cells) is required for patients to receive first line pembrolizumab monotherapy. Assessing expected PD-L1 expression rates in real-world specimens is an important factor in ensuring patients are accessing the most effective treatments available. The aim of this retrospective assessment was to review the local prevalence of PD-L1 expression in NSCLC and compare different specimen types. **Method:** We retrospectively reviewed cases of NSCLC stained with PD-L1 IHC Ventana SP263 assay between January 2017 and March 2019. PD-L1 expression was assessed as a tumor proportion score (TPS) of 0-<1%, 1-49% or ≥50% positive membrane staining within tumor cells. Results were compared with specimen type and mutation status. **Result:** PD-L1 expression was assessed in 264 cases of NSCLC during the 51 month period. The median patient age was 70 years, 64.4% were >65 years old and 60.9% were male. Histologically, 79.9% were adenocarcinoma, 10.6% squamous cell carcinoma and 9.5% NSCLC-NOS. Overall 29.5% of NSCLC showed high PD-L1 expression (≥50%), 43.9% low (1-49%), and 26.5% no expression (<1%). In known *EGFR/ALK* negative cases (n=176), high, low and negative PD-L1 was seen in 34.7%, 43.2% and 22.1% respectively. Histology samples accounted for 80.7% of cases and 19.3% were cytology. Lung resections accounted for 27.7% with other specimen types (small biopsies, cytology and metastatic resections) accounting for 72.3%. 61.0% were primary tumors and 39.0% were from metastases. A PD-L1 TPS of ≥50% was seen in 29.1% of

histology and 31.4% of cytology specimens, with no statistically significant difference (p=0.55). Amongst lung resections, high PD-L1 expression was observed in 19.2% of cases compared to 33.5% in other specimen types (p<0.01). In primary tumors, high PD-L1 expression was seen in 27.3% compared to 33.0% in metastases (p=0.51) Of the cases that had mutation results available, only 8.8% of NSCLC haboring *EGFR* mutations expressed high PD-L1 expression (≥50%) compared to 44.1% of tumors with *KRAS* mutations (p<0.01). **Conclusion:** Our overall prevalence of PD-L1 expression in cases of NSCLC is in keeping with rates demonstrated in a large clinical trial investigating the efficacy of pembrolizumab as first line treatment in NSCLC. The same rates of high PD-L1 in cytology and histology specimens suggest cytological specimens are valid for assessment.

P1.09-27 INTEROBSERVER VARIATION IN THE CYTOLOGICAL DIAGNOSIS OF PULMONARY ADENOCARCINOMA PRESENTING WITH GROUND-GLASS OPACITY NODULES

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Background: Wide use of chest CT for cancer surveillance and health check-up has led to increase the number of CT-detected small lung nodules with ground-glass opacity (GGO) in South Korea. For persistent GGO lesions larger than 1cm, American College of Chest Physicians recommends a further evaluation such as transthoracic needle aspiration biopsy. Despite these guidelines, cytologic evaluation of GGO nodules is often not used due to the limited access to interventional thoracic radiology and difficulties in the cytologic distinction between benign and well differentiated adenocarcinoma. Herein, we evaluate the cytologic features of small lung adenocarcinoma presenting with GGO nodules and interobserver variation in the cytological diagnosis. **Method:** Sixteen patients with GGO nodules who underwent surgical resection were enrolled in this study. The lesions were identified in fresh state on gross examination. Scrapings were collected by using a glass slide to scrape the cut surface of the nodule. Scraped material was then transferred to another glass slide and smeared using a pull/slide-over-slide technique. All slides were stained with Papanicolaou staining. Three pathologist reviewed the slides and cytological diagnosis was categorized as negative/benign, atypical, suspicious for malignancy, and positive for malignancy. **Result:** The study population consisted of 4 male and 11 female patients. There were 8 invasive adenocarcinoma, 4 adenocarcinoma in situ, and 4 minimally invasive adenocarcinomas. The mean tumor size was 1.27cm, ranging 0.6cm to 3.3cm. The overall concordance rate for cytological diagnosis was 62.5% (mean kappa, 0.51). Totally concordant and cytologically negative cases were 31.2% (5 out of 16) and significantly smaller than 1cm (p=0.037). Discordant cases tends to be either adenocarcinoma in situ or minimally invasive adenocarcinoma, but statistically in significant. **Conclusion:** Cytological diagnosis of pulmonary adenocarcinoma presenting with GGO nodules showed interobserver variation. False negative result could be considered especially in cases with tumor size less than 1cm.

Keywords: cytological diagnosis, lung adenocarcinoma, ground-glass opacity nodule

P1.09-28 A SIGNIFICANT DISCORDANCE BETWEEN PANAMUTYPER™ AND TARGETED DEEP SEQUENCING FOR DETECTING EGFR MUTATION IN NSCLC

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Background: Activating mutations in the tyrosine kinase domain of *EGFR* are predictive biomarkers for response to *EGFR*-tyrosine kinase inhibitor (TKI) therapy in non-small cell lung cancer (NSCLC). This study aimed to screen *EGFR* mutations by PNA clamping-assisted fluorescence melting curve analysis (PANAMutyper™) and targeted deep sequencing, and to evaluate the feasibility of targeted deep sequencing for detection of the mutations. **Method:** We examined EGFR mutations in exons 18, 19, 20, and 21 using PANAmutyper™ for consecutive 2170 NSCLC tissues from November 2016 to March 2019. Of these, targeted deep sequencing was performed in 74 patients. **Result:** *EGFR* mutations were identified in 46.4% (1007/2170); 479 (47.6%) had mutations at exon 19, 442(43.9%) at exon 21, 156(15.5%) at exon 20 (including 97 cases with T790M), and 46(4.6%) at exon 18. *EGFR* mutations were significantly more common in women (63.9%) than men (31.4%) (p <0.001), in adenocarcinoma (54.7%) compared to non-adenocarcinoma (15.3%) (p <0.001). 11.3% (11/97) of T790M mutations was identified in TKI-naïve patients. Interestingly, 27.3% (3/11) of the primary T790M existed alone without L858R or exon 19 deletions. We observed a significant discordance (24.3%: 18/74) of the *EGFR* mutation between PANAMutyper™ and targeted deep sequencing. Moreover, targeted deep sequencing revealed eight nonsynonymous single-nucleotide variations, ten insertion-deletion variations and one amplification in EGFR, which were not detectable by the PANAMutyper™. In 2 out of 18 discordant cases, *EGFR* mutations were detected only in PANAMutyper™. **Conclusion:** *EGFR* mutations were found frequently in non-adenocarcinomatous NSCLCs, emphasizing that testing for *EGFR* mutations is essential for all NSCLC patients. As T790M was found in TKI-naive patients, we cannot exclude the possibility of this mutation being a rare mutation existing from the beginning. Taken together, our study demonstrates that primary T790M alone exists and there is a significant discordance between PANAMutyper™ and targeted deep sequencing. The significance of these discrepancies should be carefully interpreted for the patient's treatment and clinical outcome.

Keywords: EGFR, Targeted deep sequencing, Non-Small Cell Lung Cancer

P1.09-29 THE CHARACTERISTICS OF LYMPH NODE METASTASIS IN PATIENTS WITH DIFFERENT ONCOGENIC DRIVER MUTATIONS AMONG T1 NON-SMALL-CELL LUNG CANCER

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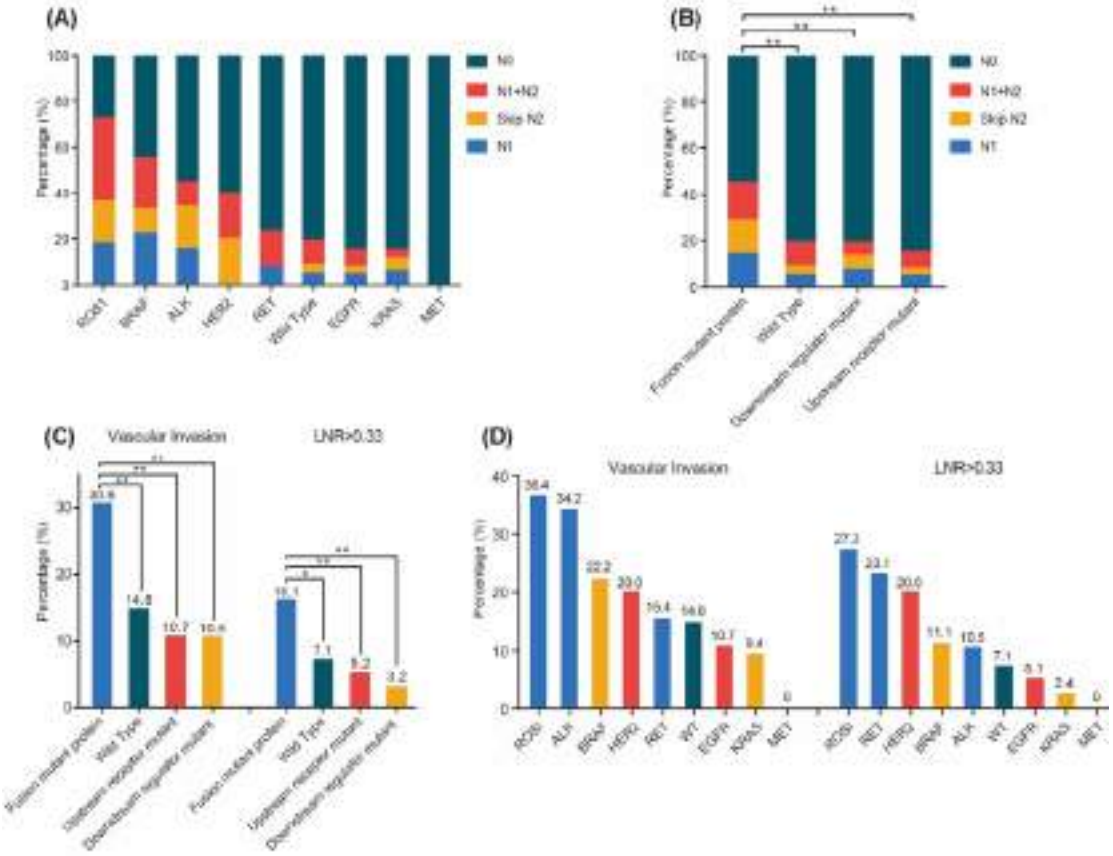
Background: Whether mutation is associated with lymph node metastases remains unknown. We aim to investigate the incidence and distribution of lymph node metastasis in patients with different gene mutations among pathological T1 non-small-cell lung cancers (NSCLC). **Method:** NSCLC cases resected in our institution between 2016 and 2018 were included. Driver mutation testing was performed in all resected tumor tissues. These patients were grouped by the type of gene mutations. On the basis of protein that mutant-genes encoded involved in the molecular pathway, the genotypes were further classified into four distinct groups: upstream receptor mutant protein (EGFR, HER2 and MET); downstream regulator mutant protein (KRAS and BRAF); fusion mutant protein (ROS1, ALK and RET) and the wild type group. The incidence of lymph node metastasis was compared among different groups. **Result:** Of the 1,052 patients enrolled, the frequency of positive mutations was 68.0%. The incidence of lymph node metastasis were as follows (Figure 1): wild type (19.3%), ROS1 (72.8%), BRAF (55.5%), ALK (44.7%), HER2 (40%), RET rearrangement (23.1%), KRAS mutation (15.3%), EGFR (15.3%) and MET mutation (0%) (Chi^2=43.45, P<0.001). The incidence of lymph node metastasis was significantly higher in fusion mutant protein group (45.1%) compared with others (wild type 19.3%, downstream signaling regulator protein 19.1%, upstream signaling receptor protein 15.3%, all P<0.001). Patients with fusion genes showed higher proportion of vascular invasion and positive lymph node ratio of greater than 0.33 compared to other (all P<0.005). In subgroup based on gender, age and smoking history, fusion mutant group was still observed with the highest proportion of node metastasis



Conclusion: Different genotypes of NSCLC have different propensity to develop lymph node metastasis. Cases of fusion gene mutations had a higher risk and burden of lymph node metastasis than other genotypes, which may indicate that more intensive treatment or surveillance strategies should be applied for these patients.

Keywords: Gene mutation, non-small-cell lung cancer, Lymph node metastasis

P1.09-30 MOLECULAR CHARACTERIZATION OF PREINVASIVE AND INVASIVE LESIONS IN MULTIFOCAL PULMONARY ADENOCARCINOMAS

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Background: Multifocal pulmonary adenocarcinomas typically present as multiple ground-glass opacities (GGOs) on computed tomography (CT) scan. Pathologically, GGOs in majority represent preinvasive lesions including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS) and rarely, invasive lesions such as minimally invasive adenocarcinoma (MIA). Given that a stepwise progression sequence from AAH to invasive adenocarcinoma (AIV) has been proposed in lung carcinogenesis, we would like to investigate the molecular features between preinvasive and invasive lesions in patients with multifocal pulmonary adenocarcinomas. **Method:** From 2011 to 2015, thirty-three patients with surgically resected preinvasive lesions of lung adenocarcinoma diagnosed in their tumor(s) were included. There were 25 female and 8 male, with a total of 87.9% being never smokers. Twenty-nine patients (87.9%) had at least one preinvasive and one invasive lesions. One hundred and nine tumor lesions composed of 18 AAH, 73 AIS and 18 AIV were analyzed for *EGFR*, *KRAS* and *TP53* mutations. **Result:** Among them, 4 (12%) patients were found to harbor one lesion, 14 (42%) two lesions, 6 (18%) three lesions, and 9 more than four lesions. In patients with more than 3 tumor lesions, these lesions were more likely to localize in the right lateral lung compared to those with lesions less than 2 ($p=0.02$). Of 109 tumor lesions analyzed, *EGFR*, *KRAS* and *TP53* mutations were 22.2%, 0% and 22.2% in AAH, 24.7%, 6.8% and 15.1% in AIS, while 66.7%, 11.1% and 16.7% in AIV. *EGFR* mutation rate of AIV, especially L8585R mutation, was higher than that of AAH and AIS ($p=0.004$). On the contrary, mutations on *KRAS* and *TP53* were randomly distributed between preinvasive and invasive lesions ($p > 0.05$). The discordant pattern of *EGFR*, *KRAS* and *TP53* mutations between AAH, AIS and AIV lesions within the same patients was also observed. Figure 1. The prevalence of *EGFR*, *KRAS* and *TP53* mutations in preinvasive and invasive tumor lesions. *EGFR* mutations are more associated with invasive components. **Conclusion:** Our results showed that *EGFR*, *KRAS* and *TP53* mutations occur early in preinvasive lesions, and only *EGFR* mutation is significantly associated with invasive components. These findings suggested that *EGFR* mutation may contribute to the invasiveness and progression of lung adenocarcinoma. Additionally, presence of distinct mutation profiles in separate preinvasive and invasive lesions from the same patient demonstrated that the emergence of these lesions may come from independent events, implying that genetic heterogeneity does occur in patients with multifocal pulmonary adenocarcinomas.

Keyword: Multifocal pulmonary adenocarcinomas, Preinvasive lesions, Mutation profile

POSTERS

P1.09-31 CLINICOPATHOLOGICAL FEATURES AND GENOMIC PROFILING OF PULMONARY BLASTOMA WITH HIGH-GRADE FETAL ADENOCARCINOMA COMPONENT

J. Zhao[1], C. Xiang[1], P. Wang[1], P. Guo[2], J. Zheng[2], H. Han-Zhang[2], K. Yu[3], R. Zhao[1], J. Zhang[1], Y. Han[1]

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Background: Pulmonary blastoma (PB) is a very rare subtype of sarcomatoid carcinoma with typically low-grade fetal lung adenocarcinoma (L-FLAC) and primitive mesenchymal components. Very few cases of PB contain the high-grade fetal lung adenocarcinoma (H-FLAC) component. The present study was designed to investigate the clinicopathological characteristics and the genomic heterogeneity of epithelial and mesenchymal in PB with H-FLAC. **Method:** Three surgically resected PB cases with H-FLAC component were enrolled in the study. The epithelial of the first case consisted of mostly H-FLAC mixed with limited amount of L-FLAC. The other two PB tumors contained pure H-FLAC and mesenchymal components. Clinic-pathologic information and prognostic data were retrospectively reviewed. Diagnostic immunohistochemistry was performed. The epithelial and mesenchymal components were macroscopically dissected to profile the genetic alterations separately using capture-based targted sequencing. A commercialized panel, consisting of 520 cancer-related genes, was used. **Result:** The cells of H-FLAC components in PB showed obvious atypia with more necrosis and enteric adenocarcinoma-like morphology. The squamoid morules were absent in H-FLAC. Proliferation index of the H-FLAC components (30%-80%) was higher than that of the mesenchymal (15%-20%). No aberrant nuclear expression of β-catenin protein and missense mutation in exon 3 of CTNNB1 gene were observed in H-FLAC and all mesenchymal cells. Within a tumor, epithelial and mesenchymal components exhibited relatively comparable molecular profile. In patient 1, 4 mutations: PB1, FAT3, PTCH1 and LRP1B were shared by both epithelial and mesenchymal components. Epithelial component had additional mutations in BCOR, CTNNB1, CTCF, FAT1 and DICER1. In patient 2, 12 mutations were shared. The epithelial component had BRCA2 mutations and the mesenchymal component had mutations in CREBBP, ALK, DNMT3A, ASXL2, MYCN and RICTOR. Patient 3 had 6 shared mutations. The epithelial component had an additional mutation in KAT6A and the mesenchymal had an additional mutation in APC. Furthermore, both epithelial and mesenchymal components showed significant interpersonal heterogeneity. In other words, the mutation spectrum of the same component (epithelial or mesenchymal)varies significantly among patients. Surprisingly, not a single common mutation was found in the same component among the 3 patients. **Conclusion:** Collectively, we observed heterogeneity between epithelial and mesenchymal components of the same tumor. In addition, we also observed significant inter-personal heterogeneity of the same component among different patients. Parallel detection of genetic abnormalities in epithelial and mesenchymal could provide further evidence to clarify the histopathological difference and molecular heterogeneity in pulmonary blastoma.

P1.09-32 CONCURRENT GENOMIC ALTERATIONS IN ALK-REARRANGED NON-SMALL CELL LUNG CANCER PATIENTS

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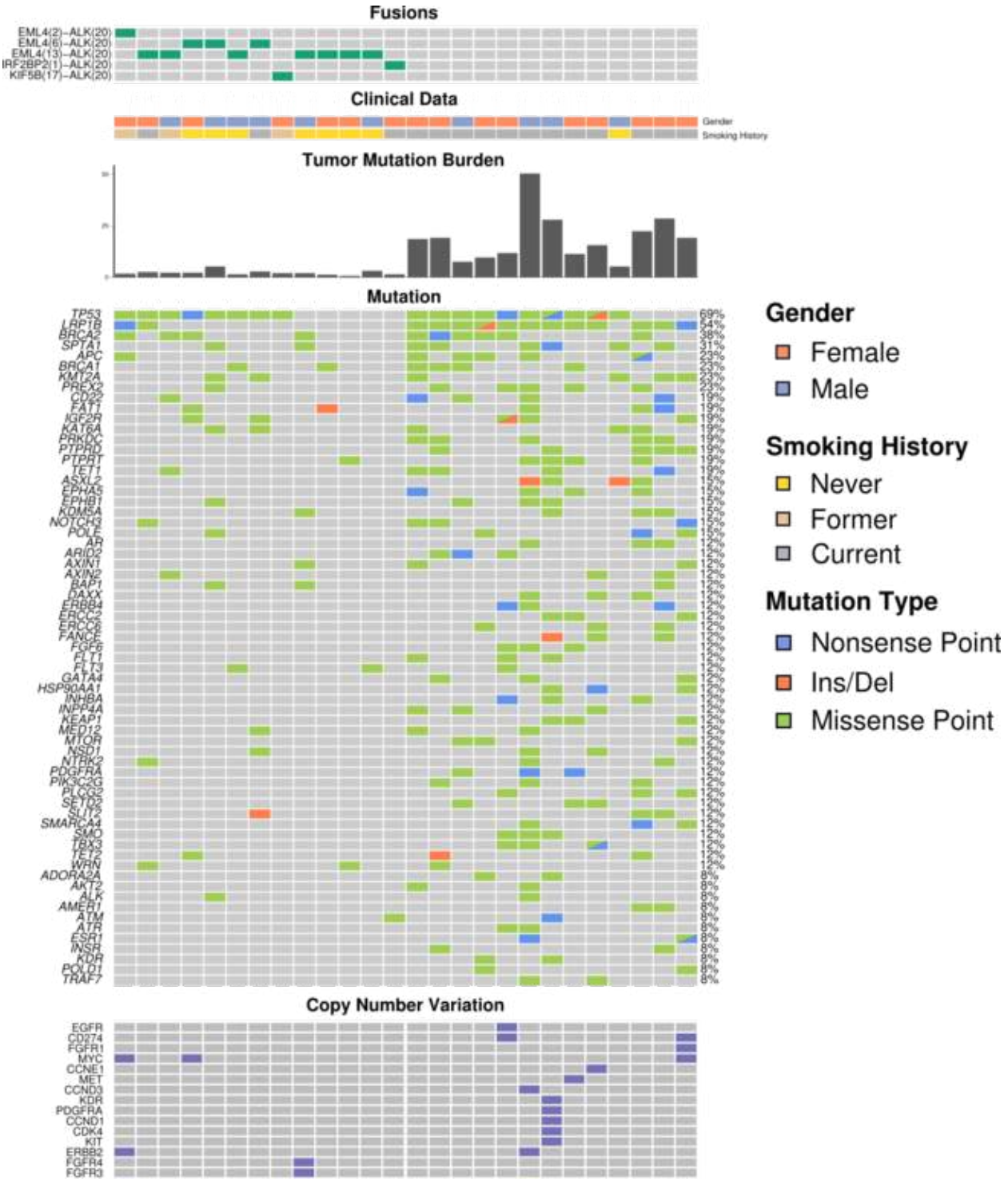
Background: Recent progress in genomic analysis using next-generation sequencing (NGS) has enabled the comprehensive detection of targetable alterations in non-small cell lung cancer (NSCLC) patients. As the detection of *ALK* gene fusions is being established by NGS, identification of concurrent alterations will lead to better characterization of the molecular landscape of *ALK*-rearranged patients. **Method:** Thirty-one NSCLC samples with known *ALK* status (18 positive and 13 negative) tested in our Institution using FISH, IHC, and NGS (Oncomine Focus Assay, ThermoFisher Scientific) were further evaluated by an expanded NGS gene panel (PGDx elio™ tissue complete assay (under developement), Personal Genome Diagnostics). This NGS panel comprises 500+ genes and screens for clinically relevant genomic alterations (single base substitutions/insertion and deletions, fusion genes and copy number variations), and provides TMB scores (expressed as mutations per megabase, exome equivalent). Statistical associations were assessed using Pearson's $\chi 2$ and Mann-Whitney U test. **Result:** *ALK* positive patients were 50% female with a median age of 59 years old and 54% of them never smokers. For the *ALK* negative cohort, young patients without any known driver alterations were selected: 69% male with a median age of 54 years old and 92% of them current smokers. Of the 18 *ALK*-positive cases identified, five were considered non-evaluable for expanded genomic analysis due to insufficient sequencing coverage (yield below minimum suggested DNA input). *ALK* fusions were detected by all techniques in the 13 *ALK*-positive cases available for analysis. *EML4*(13)-*ALK*(20) was the most prevalent gene fusion detected in seven out of 13 cases (54%). Remarkably, we detected a rare *ALK* gene fusion that has not been yet described: *IRF2BP2*(1)-*ALK*(20). The concurrent alterations identified by expanded genomic analysis are shown in an OncoPrint figure comparing both groups. The most frequent concomitant alteration was *TP53* mutation: 62% in *ALK*-positive and 69% *ALK*-negative (p> 0.05). Regarding gene amplifications, we identified three *ALK*-positive cases with copy number alterations of which we highlight *MYC* in two of these cases. Interestingly, a high TMB was significantly associated with *ALK*-negative cases with a median of 19.9 mut/Mb compared to 7.0 mut/Mb in *ALK*-positive (p= 0.001).



Conclusion: We have studied the presence of *ALK* fusion genes with a novel NGS panel that showed excellent correlation with standard techniques. *ALK* fusions can be interpreted as early strong drivers to carcinogenesis due to the low frequency of concurrent alterations. It remains to determine the clinical impact of these alterations in larger series.

Keywords: ALK rearrangement, Concurrent alterations, Next-generation sequencing

P1.09-33 MORE THAN 40% OF LOCALLY ADVANCED OR METASTATIC NSCLC PATIENTS WITHOUT EGFR/ALK ALTERATIONS HAVE PD-L1 TPS >= 1% IN CHINA

S. Ben[1], X. Pan[2], S. Wen[3], Y. Jiang[4], J. Guo[5], X. Fan[6], Y. Dai[2], D. Chen[2], K. Wang[2], X. Dong[2], S. Zhang[7]

[1]*Shanghai General Hospital, Shanghai/China,* [2]*Origimed, Shanghai/China,* [3]*Fourth Hospital of Hebei Medical University, Shijiazhuang/China,* [4]*Shandong Provincial Hospital Affiliated to Shandong University, Jinan/China,* [5]*Xingtai People's Hospital, Xingtai/China,* [6]*Qilu Hospital Qingdao Branch, Qingdao/China,* [7]*OrigiMed, Shanghai/China*

Background: Very recently, it was suggested that pembrolizumab monotherapy can be extended as first-line therapy to patients (pts) with locally advanced or metastatic non-small-cell lung cancer (NSCLC) without sensitizing *EGFR* or *ALK* alterations and with low PD-L1 Tumor Proportion Score (TPS). Then screening the subset of pts with PD-L1 TPS >= 1% from all the *EGFR*-, *ALK*- locally advanced or metastatic NSCLC pts became important. However, less was known about the percentage of this subset in China. We investigated this percentage taking advantage of the retrospective NSCLC cohort collected by Origimed. **Method:** The Origimed-based NSCLC cohort was a retrospective cohort consisted of more than one thousand Chinese NSCLC pts who underwent both NGS panel sequencing and PD-L1 immunohistochemistry (IHC) in a College of American Pathologists (CAP) certified and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory during the year 2017 and 2018. Antibodies used in the PD-L1 IHC assay included 22C3 and 28-8. TPS was applied. All the slides were reviewed by the same senior pathologist. All the *EGFR* and *ALK* alterations were manually reviewed in Integrated Genomics Viewer for confirmation. Stage III or IV at diagnosis was used as an approximation to the criteria "locally advanced or metastatic". **Result:** Excluding sensitizing *EGFR/ALK* alteration carriers, there were totally 27 locally advanced or metastatic NSCLC pts whose 22C3 PD-L1 TPS were available and 202 locally advanced or metastatic NSCLC pts whose 28-8 PD-L1 TPS were available in the cohort. Among them, 55.6% (15/27) 22C3 stained samples had TPS >= 1%, and 40.6% (82/202) 28-8 stained samples had TPS >= 1%. **Conclusion:** More than 40% of locally advanced or metastatic NSCLC pts without *EGFR/ALK* alterations have PD-L1 TPS >= 1% in China. These pts may benefit from first-line pembrolizumab monotherapy.

Keywords: PD-L1, NSCLC, Pembrolizumab

PREVENTION AND TOBACCO CONTROL
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.10-01 PATTERNS OF BIRTH COHORT-SPECIFIC SMOKING HISTORIES BY RACE AND ETHNICITY IN THE US, 1965-2017

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Background: Smoking prevalence varies greatly by race and ethnicity in the US. However, little is known about how smoking prevalence or the rates of initiation and cessation vary by birth cohort among different sociodemographic groups. **Method:** Data from the National Health Interview Survey 1965-2017 were utilized to obtain smoking-related information for U.S. adults. We developed age-period-cohort models with constrained natural splines to estimate smoking prevalence among different racial/ethnic groups; non-Hispanic Whites (NHW), non-Hispanic Blacks (NHB), Hispanics, American Indians and Alaskan Natives (AIAN), and Asians and Pacific Islanders (API). Annual probabilities of smoking initiation, cessation and intensity by age, birth cohort (1890-1990), sex, and race/ethnicity were also estimated. **Result:** Age-specific probabilities of smoking initiation were highest among AIAN, second highest among NHW and lowest among API and Hispanics (Fig1). Initiation probabilities among NHB were comparable in the past to NHW's, but have decreased relatively more rapidly in recent birth cohorts. In general, cessation probabilities were lowest among AIAN and NHB, and highest among NHW and API across birth cohorts and ages. Taken together the initiation and cessation probabilities result in the observed race/ethnicity patterns of smoking prevalence by race/ethnicity, birth-cohort and age (Fig2), where for instance prevalence among AIAN is generally highest across all ages and birth cohorts. Or where prevalence among NHB, particularly men, is lower than that in NHW for young ages but higher for older ages.

P1.10-02 ROLE MODELS AND LUNG CANCER AWARENESS: DOES IT CHANGE THE MIND-SET AND PERCEPTION OF GENERAL POPULATION?

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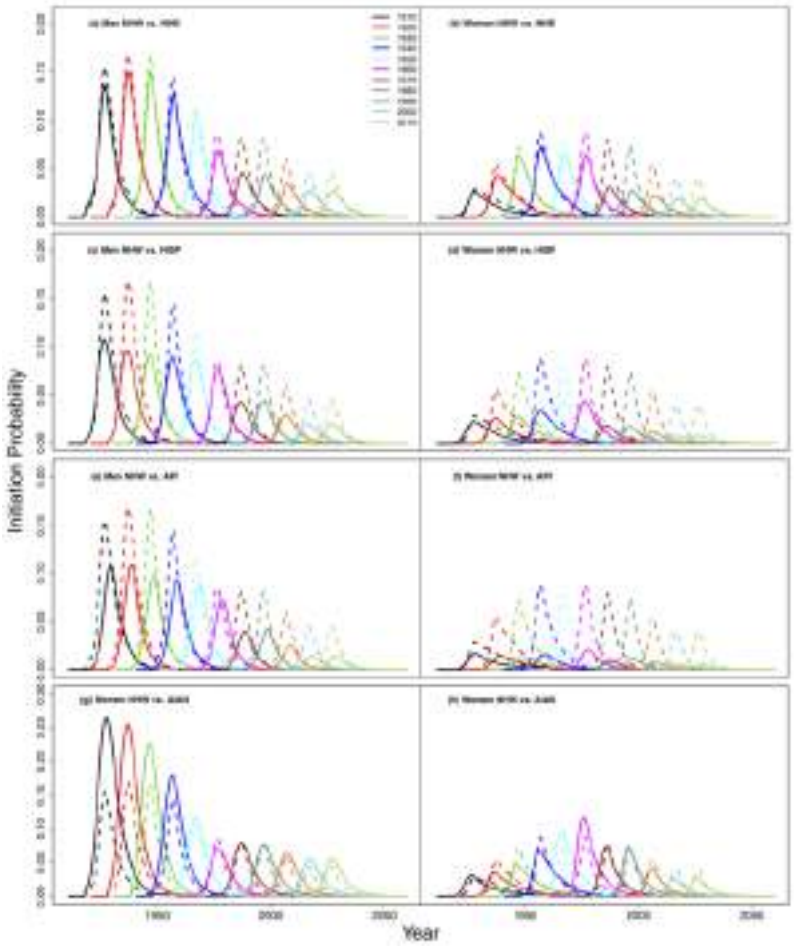
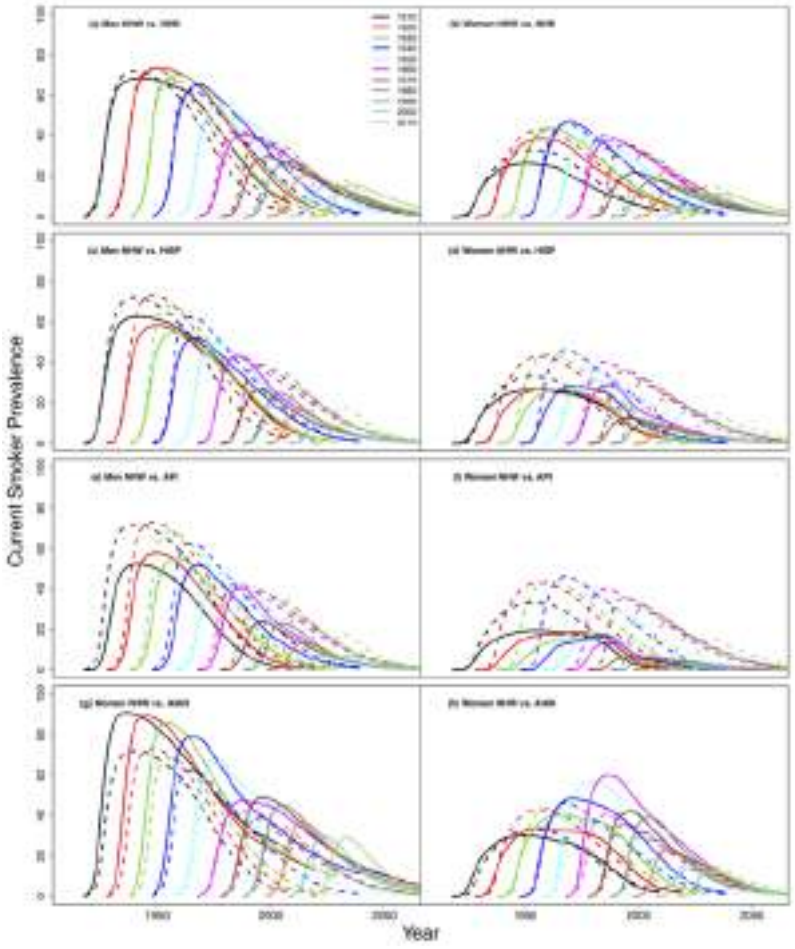
Background: Lung cancer has become a major health concern, though easily preventable, with smoking and air pollution being major risk factors. Intentional or unintentional advertisement or use of tobacco product by society role models may affect their attitude towards the smoking and related lung cancer. This study analysed the people mindset and perception for their role models in tobacco advertisement and lung cancer awareness. **Method:** The survey was conducted at various market and public places in Delhi, India. People were interviewed about what is their perception about their role model advertising or using tobacco products. **Result:** Among total participants of 2571, 42.6% people strongly agreed that actors/actresses should not smoke in film or in TV serials. In one subset of people, 50 years and above strongly agreed about film stars should not use cigarettes in movies or serials (p= 0.01). People strongly agreed about banning billboard advertisement of tobacco products near tobacco shops (p= 0.02). Approximately half of the people strongly agreed that TV channels should not display the advertisement of tobacco-related products along with the roadside display. In this study, 57.6% of people felt dissociated from their role models if they see them endorsing or promoting tobacco products. All of the participants strongly agreed about using role models to promote lung cancer awareness in India. People who were less educated were significantly influenced by role models in adopting smoking habits. (p= 0.005). Person with family history of cancer was not affected by his/ her role models (p= .04). **Conclusion:** Role models have an important role to influence people to adopt smoking habits. Role models can be used as an important tool in promoting lung cancer awareness in India. There is an urgent need to ban promotion and advertisement of tobacco products by role models in Television, Internet and display boards. There is also a need to start population-based intervention aiming for behavioural modification and role models can play a vital role to make these campaigns successful.

Keywords: Lung cancer, Role model, Cancer awareness





Conclusion: This study explored in depth historical smoking patterns by race/ethnicity in the US, identifying important differences not only in prevalence, but also on cohort- and age-specific initiation and cessation rates. These differences need be taken into account when planning tobacco control interventions. Among the demographic groups analyzed, AIANs remain as the group with the highest smoking prevalence and initiation and the lowest cessation rates, and thus deserve specific interventions.

Keyword: smoking disparities, smoking initiation and cessation, patterns by birth-cohort

P1.10-02 IMPLEMENTING AN OPT-OUT APPROACH TO SMOKING CESSATION REFERRALS FOR CANCER PATIENTS IN ONTARIO, CANADA

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Background: Smoking is responsible for approximately 30% of all cancer deaths in Canada and more than 85% of lung cancer cases. Continued smoking results in decreased cancer treatment efficacy and safety, increased toxicities, greater risk of cancer recurrence and second primaries, poorer quality of life and decreased survival. Quitting smoking can reduce these adverse effects. In 2013, Cancer Care Ontario (CCO) implemented a smoking cessation program across 14 Regional Cancer Centres (RCCs) in the province of Ontario, Canada, employing a 3As (Ask, Advise, Act) brief intervention model. **Method:** In the first few years of the program, smokers could "opt-in" to smoking cessation services by stating a readiness to quit. However, the provincial rate of smokers accepting support was low. In 2018, CCO adopted an "opt-out" approach, based on emerging evidence and feedback from an expert Advisory Committee. With this approach, healthcare providers (HCPs) automatically refer all smokers to a cessation service, without assessing the patient's readiness to quit. Patients can refuse the referral if they choose. This program change was communicated to the RCCs through a revised program framework, site-specific action plans, and discussion during monthly knowledge exchange meetings with Regional Champions. Communications resources (posters and pocket cards) were created to support HCPs, with suggested scripts. **Result:** The Accepted a Referral (proportion of smokers accepting referral to cessation services) performance metric was used to monitor program implementation. With an opt-in approach, the annual provincial rate of Accepted a Referral improved only slightly over three years (18.1% in 2015/16 to 22.5% in 2017/18). Just prior to launching the opt-out approach in Q3 of 2017/18, the provincial rate of Accepted a Referral was 23.3% (range 9.2% to 37.9% amongst 14 RCCs). One year later, the provincial rate had increased substantially to 31.9% (range 12.9% to 88.7%). Several RCCs showed dramatic increases, while others demonstrated little or no improvement. **Conclusion:** In an effort to help more patients quit smoking and to achieve the best treatment outcomes possible, CCO adopted an opt-out approach to cessation referrals. Overall, there has been a substantial increase in the provincial rate of smokers accepting support, but implementation has varied amongst RCCs. Feedback indicates that while some HCPs found the approach relatively easy to implement, others have been resistant to change, expressing concern about the ethics of referring patients without assessing willingness to quit. Further research into the reasons behind the variable uptake of the opt-out approach will inform future implementation efforts.

Keyword: smoking cessation

P1.10-03 GUT MICROBIOTA AND LUNG CANCER: A MENDELIAN RANDOMISATION STUDY

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Background: Several studies have highlighted the association between the gut microbiota and lung cancer. However, robust epidemiological evidence able to discern this causal relationship does not exist. We aimed to investigate whether gut microbiota is causally associated with lung cancer through a two-sample Mendelian randomisation (MR) approach. **Method:** Genetic instrumental variables of 23 genera at genome-wide significance ($P < 5\times10\text{-}8$) were obtained from five available genome-wide association study (GWAS) of the gut microbiota. We conducted a two-sample MR analysis to access the causality between 23 genera of gut microbiota and lung cancer, based on the publicly available GWAS summary data from the International Lung Cancer Consortium (ILCCO, 11 348 lung cancer cases and 15 861 controls) and other consortiums. We applied several different MR methods for deriving causal estimates: Wald ratio, inverse-variance weighted, weighted median, and MR-Egger. Additional sensitivity analyses were utilized to detect potential pleiotropy bias. **Result:** Among 23 genera, a 1 allele increase in single nucleotide polymorphisms related to higher *Oscillospira* was associated with a 26.1% lower risk of lung cancer (odds ratio (OR) 0.739, 95% confidence interval (CI) 0.570 to 0.959, P = 0.023). We also identified genetic predisposition towards higher *Weissella*, based on 1 SNP, was associated with lower risk of lung cancer (OR 0.804, 95% CI 0.693 to 0.933, P = 0.004). No associations were found for the other 21 genera, namely *Acidaminococcus*, *Acinetobacter*, *Aggregatibacter*, *Anaerostipes*, *Atopobium*, *Bacteroides*, *Bifidobacterium*, *Coprococcus*, *Desulfovibrio*, *Dorea*, *Eggerthella*, *Eubacterium*, *Faecalibacterium*, *Lachnospira*, *Lactobacillus*, *Leuconostoc*, *Megamonas*, *Mogibacterium*, *Pseudobutyrivibrio*, *Roseburia*, and *Slackia*. Table 1. Mendelian randomisation estimates of the associations between 23 gut microbiota and risk of lung cancer.

Microbiota	SNP	IVW / (Wald ratio, SNP<3)		Weighted median		MR-Egger	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Acidaminococcus	5	1.001 (0.999, 1.004)	0.355	1.001 (0.998, 1.004)	0.424	1.000 (0.996, 1.005)	0.894
Acinetobacter	1	1.193 (0.984, 1.447)	0.073				
Aggregatibacter	1	0.960 (0.884, 1.043)	0.335				
Anaerostipes	2	0.989 (0.933, 1.048)	0.701				
Atopobium	1	0.940 (0.876, 1.008)	0.083				
Bacteroides	5	0.999 (0.997, 1.000)	0.134	0.999 (0.997, 1.000)	0.152	0.999 (0.997, 1.000)	0.213
Bifidobacterium	2	1.008 (0.934, 1.087)	0.844				
Coprococcus	1	1.138 (0.732, 1.769)	0.567				
Desulfovibrio	2	0.992 (0.958, 1.028)	0.658				
Dorea	1	1.058 (0.984, 1.137)	0.128				
Eggerthella	1	1.001 (0.998, 1.005)	0.442				
Eubacterium	1	0.999 (0.922, 1.083)	0.987				
Faecalibacterium	3	1.004 (0.952, 1.058)	0.889	1.002 (0.947, 1.060)	0.949	0.990 (0.907, 1.080)	0.852
Lachnospira	1	1.028 (0.925, 1.141)	0.609				
Lactobacillus	2	0.972 (0.897, 1.054)	0.497				
Leuconostoc	1	0.964 (0.860, 1.081)	0.533				
Megamonas	3	1.016 (0.990, 1.043)	0.231	1.016 (0.985, 1.048)	0.307	0.908 (0.725, 1.137)	0.556
Mogibacterium		0.998 (0.897, 1.110)	0.973				
Oscillospira	1	0.739, (0.570, 0.959)	0.023*				
Pseudobutyrivibrio	1	0.961 (0.877, 1.053)	0.397				
Roseburia	1	0.980 (0.843, 1.140)	0.796				
Slackia	1	0.980 (0.935, 1.027)	0.401				
Weissella	1	0.804 (0.693, 0.933)	0.004*				

*: P value < 0.05; IVW: inverse-variance weighted; OR: odds ratio; CI: confidence interval. **Conclusion:** Our present mendelian randomisation study provided evidence of a causal effect of the gut microbiota on lung cancer, suggesting *Oscillospira* and *Weissella* might be the focus of future research. Further studies are needed to confirm these causality and elucidate the potential mechanisms.

Keywords: Gut microbiota, Lung cancer, Mendelian randomisation

P1.10-04 LUNG CANCER IN PATIENTS WITH HIV DISEASE - UNIQUE CLINICAL AND BIOMARKER FEATURES IMPACTING LUNG CANCER SCREENING AND MANAGEMENT

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Background: Patients with HIV (PWH) are diagnosed with lung cancer at a higher frequency than the general population and lung cancer is emerging as the most common malignancy afflicting PWH. We aimed to study the epidemiological and clinico-pathological characteristics of lung cancer in PWH at an NCI-designated Cancer Center in a service area with a high prevalence of HIV. **Method:** We reviewed charts of 178 PWH who were diagnosed with lung cancer between 2000 and 2018. 126 patients with available pathology specimens were included in this study. Demographics, clinico-pathological characteristics and treatment data were collected. Age and disease stage of this patient group was compared to the overall group of patients with lung cancer at our institution. In 28 patients where sufficient tissue was available, biomarker studies including PD-L1 TPS score assessments were performed (22C3 antibody). **Result:** PWH diagnosed with lung cancer had a mean age at diagnosis of 56.8 years (range 25-71), 67% were men, 45% black, and 25% Hispanic. 98% of patients reported a history of smoking where information was available. At the time of lung cancer diagnosis, 68% had stage IV disease, average CD4 count was 370/mcL and 33% had a CD4 count of less than 200/mcL. Adenocarcinoma was the most common histological type (51%). Patients who were not on ART were younger than those who were on ART (p = 0.010). In comparison with the overall group of patients with lung cancer, PWH were younger (mean age 68.0 vs 56.8, p = 0.014) and had a higher percentage of advanced disease at diagnosis (49% vs 68%, p < 0.001). PD-L1 testing showed a remarkably low rate of PD-L1 positivity (TPS score <1%- 78%, 1-50%- 14% and >50%- 8%). 11 patients received immunotherapy (8 single-agent immunotherapy), 2 subjects had a partial response and 3 patients had stable disease as best response. No patients had any grade ¾ immune adverse events (1 episode of grade 2 colitis and one episode of grade 2 dermatitis – both of unclear association with therapy and no episodes of thyroiditis) and in general checkpoint inhibitor therapy appeared very well tolerated. **Conclusion:** Conclusions: Our cohort study describing one of the largest experiences amongst PWH and lung cancer demonstrates multiple unique features such as significantly younger age and very frequent advanced stage at presentation as compared to the overall patient population with lung cancer calling for dedicated screening measures to reduce lung cancer-related mortality. In addition, a strikingly low frequency of PD-L1 expression was noted in available tumor specimens which might be related to baseline immune suppression and T cell anergy, however at least some patients could benefit from checkpoint inhibitor therapy which was very well tolerated –suggestive of unique immune biology and treatment considerations in this at-risk patient population.

Keywords: lung cancer screening, immune biology, HIV

P1.10-05 TOBACCO RETAIL AVAILABILITY AND TOBACCO CESSATION AMONG LUNG CANCER SURVIVORS

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Background: Continued smoking after a lung cancer diagnosis is associated with poorer outcomes. Tobacco retail availability is negatively associated with cessation in non-cancer patients but this has not been explored in cancer survivors. We evaluated the impact of tobacco retail availability on tobacco cessation in lung cancer survivors. **Method:** Lung cancer survivors from Princess Margaret Cancer Centre (Toronto, Canada) completed questionnaires at diagnosis and follow-up evaluating changes in tobacco use with a median of 26 months apart. Validated tobacco retail location data were obtained from Ministry of Health and patient home addresses were geocoded using ArcGIS 10.6.1, which calculated walking time/distance to nearest vendor, and vendor density within 250 meters (m) and 500m from patient residences. Multivariable logistic regression and Cox proportional hazard models evaluated the impact of vendor availability on cessation and time to quitting after diagnosis respectively, adjusting for significant clinico-demographic and tobacco covariates. **Result:** 242/721 lung cancer survivors smoked at diagnosis; subsequent overall quit rate after diagnosis was 66%. Mean distance and walking time to a vendor was 0.8 km (range 0-13) and 10 min (range 0-157). On average, there was one vendor (range 0-19) within 250m and five vendors (range 0-36) within 500m from pts; 40% and 64% of pts lived within 250m and 500m from at least one vendor respectively. Greater distance (aOR 1.28 per 1000m [95% CI 0.97-1.70] p = 0.08) and increased walking time (aOR 1.02 per minute [1.00-1.05] p = 0.08) to a tobacco vendor had a non-significant trend towards increased chances of quitting at one year. Living within 250m (aOR 0.43 [0.25-0.74] p = 0.003) or 500m (aOR 0.50 [0.28-0.88] p = 0.02) to at least one vendor reduced quitting at one year. Living near more vendors within 500m had a non-significant trend towards having an increasing dose effect on reducing cessation rates at one year (aOR 0.97 per vendor [0.94-1.00] p = 0.08). Living within 500m to a vendor reduced chance of quitting at any time (aHR 0.70 [0.50-1.00] p = 0.05). **Conclusion:** Close proximity to tobacco retail outlets is associated with reduced cessation rates for lung cancer survivors. Reducing density of tobacco vendors is a cessation strategy that could positively impact lung cancer patient outcomes.

Keywords: Tobacco Cessation, Cancer Survivorship, Geocoding

P1.10-06 PATHOLOGICAL CHARACTERIZATION OF RADON-INDUCED LUNG CANCER IN RATS

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Background: Radon is a radioactive gas, considered the leading cause of lung cancer in non-smokers. Although the risk of lung cancer is linear, there is no safe level and even low dose can be associated with risk. In humans, no specific pathological subtypes of lung cancer have been clearly associated with radon. In animals, the French Atomic Energy Commission (CEA) exposed to low dose of radon (25 working level month, WLM) a large cohort of rats in a radon-exposure chamber, showing lung cancer induced by low exposure (Chameaud J, Radiation Prot Dosimetry 1984). We aimed to describe pathological features of radon-induced tumors in rats from the CEA's cohort. **Method:** Retrospective assessment of archival samples available of the rats exposed to low-dose radon in the Laboratoire de Pathologie Pulmonaire Experimentale, COGEMA (France), between 1989 and 1992. Autopsy reports were also reviewed. The pathological assessment was performed for a thoracic oncology pathologist (JA) in H&E staining slides according to the current WHO histological classification. **Result:** Samples from 117 rats were collected. Among 104 tumors, to date the analysis has been performed in 94. Forty tumors (43%) were classified as malignant, 28 (30%) as uncertain malignant potential (UMP) and 26 (28%) benign. In 2 rats (2%) synchronous malignant and non-malignant tumors were observed. Among the malignant tumors, 23 (58%) were epithelial and 17 (42%) non-epithelial. Lung carcinoma was the most common primary epithelial tumor (n=10, 43%), followed by abdominal area tumors (n=5, 22%), and thyroid (n=3, 13%). In the UMP group, 7 (25%) were epithelial and 21 (75%) non-epithelial, with no lung tumors observed. In the benign group, most of them (n=24, 92%) were epithelial, with 4 cases with lung atypical adenomatous hyperplasia-like lesions; 2 synchronous with other malignant tumors (n=1 lymphoma, n=1 cutaneous squamous cell carcinoma). A total of 26 tumors (27%) had thoracic involvement: 4 (15%) primary lung non-malignant lesions, 11 primary lung malignancies (42%) and 11 with metastases from other tumors (42%). As primary malignant lung tumors, we observed: 7 (64%) adenocarcinoma in situ, one papillary adenocarcinoma, one undifferentiated large cell carcinoma with bilateral metastases, one metastatic squamous carcinoma and one metastatic undifferentiated tumor, compatible with sarcoma **Conclusion:** In this cohort of radon-induced tumors in rats, we observed different tumor types, from non-malignant lesions to aggressive malignancies, with predominance of epithelial tumors. Lung carcinoma was the most common primary tumor and adenocarcinoma the histological subtype more observed, with histological similarities with humans.

Keywords: Lung cancer, rats, Radon

P1.10-07 CHARACTERISTICS OF CURRENT AND FORMER SMOKERS WHO ACKNOWLEDGE THEIR RISK OF LUNG CANCER: RESULTS FROM THE EDIFICE6 SURVEY

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Background: Self-assessment of personal cancer risk may be a determining factor for lifestyle changes, risk factor control, or adherence to screening. We studied the characteristics of individuals who assessed their own risk of lung cancer (LC) as higher than that of the average population, and the impact of current smoking status in former and current smokers. **Method:** The French nationwide observational survey, EDIFICE 6, was conducted online (June 26-July 28, 2017) on a core sample of 12 046 individuals (18-69y). Representativeness was ensured by quota sampling on age, sex, profession, and stratification by geographical area/type of urban district. **Result:** In the whole population (N = 11 307), current smoking had the strongest correlation (OR = 7.89). Former smoking (quitting age ≥45y) and use of e-cigarettes were also strongly correlated. Current and former smokers represented 54% and 19%, respectively, of those who assessed their own risk of LC as higher than average (N = 3 544). In multivariate analysis, features associated with this perception were (1) among former smokers: ceased tobacco use ≥45y (OR = 2.56 [2.02-3.25]), male (OR = 1.60, [1.31-1.94]), manual work (OR = 1.42, [1.01-1.99]), and social vulnerability (OR = 1.37, [1.14-1.65]); (2) among current smokers: self-employed (OR = 1.82, [1.18-2.89]), and rating cancer prevention programs as ineffective (OR = 1.39, [1.19-1.63]). Current e-cigarette use and being close to someone with cancer or accompanying someone during cancer treatment were common features to former (OR = 1.98, [1.45-2.70], OR = 1.38, [1.15-1.65]) and current smokers (OR = 1.29, [1.05-1.59], OR = 1.20, [1.02-1.41]). **Conclusion:** Our results show that among individuals who assess their own risk of LC as higher than the average of the general population, current smokers belonged to the wealthiest socioprofessional categories and gave little importance to cancer prevention. Former smokers were more likely to be men, who ceased tobacco use ≥45y, and come from a modest social background. Additionally, both groups were more likely to have experienced cancer in someone close, and to be e-cigarette users.

Keywords: lung cancer screening, Risk Factors, smoking cessation

P1.10-08 THE USEFULNESS OF INPATIENT SMOKING CESSATION PROGRAM AT SINGLE CANCER CENTER

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Background: Smoking is a well-known risk factor for the development of several diseases including cancer, but smoking cessation is a difficult problem even in patients who need hospitalization. The purpose of the study was to investigate the usefulness of inpatient smoking cessation consultation program. **Method:** This study included patients who admitted to Chonnam National University Hwasun Hospital and were requested for Inpatient smoking cessation program by doctors or nurses from January to December 2018. We assessed the cessation rate at 4 weeks and 6 months, and evaluated clinical characteristics associated with success by electronic medical record system. Enrolled patients got counseling regularly for 6 months, and the success rate was confirmed by urine cotinine and exhaled carbon monoxide level. And we analyzed the differences of clinical characteristic and survival according to the registration status in lung cancer patients. **Result:** A total of 571 patients were requested and 170 (29.8%) were enrolled to this program. One hundred thirty-eight (81.2%) patients had cancer and the majority was lung cancer (42.9%) followed by gastric cancer (11.2%). One hundred eleven (65.3%) patients were enrolled during their first admission. Only 6 (3.5%) patients took smoking cessation drugs in addition to counseling. The smoking cessation rate was 78.5% at 4 weeks and 39.2% at 6 months. The 4 week-cessation rate of cancer patients was higher than non-cancer (63.8% vs. 21.9%, p=0.000) and the rate of first admission group was higher than that of re-admission group, but it was not statically significant (67.0% vs. 47.8%, p=0.098). Also, the 6 month-cessation rate of cancer group was higher than non-cancer (45.7% vs. 3.8%, p=0.000) and the rate of first admission group was higher than that of re-admission, but not statically significant (49.3% vs. 29.4%, p=0.180). And 4 week-successful cessation group showed lower nicotine dependency than failed group (66.2% vs. 33.8%, p=0.046). In 155 of lung cancer patients, 73 (47.1%) were registered and 82 (52.9%) were refused. The registration rate of early stage group was higher than advanced stage group (83.3% vs. 34.4%, p=0.011). And the registration rate of operation group was higher than non-operation (64.5% vs. 42.7%, p=0.043) but the rate of chemotherapy group was lower than non-chemotherapy (41.2% vs. 58.5%, p=0.044). And the Progression free survival and Overall survival of registration group was better than refusal group, but not statically significant (p=0.199, p=0.215). **Conclusion:** Inpatient smoking cessation program was useful with high abstinence rate. Most patients could keep cessation without medication, so the diagnosis of cancer itself might be enough motivation. And smoking cessation after cancer diagnosis could improve survival rate in lung cancer.

Keywords: smoking cessation, Inpatient, cancer

P1.10-09 CESSATION RATES OF AN EXPANDED PHARMACY-DRIVEN SMOKING CESSATION PROGRAM

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Background: In the United States, smoking accounts for approximately one-third of all cancer related deaths. While national oncology organizations advocate smoking cessation integrated into cancer management, only 30-40% of oncologists provide assistance with quitting. Barriers to providing this service are well documented. Pharmacy learners are positioned to provide this intervention with the incorporation of smoking cessation therapies in accredited PharmD curricula. Previous pharmacist-driven programs reported 30-day quit rates of 23%. The purpose of this study is to characterize the smoking cessation rates of a pharmacy-driven smoking cessation program for upper-aerodigestive cancer patients or patients with a pulmonary precancerous diagnosis. **Method:** Patients seen in a multidisciplinary upper aerodigestive clinic between April 2017 and July 2018 were screened. All active smokers and former smokers, who quit in the last 90 days, were eligible and offered enrollment in the program. The primary endpoint is to describe participant's quit-rates at 30, 90, and 180-days and number of patients who abstained from smoking from 30 to 90 days and 30 to 180 days. Tobacco use assessments and smoking cessation counseling were performed and documented by a pharmacy learner (pharmacy resident or student). A licensed pharmacist oversaw learner activity and documentation. Nicotine replacement therapy was provided immediately to eligible participants in a dose based on tobacco use. Participants received follow up via phone or in clinic every two weeks for the first three months, at six, nine, and twelve months of program enrollment. Two follow up phone call attempts were made at each time point to determine if not successfully reached. **Result:** Seventy-seven patients were enrolled in the pharmacy-driven smoking cessation program. The majority of patients were male, 52% (40), and younger than 65 years old, 56% (43). Patient-reported smoking cessation rates at 30-days, 90-days, and 180-days post enrollment were 38% (29), 38% (29), and 30% (23), respectively. Sustained quit-rate from 30-90 days was 29% (22). Sustained quit-rate from 30-180 days was 20% (15). At one, three, and six months, 4%, 9%, and 26% of patients, respectively, were unavailable by phone. **Conclusion:** Thirty percent of participants were successful in smoking cessation at 180 days from program enrollment, which compares favorably to previous pharmacist interventions. Telephone follow up continues to be challenging, especially later in the program. Future efforts will compare pharmacy-driven smoking cessation program to standard of care smoking cessation efforts and explore impacts of smoking cessation on clinical outcomes in patients who are receiving cancer care.

Keywords: smoking cessation, pharmacy, nicotine dependence

P1.10-10 SOCIAL VULNERABILITY AND SURVIVAL IN LUNG CANCER IN EMERGING COUNTRY

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Background: The association between lung cancer and socioeconomic conditions has been reported more frequently in the last years. Demographical and epidemiological characteristics have changed over time, and these changes are observed mainly in big metropolitan areas of emerging countries with high inequalities scores. Our objective was to analyze the impact of social vulnerability in lung cancer survival in a big urban area of an emerging country. **Method:** We retrieved data from a local cancer database (RHC) including sociodemographic (Paulista Index of social vulnerability-IPVS and educational level), clinical (tumor characteristics, treatment) and survival data. We used median and interquartile range to show the descriptive results, frequencies and proportions to categorical variables. The survival curve was calculated by Kaplan-Meier and Log-rank. **Result:** 8631 patients were diagnosed with lung cancer between 2000 to 2013 and registered in the RHC database. In our population we found a predominance of men (61%), mean age 63 years (SD±11.4), and 52.5% of them were living in areas with low social vulnerability (Index 2). The most frequent histological type was adenocarcinoma (39%), and most patients were at clinical stage IV at diagnosis (56%); 31.4% received chemotherapy and 24.5%, chemotherapy+radiotherapy as a definitive treatment. The mean time from diagnosis to definitive treatment was 44 days (SD±93). The overall survival was 10 months (4-23). When adjusted for clinical stage, the probability of survival was better for patients living in areas of low social vulnerability (p<0.000) and for those who had completed >12 years of schooling (p<0.000).

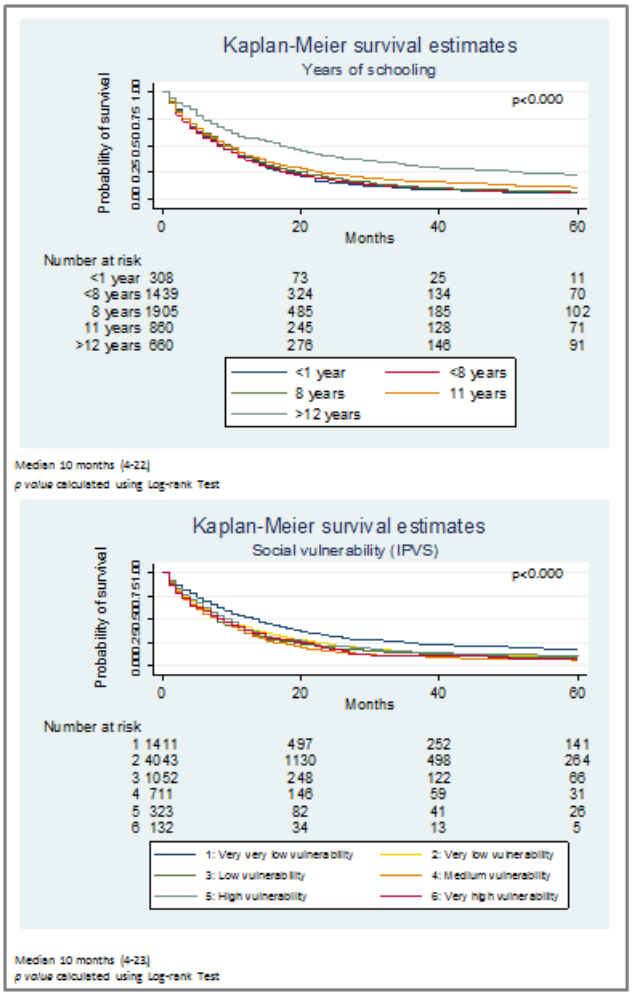

Figure 1. Kaplan-Meier survival curves

Conclusion: Social vulnerability and years of schooling are directly related with survival in lung cancer, even when adjusted for clinical stage. Our results highlight the impact of inequality in health outcomes.

Keywords: Lung cancer, Survival, socioeconomic

P1.10-11 EXAMINATION OF LIFESTYLE FACTORS AND ASSOCIATIONS WITH GENETIC MUTATIONS IN LUNG CANCER CASES

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Background: With the advent of targeted therapy it is extremely useful to know what factors may be associated with specific mutations in order to better target treatment therapies. Few reports have assessed factors related to targeted therapies for lung cancer, especially in the United States. Common driver mutations relevant to lung cancer include EGFR, ROS1, ALK, KRAS and RET. In this report, we examined demographic, clinical and selected lifestyle factors, including age, sex, smoking, body mass index (BMI) and NSAID use and their association with lung cancer specific mutations. **Method:** Electronic medical records were reviewed for lung cancer cases (ICD-9: 162.2-9; ICD-10: C34.X) from the Ohio State University James Cancer Hospital from 2013-2018; demographic, clinical and lifestyle data were extracted, including age, sex, smoking, body mass index (BMI), NSAID use, as well as any driver mutations (EGFR, ROS1, ALK, KRAS and RET). Due to the small sample sizes for some of the mutations, they were combined into one overall mutation variable. Logistic regression analysis was performed to assess whether any associations exists between the risk factors and the presence of a mutation. Odds Ratios (ORs) were used to estimate the associations with alpha=0.05. **Result:** We identified 892 lung cancer cases in which tumor specimens were examined for mutations. Four types of mutations were identified: EGFR (n=89), ALK (n=19), ROS1 (n=8) and RET (n=12), for a total of 127 cases with mutations compared to 765 without mutations. The mean age for both groups was 65 years, with over 61% of the mutation group being female versus 54% of the non-mutation group). Overall, 84% of cases were white race, with slightly more non-whites in the mutation group (86% versus 83%). Logistic regression analyses revealed that age <50 years (OR=1.9; 95%CI=1.1, 3.6), female gender (OR=2.1, 95%CI=1.4, 3.1), and never smoking (OR=7.5, 95%CI=4.08, 3.5) were significantly associated with increased odds of having a mutation after controlling for other factors. Having a BMI>30 approached significance (OR=1.01, 95%CI=0.99,1.02) but NSAID use (aspirin, ibuprofen and/or acetaminophen) did not show significant associations with the presence of lung cancer mutations in this analysis. **Conclusion:** This study revealed significant associations between younger age (<50 years), female gender and never smoking with the presence of driver mutations in lung cancer cases. Previous reports have not assessed the relationship between BMI, NSAID use and lung cancer driver mutations to our knowledge. We also understand the significant limitations in obtaining quality data on NSAID use from the medical charts, and a more in-depth review is being planned. Nevertheless, this report confirms several known predictive factors related to driver mutations, and for the first time shows a lack of correlation with NSAIDs and potentially BMI. Future reports should also aim to assess more diverse populations.

Keyword: NSAIDS, driver mutations, lung cancer

P1.10-12 ROLE MODELS AND LUNG CANCER AWARENESS: DOES IT CHANGE THE MIND-SET AND PERCEPTION OF GENERAL POPULATION?

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Background: Lung cancer has become a major health concern, though easily preventable, with smoking and air pollution being major risk factors. Intentional or unintentional advertisement or use of tobacco product by society role models may affect their attitude towards the smoking and related lung cancer. This study analysed the people mindset and perception for their role models in tobacco advertisement and lung cancer awareness. **Method:** The survey was conducted at various market and public places in Delhi, India. People were interviewed about what is their perception about their role model advertising or using tobacco products. **Result:** Among total participants of 2571, 42.6% people strongly agreed that actors/ actresses should not smoke in film or in TV serials. In one subset of people, 50 years and above strongly agreed about film stars should not use cigarettes in movies or serials (p= 0.01). People strongly agreed about banning billboard advertisement of tobacco products near tobacco shops (p= 0.02). Approximately half of the people strongly agreed that TV channels should not display the advertisement of tobacco-related products along with the roadside display. In this study, 57.6% of people felt dissociated from their role models if they see them endorsing or promoting tobacco products. All of the participants strongly agreed about using role models to promote lung cancer awareness in India. People who were less educated were significantly influenced by role models in adopting smoking habits. (p= 0.005). Person with family history of cancer was not affected by his/ her role models (p= .04). **Conclusion:** Role models have an important role to influence people to adopt smoking habits. Role models can be used as an important tool in promoting lung cancer awareness in India. There is an urgent need to ban promotion and advertisement of tobacco products by role models in Television, Internet and display boards. There is also a need to start population-based intervention aiming for behavioural modification and role models can play a vital role to make these campaigns successful.

Keywords: Lung cancer, Role model, Cancer awareness

P1.11-01 THE IMPLEMENTATION OF THE LUNG-RADS™ IN PILOT SILESIAN STUDY WITH LDCT - AN OPPORTUNITY FOR BETTER CONTROL OF OVERDIAGNOSIS

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Background: A high percentage of false positive results observed in lung cancer screening (LCS) studies with LDCT was the reason for the modification of radiological assesement methods. Originally, all non-calcified nodules with a dimension ≥ 4 mm were considered as positive, whereas the implementation of the Lung-RADS™ recommends additional testing only for nodules ≥ 6 mm in categories 3 and 4. This allowed for the reduction of false positive results and avoiding the effect of "overdiagnosis" (unnecessary interventions). **Method:** We retrospectively analyzed 601 of first round LDCT scans, performed in 2010-2012 in asymptomatic volunteers of Pilot Silesian Study of Early Lung Cancer Detection with Low-Dose CT, with a smoking history of at least 20 pack-years, who actively smoked tobacco or quit smoking in the last 15 years. The analysis of non-invasive (additional examinations with contrast CT) and invasive interventions (bronchoscopy, EBUS, biopsies, surgery) done in screening participants was performed, followed by assessment of nodules according to the Lung-RADS ™ system, grouping them to 2, 3, 4A and 4B categories. Then the percentage of interventions that could be avoided using the ACR LungRADS™ criteria was estimated. **Result:** In total, 1016 nodules of solid, partial-solid and non-solid morphology were identified in 265 participants. In the entire screening cohort 87 interventions were performed, including 58 (66.6%) non-invasive and 29 (33.3%) invasive. Among nodules belonging to category 4A and B, 8 invasive lung cancers were identified, 1lung cancer was overlooked (false negative) and in 1 case metastases from colorectal cancer were diagnosed. With the using of LungRADS™ criteria, 34.4% of non-invasive and 8% of invasive interventions in categories 2 and 3 could be avoided. **Conclusion:** The LungRADS ACR classification system proved to be a practical tool for assessing lung nodules, which allowed to significantly reduce the effect of "overdiagnosis" especially in category 2 where the probability of lung cancer is low (<1%).

Keywords: lung cancer screening, Lung-RADS, LDCT (low dose computed tomography)

P1.11-02 ACCELERATION OF LUNG CANCER DIAGNOSIS: UTILITY STUDY FOR AI-BASED STRATIFICATION OF PULMONARY NODULES

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Background: Lung cancer diagnostic pathway guidelines promote the use of risk stratification models. Artificial Intelligence (AI)-based risk models have been shown to achieve better diagnostic accuracy than clinical models like Mayo Clinic (Mayo) for particular clinical populations. The aim of this study is to examine whether this could translate into faster diagnosis for high-risk cancer patients. **Method:** 116 patients (116 nodules) have been collected from a retrospective consecutive cohort acquired at Vanderbilt University Hospital. Time to diagnosis (TTD) was defined as the number of days between the CT scan and diagnosis date. Mean TTD was calculated on the cohort on which TTD could be defined, and on a reduced group comprising of TTD >31 days only. Risk scores for each nodule were found using the Mayo model and an AI-based Lung Cancer Prediction model (LCP) based on CT images alone. A 65% risk of cancer was taken to be the threshold at which surgical intervention is indicated (according to ACCP guidelines). **Result:** Seven patients were dropped due to negative TTD, and six for having no definitive diagnosis date. The eventual cohort contained 61 cancer patients and 42 controls. Mean TTD is 140 days (Interquartile Range – IQR 1-77 days). 25 patients have TTD=0, 60 are within 31 days (28 cancers, 32 controls) and 43 (33 cancers, 10 controls) are above 32 days. On the full cohort: Mayo risk score is >=65% for 15 cancers and 4 controls (sensitivity, 24.6%, specificity 90.5%), with a mean cancer TTD of 75 days. The LCP scores >=65% in 43 cancers and 10 controls (sensitivity, 70.5%, specificity 76.2%), mean cancer TTD 81 days. On the reduced group: Mayo >=65% for 7 cancers and 2 controls (sensitivity, 21.2%, specificity 80.0%) with mean cancer TTD 150 days. The LCP scores >=65% in 21 cancers and 4 controls (sensitivity, 63.6%, specificity 60.0%), with mean cancer TTD 156 days. **Conclusion:** The LCP risk model could potentially accelerate the diagnosis in 40% more cancer patients who were not worked up fully in the month following a scan (the jump in sensitivity going from Mayo to LCP risk >=65% is 42.4%). For these patients, time to a cancer diagnosis and treatment could be shortened by up to 156 days compared to recommendations if applying the Mayo risk model.

Keywords: Risk model, Diagnosis management, Lung cancer stratification

P1.11-03 DISPARITIES AND NATIONAL LUNG CANCER SCREENING GUIDELINES IN THE U.S. POPULATION

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Background: Current U.S. Preventive Services Task Force (USPSTF) lung cancer (LC) screening guidelines are based on smoking history and age (55-80). These guidelines may miss those at higher risk, even at younger ages, due to other risk factors such as race or family history. In this study, we characterize the demographic/clinical profiles of those who are selected by risk-based screening criteria, but missed by USPSTF in younger (45-54) or older ages (71-80). **Method:** We used data from the National Health Interview Survey, the CISNET Smoking History Generator, and logistic prediction models for non-smoking risk factors to simulate life-time LC risk-factor data for 100,000 men and women in the U.S. 1950-1960 birth cohorts. We calculated age-specific 6-year LC risk (*r*) for each individual from ages 45-90 using the PLCOm2012 model. We evaluated age-specific screening-eligibility by USPSTF guidelines and by risk-based criteria (varying thresholds between 1.3%-2.5%). **Result:** In the 1950 cohort, 6.73% would be missed for screening in their younger ages by the USPSTF-criteria, but would have been screened by the risk-based criteria. Similarly, 13.97% of the cohort would be ineligible for screening by USPSTF in older ages. Notably, a higher proportion of African Americans will be ineligible for screening by USPSTF at younger (25.6%) or older (19.7%) ages, which is significantly higher than for Whites (7.7% and 15.75% respectively). Similar results were observed for other risk thresholds and for the 1960 cohort.

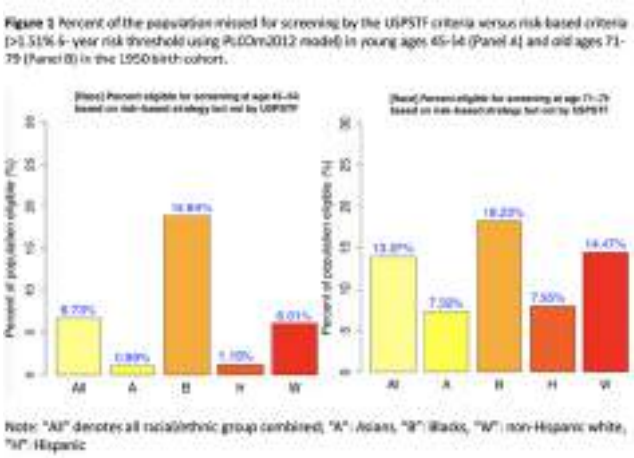

Figure 1 Percent of the population missed for screening by the USPSTF criteria versus risk-based criteria (>1.51% 6-year risk threshold using PLCOm2012 model) in young ages 45-54 (Panel A) and old ages 71-79 (Panel B) in the 1950 birth cohort.

Note: "All" denotes all racial/ethnic group combined; "A": Asians, "B": Blacks, "W": non-Hispanic white, "H": Hispanic

Conclusion: Further consideration is needed to incorporate comprehensive risk factors, including race/ethnicity, into lung screening criteria to reduce potential racial disparities.

Keyword: national lung cancer screening guidelines, racial disparity, Low dose CT screening

P1.11-04 UTILIZING DNA REPAIR ACTIVITY BIOMARKERS FOR LUNG CANCER RISK ASSESSMENT AND EARLY DETECTION

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Background: Early detection dramatically increases the 5-year survival rates of lung cancer patients. Yet, current early detection screening criteria miss most cases, highlighting the need to improve risk assessment markers. Because of the crucial role of DNA repair in eliminating DNA damage and mutations, and preventing cancer, we examined the usefulness of a panel of DNA repair blood tests for lung cancer risk assessment. The panel consisted of the DNA repair enzyme activities of OGG1 (8-oxoguanine DNA glycosylase), MPG (methylpurine DNA glycosylase) and APE1 (apurinic/apyrimidinic endonuclease 1), which act primarily on oxidative and methylation DNA damage. **Method:** A case-control study with 150 non-small cell lung cancer cases and 143 controls, blinded to the experimentalists, was conducted in the UK population, with tests and analyses performed in Israel. For each study participant, DNA repair enzymes activities were measured in protein extracts prepared from peripheral blood mononuclear cells, and used to calculate an integrated personalized DNA repair score. Personal characteristic of cases and controls were compared using unpaired t-tests for continuous variables and chi-squared tests for categorical variables. Associations were calculated using logistic regression. **Result:** The mean DNA repair score was lower in lung cancer cases than in control subjects, regardless of the disease stage. Individuals at the lowest tertile of DNA repair score had increased risk of lung cancer compared to individuals at the highest tertile, with OR=7.2, 95%CI 3.0-17.5; P<0.001, which was smoking-independent. ROC analysis yielded an AUC of 0.89. Integrating the DNA repair score into a commonly used risk model based on age and smoking status, led to 4-5-fold increase or decrease in the estimated 5-year risk to develop lung cancer, for low or high DNA repair score, respectively, compared to the risk model without the DNA repair score. **Conclusion:** The results of this study performed in the UK population confirm and extend a similar independent study performed in the Israeli population (Sevilya *et al* 2014 *Cancer Prevention Res*. 7, 398-406; Leitner-Dagan *et al* 2012 *J. Natl. Cancer Inst.* 104, 1765-1769). It validates low DNA repair score as a mechanism-based lung cancer risk biomarker, and can significantly improve current risk models. The DNA repair score can assist in identifying high-risk individuals for early detection by CT scanning, and can perhaps aid in predicting potential malignancy of indeterminate pulmonary nodules.

Keywords: DNA repair, CT screening, Lung cancer risk assessment

P1.11-05 GENETIC ARCHITECTURE OF LUNG CANCER USING MACHINE-LEARNING APPROACHES IN GENOME-WIDE ASSOCIATION STUDIES

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Background: Genome-wide association studies (GWAS) consisting of up to millions of single nucleotide polymorphisms (SNPs) have studied genetic influences to complex diseases and have identified thousands of associations. Few GWAS have explored interactions among SNPs that influence disease risks. **Method:** Machine learning applications can define how SNPs jointly influence disease risks through interactions. Tree-based machine-learning applications; classification and regression trees (CART) and random forest (RF) methods are popular and convenient tools for understanding interactions influencing disease development. Here we apply these methods to elucidate the higher-order interactions that influence lung cancer risk. We applied tree-based approaches using 18,444 cases and 14,027 controls from lung cancer OncoArray GWAS data. We first selected the SNPs very significantly associated (p<0.00001) with lung cancer risk. RF, which consists of systematically fitting classification trees, was run 1,000 times to identify the most influential SNPs. Subsequently we applied CART to summarize and visualize interactions that predict risk. **Result:** The final parsimonious tree included effects from genetic variants in CHRNA5, CLPTM1L, ZNRD1ASP, HCG9, TERT, CHRNB4, and DNAJC5 for overall lung. The final tree for adenocarcinoma lung showed the combination of genetic effects in or near ATM, CLPTLM1L, TERT, FSTL5, and DCTN4. The final tree for squamous cell carcinoma included CHRNA5, MRPL21, HLA, CASP8, and TAP2. **Conclusion:** Our results confirmed associations with CHRAN5, TERT, and HLA observed in previous study (McKay et al., 2017). Machine learning methods in genomics provide some benefits over logistic regression model with respect to identifying subgroups at higher risk of lung cancer development on the basis of genetic characteristics.

Keywords: Machine-learning, Genetic Interactions, GWAS

P1.11-06 EXPANDING CRITERIA FOR LUNG CANCER SCREENING REDUCES GENDER DISPARITY

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Background: Women smokers may be more susceptible to lung cancer with less cigarette exposure than men. The NLST found borderline greater mortality benefit to high-risk women screened for lung cancer than men. The NELSON trial found significantly greater mortality benefit for women than men (39-61% for women vs 26% in men at 10 years). Since the NELSON trial included individuals ≥50 years old and ≤20 pack-years smoking history (similar to the NCCN moderate risk group) the aim of this study was to evaluate a cohort of lung cancer patients to determine differences in meeting the USPSTF criteria versus the NCCN moderate risk criteria on the basis of gender. **Method:** Gender, demographics, and smoking history were collected in a retrospective analysis of 703 smokers (current and former) diagnosed with lung cancer between 2010 – 2017 at an urban Chicago academic medical center. Cases were assessed for whether they would have met USPSTF (includes age 55-80, current smoker or former smokers quit time ≤15 years, ≥30 pack-years) and the NCCN moderate risk (includes age ≥50, current or former smokers, ≥20 pack-years) screening eligibility criteria. **Result:** Women smoked less overall, were less likely to smoke ≥30 pack-years (p=0.0002) and less likely to meet USPSTF screening guidelines (46.7% women vs 61.0% of men, p=0.0007) than men (Table 1). This gender disparity in meeting eligibility criteria was reduced by >40% (from 14.4% to 8.0%) when expanding from USPSTF (61.0% men vs 46.7% woman) to the NCCN moderate risk criteria (80.7% men vs. 72.7% women). Women were diagnosed at an earlier stage than men (p=0.02). **Conclusion:** Women diagnosed with lung cancer had a lighter smoking history and were less likely to meet the USPSTF screening criteria than men. Expanding USPSTF criteria to include individuals age ≥50 and ≥20 pack-year smoking history decreased the gender disparity in meeting lung cancer screening guidelines. Table 1: Gender Variation in Lung Cancer Current and Former Smokers

	Gender		p-value
	Men	Women	
Total N = 703 (%)	403 (57.33)	300 (42.67)	
Age Mean (SD)	64.36 (9.55)	64.66 (9.15)	0.7284
Race/Ethnicity (%)			0.1341
Black, Non-Hispanic	215 (53.35)	182 (60.67)	
White, Non-Hispanic	135 (33.50)	88 (29.33)	
Hispanic/Other	53 (13.15)	30 (10.00)	
Smoking History (%)			0.8515
Current	258 (64.02)	190 (63.33)	
Former	145 (35.98)	110 (36.67)	
Pack Years of Smoking Mean (SD)	45.33 (27.92)	36.02 (23.38)	0.0002
Pack Years of Smoking (%)			
≥30	305 (75.68)	181 (60.33)	
20- 30	48 (11.94)	55 (18.33)	
10-19	38 (9.43)	43 (14.33)	
0.5-9	12 (2.99)	21 (7.00)	
Quit-years for Former Smokers Mean (SD)	12.98 (11.04)	13.44 (11.93)	0.7497
Quit-years for Former Smokers[a] (%)			
0.5-15	97 (68.79)	67 (62.04)	
>15	44 (31.21)	41 (37.96)	
Met Screening Criteria (%)			0.0007
USPSTF	246 (61.04)	140 (46.67)	
NCCN moderate risk group[b] minus those that met USPSTF criteria	79 (19.60)	78 (26.00)	
NCCN moderate risk group[b] (includes USPSTF)	325 (80.65)	218 (72.67)	
Did not meet USPSTF or NCCN	78 (19.35)	82 (27.33)	
Stagec (%)			0.0224
I	51(13.28)	63 (22.26)	
II	25 (6.51)	18 (6.36)	
III	90 (23.44)	55 (19.43)	
IV	218 (56.77)	147 (51.94)	

[a]N=249 (number of former smokers with known quit-year data) [b]NCCN moderate risk (age ≥50 with a smoking history of ≥20 pack years) [c]N=667 (number of lung cancer cases with known staging data) Abbreviations: NLST = National Lung Screening Trials; NELSON = Nederlands-Leuvens Longkanker Screening Network; USPSTF = United States Preventative Services Task Force; NCCN = National Comprehensive Cancer Network; N = number of cases; SD = Standard Deviation

Keywords: Health disparities, lung cancer screening, Gender Disparities

P1.11-07 CFDNA FROM BRONCHOALVEOLAR LAVAGE FLUID FOR THE IDENTIFICATION OF SOLID PULMONARY NODULES: A NEW MEDIUM OF LIQUID BIOPSY

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Background: The pulmonary nodule especially small solid nodule (<2cm) represents a common diagnostic challenge for clinicians, which are sometimes very difficult to diagnose by radiographic techniques. In addition, complications of invasive diagnostic procedures of lung cancer are common in clinical practice. Bronchoalveolar lavage fluid (BALF), flushed into a small part of the lung and then recollected for examination, is routinely performed for the diagnosis of lung infections, interstitial lung diseases and sarcoidosis. However, limited evidences support the use of BALF for lung cancer diagnosis. The aim of this study is to investigate the potential value of BALF as liquid biopsy for differential diagnosis of pulmonary nodule characteristics. **Method:** A total of 36 patients with solid pulmonary nodule (<2 cm) at department of respiratory medicine of the first affiliated hospital of soochow university were enrolled. BALF supernatant cfDNA and matched tissue samples were profiled using 168-cancer-related gene panel, with median sequencing depths of 45259× and 2007×, respectively. Patients were eventually diagnosed by surgery, tracheoscopy, transthoracic needle aspiration or follow-up. The consistency of diagnoses based on genomic profiling of BALF and pathological examination were evaluated. **Result:** Of the 36 patients with solid pulmonary nodule (<2 cm), 15 cases were finally diagnosed as malignant nodules (11 by surgery, 4 by tracheoscopy), 16 with benign nodules (5 by surgery, 10 by tracheoscopy and fellow-up ,1 by TTNA), and 5 with uncertain nodules for the present. Using BALF mutation spectrum for diagnosis of pulmonary nodule characteristics, the sensitivities of 168 genes and 10 key genes (*EGFR*, *ERBB2*, *ROS1*, *BRAF*, *RET*, *ALK*, *KRAS*, *MET*, *TP53* and *RB1*) from NGS panel were 80% and 73%, the specificities were as high as 75% and 100%, positive predictive values were 75% and 100%, and negative predictive values were 80% and 80%, respectively. NGS detection consistency between BALFs and tissues was analyzed in paired BALF and tissue samples from 14 malignant patients. Alterations were detected in 11 (78.6%, 11/14) BALF supernatant samples and all the 14 (100%, 14/14) tissues. In total, 45 mutations were detected in paired BALF and tissue samples, of which 27 were detected in BALF samples and 40 in tissue samples,the consistency between tissue and BALF supernatant was 48.9%. **Conclusion:** BALF supernatant cfDNA could reveal the genetic profiles of patients with lung cancer and distinguish benign or malignant solitary pulmonary nodule (<2cm) with high specificity. It should be considered as liquid biopsy medium for identification the solitary pulmonary nodule in clinical practice.

Keywords: BALF, pulmonary nodule, NGS

P1.11-08 ARE RISK PREDICTION MODELS SUPERIOR OVER STANDARD CRITERIA FOR LUNG CANCER SCREENING IN EUROPE? MACROSCALE SIMULATION ON LARGE POLISH COHORT

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Background: Inauguration of the national lung cancer screening programme in Poland is to take place in 2019. Yet, issues such as optimal selection criteria remain unresolved. A computational macroscale simulation of lung cancer risk prediction models' implementation and comparison in a large lung cancer screening cohort of 5,534 individuals from a single, experienced European center was performed. **Method:** A total of 5,534 healthy volunteers (aged 50-79, smoking history ≥30 pack-years) were enrolled in the Moltest Bis Programme (Moltest) between 2016 and 2017. Inclusion criteria were based on the Lung Cancer Screening National Comprehensive Cancer Network Clinical Practice Guidelines. Each participant underwent a low-dose computed chest tomography scan and selected participants underwent a further, diagnostic work-up. A computational macroscale simulation of Tammemagi $PLCO_{m2012}$, Liverpool Lung Project (LLP) and Bach risk models' implementation was applied. Jupyter notebook v.1.0 scientific environment was used to calculate lung cancer probability of all Moltest participants.

Patients i) with 6-year lung cancer probability ≥1.3% were considered as high risk in $PLCO_{m2012}$ model, ii) in LLP model with 5-year lung cancer probability ≥5.0%, and iii) in Bach model with 1-year lung cancer probability ≥2.0%. Such selected patients were eligible for the inclusion to the simulated lung cancer screening programme. Boolean functions were created and data frames containing patients' epidemiological characteristics were joined using Pandas Python Library v.0.23 for Python v.3.7. **Result:** In a computational macroscale simulation 3,897 (70.4%), 3,118 (56.3%) and 925 (16.7%) out of 5,534 Moltest participants met the threshold criteria of lung cancer probability in $PLCO_{m2012}$, LLP and Bach models, respectively. With 199 (3.6%) Moltest individuals initially referred for diagnostic work-up in the programme, lung cancer was confirmed in 105 (1.9%) cases. Contrarily, among high-risk individuals selected based on $PLCO_{m2012}$, LLP and Bach models, respectively, 103 (2.6%), 56 (1.8%) and 24 (2.6%) constituted the lung cancer cases primarily detected in the Moltest programme. Thus, in $PLCO_{m2012}$, LLP and Bach models the proportions of screen-detected lung cancer cases were 98.1%, 53.3% and 22.9%, respectively. **Conclusion:** Risk prediction models provide a vast disparity in selecting lung cancer high-risk individuals. Lung cancer screening enrollment based on Tammemagi's $PLCO_{m2012}$ risk prediction model is superior over LLP, Bach models and standard selection criteria based on age and pack-years.

Keywords: lung cancer screening, risk prediction model, low-dose computed tomography

P1.11-09 RISK OF SECOND PRIMARY MALIGNANCY AFTER NON-SMALL-CELL LUNG CANCER: A COMPETING RISK NOMOGRAM BASED ON THE SEER DATABASE

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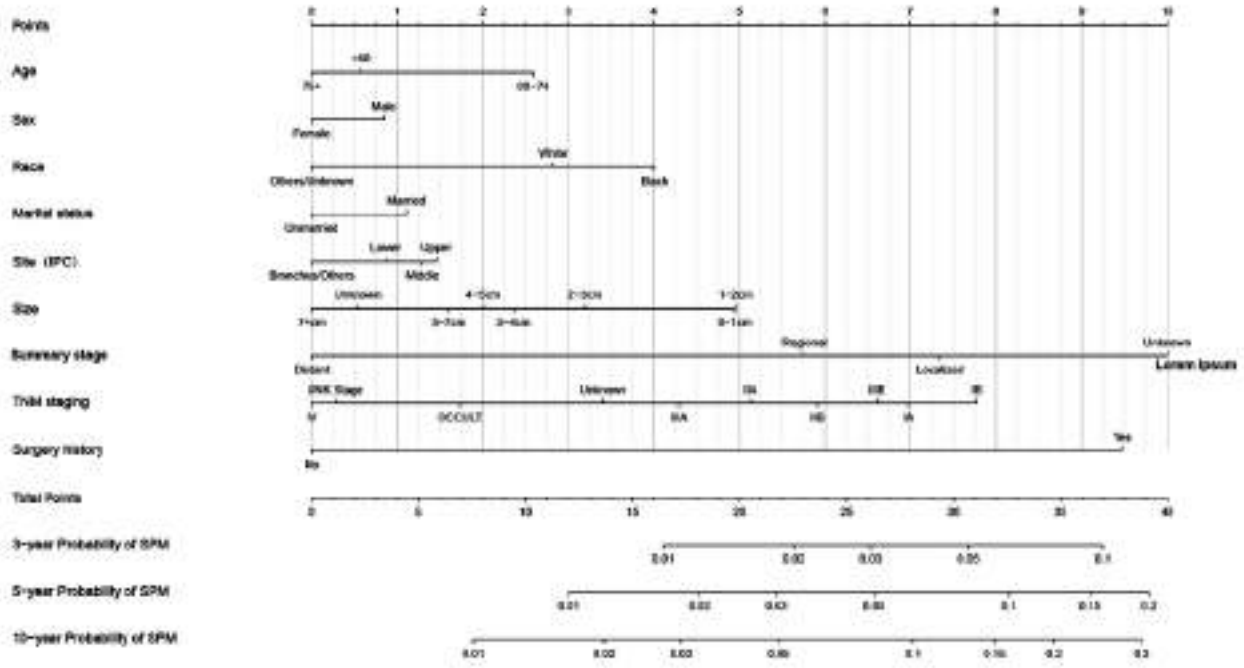
Background: With the improvement of survival for non-small-cell lung cancer (NSCLC), research focused on second primary malignancy (SPM) in NSCLC survivors is becoming urgent. This study aimed to estimate the incidence and risk of SPM in NSCLC patients. **Method:** We retrospectively analysed 78,175 NSCLC patients diagnosed between 2004 and 2010 in SEER database, with 3,161 (4.04%) SPM cases observed. We firstly evaluated the crude and cumulative incidence of SPM. SPM incidence in NSCLC survivors compared to that in the age-specific reference population was calculated as standardized incidence ratio (SIR). A competing risk nomogram was also built, to predict the risk of SPM. **Result:** The crude and 10-year cumulative incidences of SPM were 4.04% and 5.05% (95% CI 4.87%-5.25%), respectively, while the SIR was 1.62 (95% CI 1.56-1.68). Initial primary cancer (IPC) diagnosed when aged 60-74 years old, male, black people, being married, IPC in the upper lobe and indicators of better prognosis of IPC were risk factors of SPM after the initial primary NSCLC. A competing risk nomogram was built for the prediction of SPM after the initial primary NSCLC. (Fig. 1) The nomogram was well calibrated and had good discriminative ability, with c-index of 0.80. It showed a significantly wide interval of SPM cumulative incidence between the first and tenth-decile according to the risk model (1.04% vs. 16.70%, p<0.05). The decision curve analysis indicated that the clinical net benefit of the risk model was larger than that in other scenarios (all-screening or no-screening) in a range of threshold probabilities (1% to 20%).



Conclusion: Our study firstly performed a systematic estimation of the incidence of SPM in NSCLC, which implied the necessity of a risk predicting model. We developed the first competing risk nomogram to predict the risk of SPM, which performed well in the evaluation and might be helpful for individualized SPM screening.

Keywords: Neoplasms, Second Primary, Carcinoma, Non-Small-Cell Lung, SEER Program

POSTERS

P1.11-10 SERUM MICRORNA BIOMARKERS FOR SCREENING OF RESECTABLE LUNG CANCER

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Background: An accurate early screening method for lung cancer would be a powerful tool for decreasing lung cancer–related mortality. Computed tomography (CT) scanning is an effective method for lung cancer screening in high-risk populations. However, screening by CT scan has a limitation of low specificity (61%) for detection of lung cancer, resulting in unnecessary follow-up CT scans or invasive lung biopsies. In this study, we investigated the diagnostic potential of serum microRNAs (miRNAs) for detection of resectable lung cancer. **Method:** Using the 3D-Gene® miRNA Labeling kit and the 3D-Gene® Human miRNA Oligo Chip (Toray Industries), we generated comprehensive miRNA profiles (expression levels of 2588 miRNAs) from 3744 serum samples obtained from 1566 patients with resectable lung cancer and 2178 participants with no cancer. We created a reliable diagnostic model for resectable lung cancer based on the combined expression levels of two miRNAs in the discovery set (208 lung cancer patients, 208 non-cancer participants). We then confirmed the diagnostic performance of the model in the validation set (1358 lung cancer patients, 1970 non-cancer participants). **Result:** The combination of miR-A and miR-B yielded the best discrimination in the discovery set (AUC, 99.3; sensitivity, 99.0%; specificity, 99.0%). We then confirmed the diagnostic performance of the model in the validation set, and showed that the model was accurate (AUC, 0.973; sensitivity, 95.0%; specificity, 99.0%). According to univariable logistic regression analysis, the odds ratio of the diagnostic model for the presence of lung cancer was 21.76 (95% confidence interval [CI], 15.98–29.63). The diagnostic index exhibited high performance for all pathological stages (IA, 96.1%; IB, 93.7%; IIA, 97.3%; IIB, 96.7%; IIIA, 90.2%; IIIB, 83.3%; IV, 100%), and histological types (adenocarcinoma, 95.1%; squamous cell carcinoma, 94.2%; small-cell lung cancer, 90.9%). **Conclusion:** A comprehensive analysis of serum levels of 2588 miRNAs in 1566 patients with lung cancer and 2178 non-cancer participants identified a combination of two miRNAs that could reliably detect resectable lung cancer. This study was the largest of its kind performed to date, and the results confirm that evaluation of serum miRNAs is an effective method for detection of resectable lung cancer. The high sensitivity and specificity of this screening model could help to decrease lung cancer–related mortality, as well as the number of unnecessary follow-up CT scans and invasive lung biopsies.

Keywords: Screening, microRNA, Lung cancer

P1.11-11 INITIAL DISCOVERY OF EXHALED SMALL POLAR ENERGETICS-RELATED METABOLITES BY GC-MS FOR LUNG CANCER RISK ASSESSMENT

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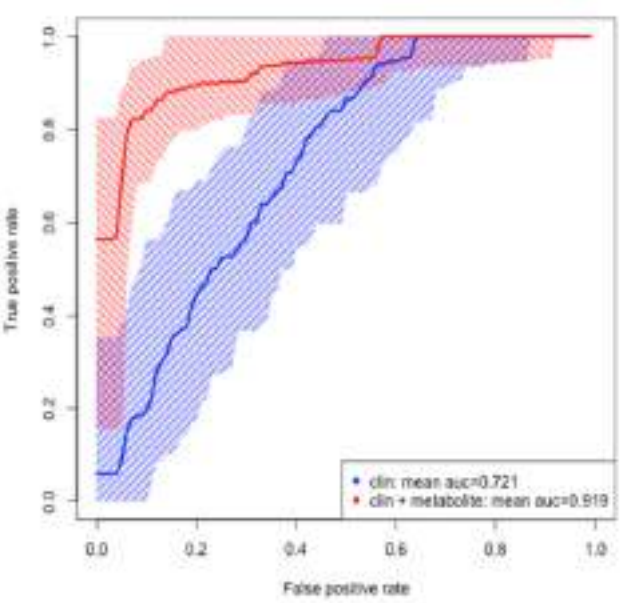
Background: There is a need for non-invasive airway-based biomarkers in lung carcinogenesis for both risk assessment, and earlier diagnosis. Exhaled breath condensate (EBC) contains airway lining fluid molecules, including small molecules of polar and non-polar lipid origin, presumably in part from epithelial cellular origins. Here we pilot a GC-MS strategy for measurement of small, polar molecules in exhaled breath condensate in EBC from lung cancer patients and controls. **Method:** Exhaled breath condensate (EBC) was collected non-invasively, using a handheld device (RTube) in ambulatory subjects engaged/recruited/consented through our pulmonary and thoracic surgery practices, under IRB protocol. A volume of 50 ul of EBC samples were combined with 200uL of methanol, containing 2 internal standards, 1nmol U13_succinate, 5nmol U13_citrate. Then, the samples were vortexed and 240 µl of supernatant was transferred to a sampling vial. The samples were dried under gentle nitrogen flow and derivatized with a two-step derivatization procedure, including a methoxyamine step for 90 minutes, and a silylation step for 60 minutes. QC sample was run multiple times during the analysis. The samples were analyzed by gas chromatography time-of-flight mass spectrometry (GC-TOFMS premier, Waters, USA). **Result:** A number of 282 variables were detected after alignment and excluding any known artificial peaks, 49 of them were annotated. The data was normalized to the intensity of the sum of all the metabolites. The data set was then imported into SIMCA-p software (Umeå, Sweden) for multivariate analysis. A multivariate case-control ROC discriminant analysis compared the clinical model (AUC 0.72) to clinical plus exhaled small polar discriminant metabolites combined (AUC 0.92), showed incremental discrimination attributable to these metabolites (p=2.22e-62).



ROC comparing clinical model (AUC 0.72) to clinical model plus metabolites (AUC 0.92); the difference attributable to metabolites was significant (p=2.22e-62). **Conclusion:** This exhaled biomarker platform can yield case-control discriminant small polar molecule sets related to known metabolic pathways, some of which are known to be deranged in cancers. Once further distilled and validated, our goal is to apply this non-invasive biomarker approach to prospective cohorts for non-invasive lung cancer risk assessment of the at-risk epithelium, in order to better select higher risk individuals to undergo effective CT screening. Supported by NIH-R21 CA192168-01; DoD-CDMRP- LC150738, NIH-NCI P60DK020541.

Keywords: metabolomics, exhale breath, lung cancer risk

P1.11-12 GENETIC LANDSCAPE AND IMMUNE MICROENVIRONMENT FEATURES IN RECURRENCE IN STAGE IA OF LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma (LUAD) leads to majority of lung cancer deaths. Various somatic mutations and copy number variations have been reported in LUAD, but their relevance to clinical prognosis of early stage LUAD is poorly understood. Besides, nearly 30% of patients with stage IA NSCLC eventually die of recurrence or metastasis in spite of the use of standard staging procedures. This study was designed to explore the genomic landscape in stage IA LUAD patients and find immune microenvironment features in recurrences. **Method:** 43 eligible stage IA LUAD patients with radical surgery and without adjuvant therapy from Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College were included in this study. Up to last follow-up in April 9th, 2018, 22 patients were relapsed and 21 were not recurrent. Clinical data were collected in the baseline data analysis. Whole-exome sequencing

and RNA IO panel sequencing were performed in tumor and normal lung tissues. **Result:** There were no significant differences in terms of clinical and pathological features comparing recurrences to non-recurrences. The most common mutated genes were TP53(48%), EGFR (18%) and KRAS (9%). Tumor mutation burden (TMB) values ranged from 0.2 to 16.4 Mutations/Mb, with a median of 2.5Mutations/Mb. Twenty-two differential genes were screened out and classified to five signatures in terms of its function. These five signatures including tumor cell proliferation, tumor antigen, cytotoxic T cells activity, T lymphocyte chemotactic factor, and natural killer cell activation were dramatically high expressed in non-recurrences ($p<0.05$). Besides, cytolytic activity was significantly higher in non-recurrences ($p<0.05$), which were represented as the log-average expression of GZMA and PRF1. Furthermore, six genes out of twenty-two genes were found to be significantly important in terms of disease-free survival (DFS) in stage IA LUAD with radical resection according to Kaplan-Meier analysis. However, there was no relation between TMB and DFS ($p=0.501$). **Conclusion:** This is the first study reporting the relation of gene landscape and immune microenvironment features with prognosis in stage IA LUAD after curative resection. Host immunity is significantly related with the recurrence, whereas tumor mutation and TMB were not. Six genes related with host immunity have been found and promised to be novel prognostic factors in prognosis of stage IA LUAD.

Keywords: Immune microenvironment features, Recurrence, Stage IA of Lung Adenocarcinoma

P1.11-13 MASS SPECTROMETRY PROTEOMICS ANALYSIS DISCOVERS BIOMARKERS IN SERUM MONTHS TO YEARS BEFORE NON-SMALL CELL LUNG CANCER: THE HUNT STUDY

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Background: The high incidence and high mortality rate of non-small cell lung cancer (NSCLC) calls for identification of methods for early diagnosis. Early diagnosis is key for effective treatment and thereby increasing survival. Searching of cancer-related proteins and proteins signature in biofluids is an emerging approach in early diagnostic of malignancies. In the present study we have used proteomics-based profiling of serum collected 2 months to 5 years before NSCLC diagnosis to search for early diagnostic biomarkers. **Method:** All serum samples in this study were obtained from the Nord-Trøndelag Health Study (HUNT) Research Centre's Biobank. *Discovery sample set (Cohort I):* Serum samples from 24 individuals that subsequently developed NSCLC (adenocarcinoma n=12, squamous cell carcinoma n=12) and 24 matched controls were obtained. *Validation sample set (Cohort II):* Serum samples from 10 future NSCLC patients (adenocarcinoma n=5, squamous cell carcinoma n=5) and 10 matched controls were obtained. The serum samples in both cohorts were collected in a time frame of 2 months to 5 years before diagnosis. All controls included were matched to the cases for smoking status (pack years and quit time), gender and age, and were cancer-free at least 5 years before blood sampling. All subjects were smokers or ex-smokers. Twenty (20) µl of serum was depleted of its high-abundant proteins and the cleaned-up peptides were analysed by LC- MS with an Orbitrap Elite mass spectrometer. Data were processed/analysed using MaxQuant software. Using Cohort I as training set, proteins most related to diagnosis were identified at first with limma univariate analysis. Reference and equivalent signatures were identified using JADbio with SES as feature selection algorithm. The JADbio matched pipeline with 50 repetitions for performance assessment (AUC with 95% CI) was used. On the basis of the top differentially expressed proteins by limma, pathway analysis was performed on Ingenuity Pathway Analysis (IPA) software using p-value threshold of 0.05 and abs log2 fold change 0.5. **Result:** In the serum samples of Cohort I, a three-protein signature (AUC=0.692 [CI 0.515-0.748]) was detected where one protein was validated in Cohort II. The pathway analysis identified the pathways catecholamine biosynthesis ($p=0.00278$), phenylethylamine degradation I ($p=0.00278$) and LXR/RXR Activation ($p=0.00312$) as the top three most enriched pathways. **Conclusion:** Proteomic analysis indicated that differential levels of a few proteins in serum may help detecting NSCLC 2 months to 5 years prior to clinical diagnosis. On the basis of the top differentially expressed proteins according to limma, IPA detected biologically relevant pathways. This is one of the first large-scale proteomics screening studies of pre-diagnostic serum of future NSCLC patients. Further validation studies are in progress.

Keywords: early detection, proteomic

P1.11-14 SGLT2 IS A DIAGNOSTIC AND THERAPEUTIC TARGET FOR EARLY-STAGE LUNG ADENOCARCINOMA

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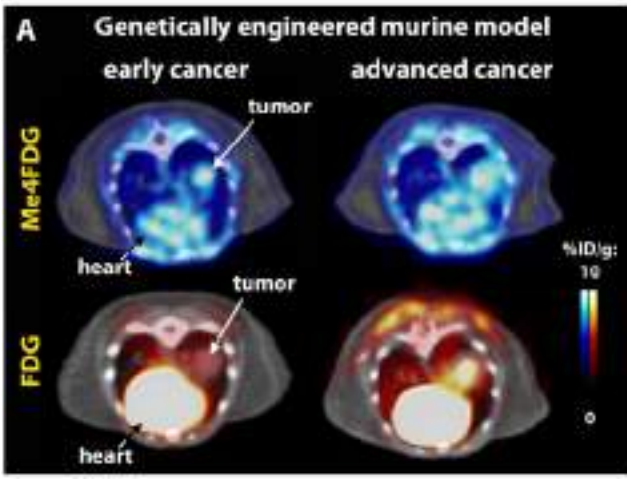
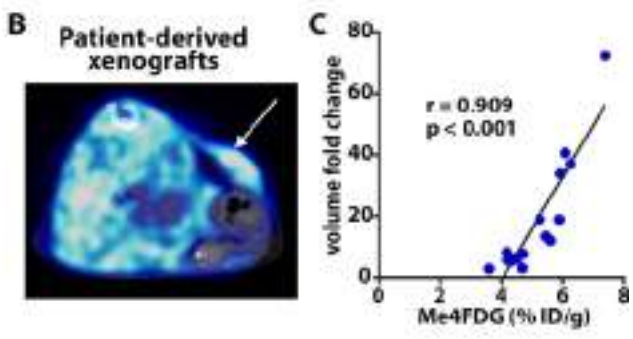
Background: Early diagnosis of lung adenocarcinoma (LUAD) is crucial. The National Lung Screening Trial showed a 20% reduction in lung cancer mortality in high risk individuals using low-dose helical computed tomography (CT). CT is highly sensitive for detecting lung nodules, but is limited by low specificity, especially for LUAD. On CT, LUAD may appear as solid or subsolid nodules. Most subsolid nodules are not cancer, and many will remain stable or resolve; however, subsolid lesions can represent premalignancy or adenocarcinoma in situ. These lesions in the early spectrum of LUAD may persist for months to years before transforming into invasive disease. As a result, current standard of care is to follow these patients with CT imaging to monitor these indeterminate lesions for radiologic signs of malignant progression. The identification of novel biomarkers to predict the malignant potential of these nodules at their initial identification is of paramount importance. **Method:** We have recently discovered that premalignant ad early invasive lesions of the LUAD spectrum rely on sodium-glucose transporter 2 (SGLT2) for glucose uptake, whereas advanced carcinomas up-regulate transporters of the GLUT family. This is consistent with the observation that positron emission tomography (PET) with 2-[^{18}F] fluorodeoxyglucose (FDG), which detects GLUT but not SGLT activity, is a standard tool for staging advanced disease, but has low sensitivity for early-stage LUAD. We measured SGLT2 activity in vivo with the PET tracer methyl-4-[^{18}F] fluorodeoxyglucose (Me4FDG). **Result:** Me4FDG detects early-stage, FDG-negative LUAD in mouse models and in patients. Importantly, Me4FDG uptake correlates with tumor growth rate in patient-derived LUAD xenografts (fig. 1). Targeting SGLT2 with FDA-approved inhibitors significantly reduces tumor growth and prolongs survival in genetic and patient-derived murine models, confirming an important role of SGLT2 in early-stage LUAD. Fig. 1. Me4FDG PET detects early lung adenocarcinoma and predicts growth rate. A) Time course of Me4FDG and FDG imaging in genetically engineered mice with LUAD. The early time point was taken when tumor nodules reached an average diameter of 7 mm (left panels), and the advanced time point was performed on the same mice 1 month later (right panels). B) Representative image of Me4FDG PET/CT imaging in mice carrying patient-derived LUAD xenografts. C) Correlation between Me4FDG uptake in the patient-derived xenografts and the fold increase in volume in a 1-month period following the PET/CT scan.





Conclusion: SGLT2 is a promising biomarker not only to diagnose early-stage tumors by PET imaging, but also to predict response to SGLT2 inhibitors.

Keywords: lung adenocarcinoma, glucose transporter, PET imaging

P1.11-15 FEASIBILITY OF A LUNG HEALTH CLINIC FOR EARLY LUNG CANCER IDENTIFICATION IN HIGH-RISK INDIVIDUALS IN SOUTH-EAST LONDON

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Background: Lung cancer screening (LCS) using low-dose CT (LDCT) reduces mortality amongst high-risk individuals in clinical trial settings. However LCS uptake remains low, especially amongst currently smoking and socioeconomically deprived individuals. It is suggested that an invitation to a lung health clinic (LHC) to holistically approach lung health in a positive manner, in addition to LCS, could increase uptake. In Southeast London, where no LCS programme exists, the feasibility of this approach is unknown, and requires quantification to inform strategic decisions on early lung cancer detection. We aimed to evaluate the uptake of LDCT when offered as part of an LHC, in patients aged 55-80 who are current or former smokers (quit within the last 15 years) in our socioeconomically deprived region in London. **Method:** A prospective cohort feasibility study used a targeted approach for scaled recruitment, identifying participants broadly meeting the criteria for age and smoking status through primary care case-finding in two deprived boroughs in South-east London (Lambeth and Soutwark). Opportunistic referrals from pharmacies, respiratory clinic, and smoking cessation clinics were also accepted. Potentially eligible high-risk (Liverpool Lung Prediction v2 lung cancer risk estimate of ≥5% over 5 years) participants were invited to an LHC assessment and offered spirometric assessment, smoking cessation referral, and same-day chest x-ray (CXR) and LDCT. Participants who declined the invitation were asked to indicate this negative engagement. LDCT interpretation by two thoracic radiologists using volumetric assessment and computer-aided detection (CAD) where possible were performed. Nodules were managed according to a protocol based on British Thoracic Society recommendations. Additional findings potentially impacting cardiothoracic health (e.g. coronary calcification) along with specific recommendations for action were communicated to the participant and their primary care physician. All participants are being followed up for a period of 12 months. We assessed the proportion of the target population eligible and recruited to the lung health clinic, the proportion accepting smoking cessation, and the number of lung cancers detected thus far. **Result:** 15,227 individuals aged 55-80 years were approached using GP case-finding. 2,949 (19.4%) engaged with the study, 2,352 responded positively (79.8% of all responders, 15.4% of total invited) and 597 negatively (20.2% of responders). No referrals from pharmacy, respiratory clinic or smoking cessation clinics were received. Following eligibility assessment, 373 participants were recruited (15.9% of positive responders, 2.4% of total invited). 10 participants had confirmed lung cancer (2.8% of total recruited), 4 at baseline and 6 at follow-up thus far. 30 (8.0%) participants accepted a smoking cessation referral, with 20 (5.4%) actually accessing the service. **Conclusion:** GP case-finding recruitment to a lung health clinic can feasibly engage high risk participants to potentially identify early lung cancer in deprived areas of South East London. However, more work is required to increase positive engagement and smoking cessation uptake which are vital to the long-term success of such efforts. The non-utilisation of alternative opportunistic referral routes suggests there may be barriers to using such routes, or that these routes require active pursuit, rather than just awareness, to drive engagement from them.

Keywords: Screening, lungcancer, low dose computed tomography

P1.11-16 SQUAMOUS CELL LUNG CANCER RISK IS ASSOCIATED WITH RARE, PATHOGENIC GERMLINE VARIANTS IN BRCA2 AND FANCONI ANEMIA GENES

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Background: Lung cancer is the leading cause of cancer deaths worldwide. Patients have substantial better prognosis in early stage as opposed to late state disease. Identifying genetic factors for lung squamous carcinoma (SqCC) risk will enable their use in risk stratification, and personalized intensive surveillance, early detection, and prevention strategies for high-risk individuals. **Method:** In this study, we analyzed whole-exome sequencing datasets of 318 cases and 814 controls (discovery cohort) and then validated our findings in an independent cohort of 444 patients and 3,479 controls (validation cohort), all of European descent, totaling a combined cohort of 765 cases and 4,344 controls. We focused on rare pathogenic variants found in the ClinVar database and used penalized logistic regression to identify genes in which such variants are enriched in cases as compared to the controls. We performed these analyses both at gene and biologically linked gene set levels. All statistical tests were two-sided. **Result:** At gene level, consistent with previous studies, we observed an overall enrichement of rare, deleterious germline variants in *BRCA2* (joint OR=3.2, *p*=8.7e-08, 95% CI=2.1–4.7). Notably, at gene-set level, we observed an overall enrichment of rare, deleterious germline variants in *Fanconi Anemia* genes in cases with SqCC (joint analysis OR=3.08, *p*=1.4e-09, 95% confidence interval [CI]=2.2-4.3). More importantly, rare deleterious germline variants were enriched in *Fanconi Anemia* genes even without the *BRCA2* rs11571833 variant that is strongly enriched in lung SqCC cases (joint OR=2.76, *p*=7.0e-04, 95% CI=1.6-4.7). **Conclusion:** Overall, the findings in this study increase our understanding of SqCC predisposition, and warrant the inclusion of all *FA* genes in current *targeted* gene sequencing studies offered in the clinic that gather data on many patients (e.g. MSK-IMPACT panel). Targeted sequencing can be performed in much larger patient cohorts due to their relatively lower price when compared to exome sequencing. Such studies will support the development of a multi-gene genetic diagnostic test that identifies high-risk individuals. Studies in other cancers have shown that high-risk individuals can benefit from personalized precision medicine based surveillance programs (frequent screening for *BRCA* risk mutation carriers in breast and ovarian cancers), as well as chemoprevention options (daily dose of aspirin for colorectal cancer) in both the affected individuals and their families. While current surveillance options for SqCC with low-dose CT scanning may be risky for individuals with *FA* variants, high-risk individuals will then greatly benefit from the development of intensive surveillance and early detection approaches.

Keywords: germline risk, Genomics, squamous lung cancer

P1.11-17 OSTEOPOROSIS, CORONARY ARTERY CALCIFICATION, AND COPD IN A LUNG CANCER SCREENING COHORT

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Background: The US Preventative Services Task Force recommends annual lung cancer screening with low-dose CT scans in adults aged 55-80 who are current smokers (or have quit within the past 15 years) with a >30 pack-years history. The advent of lung cancer screening programs provides an opportunity to assess the resultant CT scans for signs of smoking-related diseases other than lung-cancer. We aimed assess the prevalence of Chronic Obstructive Pulmonary Disease

(COPD), coronary artery calcification, and osteoporosis within a lung cancer screening cohort. **Method:** We recruited subjects from the National Jewish Health Lung Cancer Screening (LCS) Program. In addition to the LCS CT-scan, participants completed a DXA scan, spirometry, a sit-to-stand test, and reported their medical history. Participants were classified by GOLD (Global Initiative for Chronic Obstructive Lung Disease) spirometry grade to correlate lung function, and co-morbid disease. **Result:** One hundred and thirty-five subjects participated in the study (68 males, 67 females). Mean age was 64.0 (5.8) years, and 32.6% were current smokers. 51% of the cohort had moderate to severe COPD (GOLD 2 or greater). While those who were GOLD 3 or 4 had all been previously diagnosed with COPD, 34% of those classified as GOLD 2 and 85% of GOLD 1 participants had not been previously diagnosed. Undiagnosed coronary artery disease (CAD) was common in the population. Eighty-three percent of those with CAC scores over 1000 did not report a prior diagnosis of CAD. Osteoporosis, or its precursor osteopenia, is present in a large proportion of the LCS cohort. The prevalence of osteoporotic disease increases with increasing COPD severity. Thirty-seven percent of GOLD 3 participants, and 44% of GOLD 4 participants have a Z-score of less than -2.5 (osteoporosis). Osteopenia (Z-score<-1.0) is more common, seen in 100% of GOLD 4 participants, 68% of GOLD 3 participants, 56% of GOLD 2 participants, 27% of GOLD 1, 65% of normal spirometry (GOLD 0), and 32% of PRISm participants. Increasing spirometric disease was associated with reduced physical function as measured by the sit-to-stand test and the SF-36 physical score. **Conclusion:** Patients enrolled in LCS programs often have disease other than lung cancer that may be detected using a low-dose chest CT scan. Clinicians should consider using these CT scans to screen for osteoporosis and coronary artery disease. Given the prevalence of undiagnosed COPD in LCS patients, further research should investigate a potential benefit of screening these patients for COPD using spirometry.

Keyword: screening, osteoporosis, comorbidities

P1.11-18 THE RESULTS OF MANDATORY SMOKING CESSATION INTERVENTION IN A POPULATION-BASED LUNG CANCER SCREENING TRIAL

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Background: A large strand of research supports the idea of implementing a population-based lung cancer screening program using low-dose computer tomography to reduce lung cancer mortality. It has been recognized that one of the key factors contributing a successful lung screening program is its combination with smoking cessation intervention. This study provides results of smoking cessation intervention in a population-based lung cancer screening trial. **Method:** Korean Lung Cancer Screening Project (K-LUCAS) is a single arm prospective nationwide lung cancer screening trial. In K-LUCAS, all currently smoking participants were provided with mandatory smoking cessation counselling. Smoking status of 5,144 currently smoking participants in K-LUCAS were surveyed by telephone 6 months after participation. There were some variations in the intervention; the department of which counselling is provided within; publically or privately operated smoking clinics; and whether or not counselling is provided simultaneously with screening results. The impact of such variations on smoking cessation is also reported. **Result:** Participant's motivation to quit smoking increased by 9.4% on average after participating in lung cancer screening. The smoking cessation rate was 24.7% and over 80% of quitters said that participation in lung cancer screening motivated them to quit smoking. The smoking cessation counselling was more effective when the smoking clinics are operated by national health insurance services than when operated privately by hospital and when counselling was provided simultaneously with screening results than when provided separately with screening results. The screening results itself also affected smoking cessation. The probability of quitting smoking for participants with positive screening results were significantly higher than participants with negative results. **Conclusion:** Smoking cessation intervention combined with lung cancer screening program encourages smoking cessation for screening participants. Our results the highlights the importance of incorporating smoking cessation intervention in lung cancer screening program which would further enhance the effectiveness of lung cancer screening program.

Keywords: Lung cancer, Screening, smoking cessation

P1.11-19 TRIAL IN PROGRESS: CANCER SCREENING STUDY WITH OR WITHOUT LOW DOSE LUNG CT TO VALIDATE A MULTI-CANCER EARLY DETECTION BLOOD TEST

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Background: Few effective screening tests exist for cancer, and each is specific to a single cancer type. A single blood test that directly measures tumor cell-free DNA and can detect several cancer types, including lung, pancreatic, colon, and head & neck cancers, with high specificity may reduce cancer burden. The SUMMIT Study is designed to validate the ability of an investigational blood test to detect multiple cancer types among a high-risk population undergoing LDCT for lung cancer screening, as well as in a lower risk population. **Method:** SUMMIT is designed to enroll 50,000 participants aged 50-77, and will follow participants for up to 10 years via medical records and the national cancer registry. There will be two groups: Group A (n=25,000), individuals at high-risk for lung and other cancers due to substantial smoking history (per United States Preventive Services Task Force LDCT screening criteria, or PLCOm2012 six-year risk estimate of ≥1.3%); and Group B (n=25,000), individuals not meeting Group A criteria. Exclusion criteria include active cancer treatments. Potential participants are identified from the records of 540 general practices across North Central and East London, and are invited by letter to attend a dedicated LDCT scanning unit (Group A) or clinical unit (Group B), where eligibility is confirmed and consent obtained. Group A participants will provide a blood sample, complete a questionnaire, and receive a baseline LDCT, and then provide a blood sample and complete a questionnaire at 12 and 24 months post-baseline. Those with a negative baseline LDCT (without lung nodules) will be randomised to either have a LDCT at 12 and 24 months or no further scans. Participants with lung nodules at baseline could have more frequent scans. Group B participants complete a questionnaire and provide a blood sample at three study appointments (baseline, 12 months, 24 months). The primary endpoint is cancer incidence and stage. Blood test performance will be determined by sensitivity and false-positive rates (specificity). Blood test results will not be returned to physicians or participants. Group A enrollment began in April 2019, and Group B enrollment is targeted to start later in 2019. The study is designed to determine the performance and cost-effectiveness of this investigational multi-cancer blood test compared to or combined with LDCT for identifying lung cancer, and in detecting cancers for which there are no effective screening tests. The SUMMIT Study may therefore inform new approaches to finding cancer early. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Screening, cell-free DNA, Next-generation sequencing

P1.11-20 IDENTIFICATION OF A THIRTEEN-GENE PROGNOSTIC SIGNATURE FOR LUNG ADENOCARCINOMA

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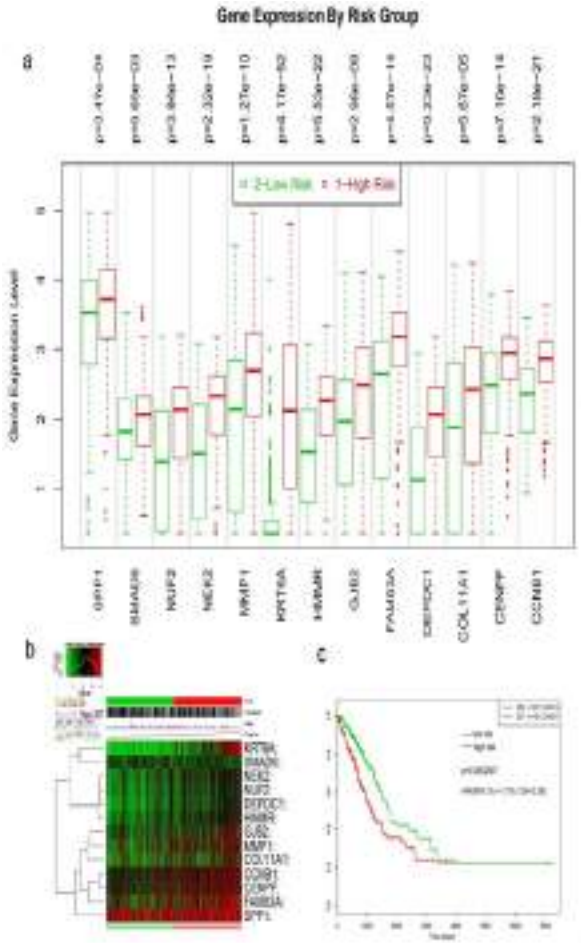
Background: The incidence of lung adenocarcinoma has gradually surpassed that of lung squamous cell carcinoma. It is especially important for the diagnosis and treatment of lung adenocarcinoma. Therefore, we used the GEO and TCGA databases to assess the integration of several gene signatures and clinical stages associated with survival. **Method:** RNA sequencing was performed on LUAD-affected tissues and paired with non-cancerous tissue samples, and the intersection of differentially expressed genes was obtained using the Gene Expression Omnibus datasets GSE117370 and GSE19188, and a protein-protein interaction network was constructed to obtain the hub genes. Then corresponding overall survival information of LUAD patients from The Cancer Genome Atlas project-LUAD were included in the present study. An analysis of the Kyoto Encyclopedia of Genes and Genomes database and Gene Ontology were carried out to study the signature mechanism. **Result:** In this study, we identified thirteen candidate genes (SPP1, SMAD6, NUF2, NEK2, MMP1, KRT6A, HMMR, GJB2, FAM83A, DEPDC1, COL11A1, CENPF, CCNB1) closely related to survival in LUAD. A linear prognostic model of the eight genes was constructed and weighted by the regression coefficient (β) from the multivariate Cox regression analysis of The Cancer Genome Atlas-LUAD cohort to divide patients into low- and high-risk groups. The prognostic ability of the signature was validated in LUAD patients at our hospital. Patients assigned to the high-risk group exhibited poor overall survival compared to patients in the low-risk group. Finally, functional enrichment analysis showed that cell division played a vital role in the development of LUAD.



Notes: *a. Box plots of expression differences of the eight-gene signature in low (green) and high (red) risk groups of TCGA-LUAD patients. X-axis, gene expression value of each gene; above the box plot, P-values of the expression difference between risk groups. b. Heatmap shows that the gene expression of the 13 genes associated with survival at risk score, with red representing high expression and green representing low expression. c. Kaplan-Meier survival plots showing that high expression of the eight-gene signatures is associated with poor survival in TCGA-LUAD patients. Abbreviations: TCGA, The Cancer Genome Atlas; LUAD, lung adenocarcinoma; HR, hazard ratio; CI, concordance index.*

Conclusion: Our results highlighted a mRNA signature including thirteen genes, which may serve as a potential prognostic marker of LUAD.

Keywords: prognosis, lung adenocarcinoma, signature

P1.11-21 LIVERPOOL HEALTH LUNG PROJECT: SIGNIFICANT INCIDENTAL FINDINGS IN A SMOKER-PREDOMINANT COHORT

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Background: The Liverpool Healthy Lung Project (LHLP) is a prospective screening cohort which recruits ever-smokers or subjects with COPD aged 58-75 with a lung cancer risk of ≥5% in 5 years by the LLP_{v2} model. It aims to identify lung cancers at a treatable stage. On chest computed tomography scans, it is common to detect incidental findings with the frequency ranging 36% - 55%, but most of them are minor findings requiring no further management. Thus, it is presumed to be cost-effective if the most significant incidental findings are managed as appropriate in lung cancer screening programmes. **Method:** In the LHLP, radiologists alert a significant incidental finding (SIF, not relevant to suspicious lung cancer or indeterminate lung nodule) in the radiological reports if the Radiologist considers an urgent intervention is required; it's referred to a specialist or general practitioner outside the project. This paper reviewed the alerted reports with SIFs and followed up their final diagnosis and corresponding interventions in three hospital clinical databases. **Result:** Among a total of 3336 eligible participants who have completed the baseline scans during Apr 2016 - Feb 2019, 124 SIFs have been identified in 122 individuals (3.7%). The most frequently reported SIFs at baseline are possible extra-pulmonary cancers (45 of 124, 36.3%), followed by lung infections (39 of 124, 31.5%) which often need (post-antibiotic) follow-up to confirm resolution. Nine extra-pulmonary malignancies (7.4% in SIFs, 0.3% in the LHLP) have been pathologically or radiologically confirmed, including 5 lymphomas/leukaemias (4.1%), 2 renal cancers (1.6%), 1 breast cancers (0.8%) and 1 liver metastasis with unknown origin (0.8%). Two lymphoma/leukaemia patients have been treated with chemotherapy and/or radiotherapy, and the other three are currently under active monitoring. Both of the two renal cancer patients have undergone laterally radical nephrectomy, without recurrence in 6 and 20 months after surgery, respectively. The remaining two established cancer patients are still under further investigation. Other common SIFs included 14 interstitial lung diseases (11.3%), three of which have progressed during a post-baseline follow-up time of 6 months - 2 years, and 10 aneurysms/dilated aortas (8.0%), of which two patients have undergone surgical repair and another one has commenced a preventive therapy of statin and anti-plate agent. **Conclusion:** Identification by radiology of these SIFs in 3.7% of our screened population facilitates urgent clinical review, and appropriate management of these important, but unexpected findings.

Keywords: lung cancer screening, significant incidental findings

P1.11-22 LUNG CANCER GROWTH: IMPACT OF DIFFERENT ASSUMPTIONS

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Background: The purpose of this study is to determine which of two models, exponential or linear best approximates growth of lung cancer so as to predict when follow up CT exams should be obtained when a nodule is found. **Method:** We reviewed our database of documented lung biopsies and identified those cases where the diagnosis of lung cancer in a solid nodule was confirmed and there were a total of three scans. Volume doubling times (VDTs) were calculated based on the first two scans using either the exponential method or the radial method and the third time point was used to determine which model best fit the actual result. We also allowed for measurement error to be considered based on the QIBA small nodule profile. **Result:** We identified 100 cases that met the inclusion

criteria. All were adenocarcinomas. On the first scan, the median nodule size was 8.2mm [Interquartile range(IQR):6.0-11.8)]. The median time between scans was 133.5 days (IQR:77.5-202 days) for the first and second scans, 75 days (IQR: 31.5-186.0 days) between second and third scans and 242.0 days (IQR: 131.5-424.0 days) between first and third scans. Median VDT from the first two scans was 139.0 days (IQR: 73.8-365.1 days). Using the calculated VDT from the first two scans, we found that 94 of the 100 cases had the third scan within 3 VDTs as estimated from the two scans. For these 94 cases, when accounting for the QIBA error measurements, both the linear or exponential models are plausible. For the 6 cases where the time interval between the second and third scan was longer, the exponential model provided a better fit for two, the linear model was better for two, and for the remaining two cases, it was not clear which model provided the better fit. **Conclusion:** When considering the short time intervals typically used in obtaining follow-up CT scans for small pulmonary nodules, we found that it had minimal impact in predicting the ultimate size of the nodule as measurement error could account for results using either method. It was only after at least 3 doubling times that the potential impact of choice of method becomes apparent as with the exponential method the doubling time remains constant while with the radial method the doubling time increases with increasing size and therefore overall growth substantially decreases with longer time interval.There remains uncertainty in terms of how nodules grow, whether it is only along the advancing edge or by all cells doubling. This has little impact clinically in terms of short term follow up. However, when considering situations where there may be long delays between CT scans such as moving the interval for screening from 1 year to 2 years, it has a very large impact.

Keywords: tumor growth models, exponential growth, linear radial growth

P1.11-23 THE IMPACT OF THE FAMILY HISTORY OF DIFFERENT CANCERS ON LUNG CANCER

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Background: The definition of the high-risk population of lung cancer screening remains controversial. People with a family history of lung cancer will have a distinctly increase risk of lung cancer, but the influence of family history of other cancers it is still unclear. **Method:** We performed a case-control study to compare the exposure of different cancer family history between lung cancer and other cancers. All cancer patients who were hospitalized in our center between 2007 and 2018 were included and records of each patient's family history were retrieved. Logistic regression analysis was conducted after excluding the patients with a family history of non-lung cancer who had diagnosed the corresponding system cancer. **Result:** This study enrolled 23,977 cancer patients including 15,120 lung cancer and 8,857 non-lung cancer. Lung cancer patients had a higher exposure to a family history of lung cancer compared with non-lung cancer patients(OR=2.418, P< 0.001), and had a potential higher exposure to the patients with the family history of pancreatic cancer(OR=1.769,P=0.597)and kidney cancer(OR=1.326,P=0.596) without statistical difference. Sex had no significantly impact on the association between cancer family history and lung cancer risk (interaction P >0.05).

Table1

Family history of cancer	OR	95%CI for Exp (B)	p-value
lung cancer	**2.418**	1.789-3.269	**0.000**
esophagus cancer	0.479	0.198-1.156	0.101
ovarian cancer	0.245	0.045-1.336	0.104
stomach cancer	0.562	0.271-1.167	0.122
breast cancer	0.693	0.331-1.452	0.331
Nasopharynx cancer	0.740	0.379-1.446	0.378
cervical cancer	0.489	0.069-3.474	0.475
prostatic cancer	0.552	0.078-3.921	0.553
liver cancer	0.835	0.432-1.614	0.592
kidney cancer	**1.326**	0.467-3.765	**0.596**
pancreatic cancer	**1.769**	0.213-14.700	**0.597**
colorectal cancer	0.938	0.476-1.848	0.853
bladder cancer	0.967	0.283-3.303	0.957

Conclusion: Patients with a family history of lung cancer should be considered a high-risk population for lung cancer screening, whereas there is no strong evidence to support that family history of other cancer will influence the risk of lung cancer. More researches are required to determine the relationship between lung cancer risk and family history of pancreatic and kidney cancers.

Keywords: family history of cancer, Lung cancer, risk

P1.11-24 IMPLEMENTATION OF AN ORGANIZED LUNG CANCER SCREENING PROGRAM IN KOREA

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Background: Lung cancer is the leading cause of cancer mortality worldwide and has a low survival rate due to difficulties concerning early detection. The Korean Lung Cancer Screening demonstration project (K-LUCAS) was started in February 2017. K-LUCAS will assess the effectiveness, harm, and feasibility of lung cancer screening in order to implement a population-based screening program. K-LUCAS will evaluate the validation of the new standard of reporting form of low-dose computed tomography (LDCT) and the quality of lung cancer screening by a web-based network system using computer-aided nodule detection program (CAD). **Method:** K-LUCAS is a population-based single arm trial conducted in 14 cancer hospitals that targets a high-risk population aged 55-74 years with at least 30 pack-year smoking history within the last 15 years from Feb. 2017 to Dec. 2018. Participants were recruited when visiting the national cancer screening centers or smoking cessation clinics based on a lung cancer risk evaluation questionnaire. Lung cancer screening was provided by LDCT with at least a 16-row multidetector CT scanner and screening results were reported by Lung Imaging Reporting and Data System (Lung-RADS). All participants should have their results explained to them by a physician and current smokers should receive smoking cessation counselling. **Result:** Total 13,692 participants had joined K-LUCAS. The positive screening rate (categories 3 and 4 in Lung-RADS) was 15.3%. Among them, 78 lung cancers were detected. Stage I and II lung cancers among confirmed lung cancer cases were 52.8% and 15.3%, respectively. CAD detects more positive findings but decreases the variation of positive rate among screening units. About 75% of abnormal findings, including emphysema, coronary artery calcification etc. besides lung nodules, were detected in K-LUCAS. Psychological anxiety level for lung cancer was decreased after screening than before. Over 70% of currently smoking participant's motivation to quit smoking was increased after counselling about lung cancer screening results. **Conclusion:** K-LUCAS shows promising results in effective detection of early stage lung cancer and controlling diagnosis quality by a web-based network system. Based on the observations from K-LUCAS, a decision will be made as to whether lung cancer screening will be included in national cancer screening program.

Keywords: Korea, Lung cancer, Screening

P1.11-25 ADJUSTMENT FOR LEAD-TIME BIAS AND OVER-DIAGNOSIS IN LUNG CANCER SCREENING

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Background: To develop an empirical method for adjustment of lead-time bias and over-diagnosis in lung cancer screening. **Method:** From 2002-2017, 113,151 nationwide lung cancer patients stratified by pathology and stage were matched by age, sex, calendar year, and comorbidities with 1,131,170 referents selected from general population. Loss-of-life expectancy (LE) was calculated as the difference between the life expectancy of patients and that of matched referents, which could be multiplied by the pathology- and stage-shifting in screening to adjust for lead-time bias. Cases without loss-of-life expectancy would be considered as over-diagnosis. **Result:** The life expectancies of bronchioloalveolar carcinoma (BAC) and stage IV non-squamous-cell lung cancer (non-SqCC) were 19.3 and 1.8 years, respectively, with a difference of 17.5 years (=19.3-1.8, as shown on the Figure). However, if we took different age, sex, and year of diagnosis into consideration

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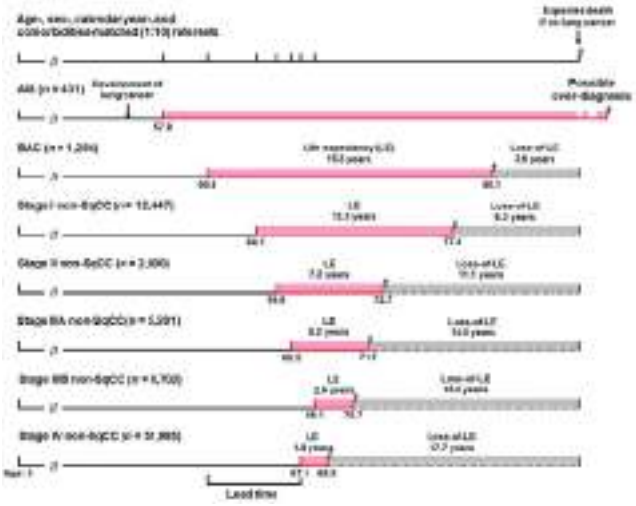
and compared the loss-of-life expectancies, the difference would be lowered down to 14.1 (=17.7-3.6) years, which implies a correction of lead time. Patients with adenocarcinoma in situ (AIS), BAC, and stage IA non-SqCC, had 18%, 9%, and 4% probabilities without loss-of-life expectancy, or, over-diagnosis.



Conclusion: Counting difference in loss-of-life expectancies could adjust for lead-time bias. The likelihoods of over-diagnosis appear modest and could possibly occur in cases with AIS, BAC, and stage IA non-SqCC.

Keywords: lead-time bias, over-diagnosis, lung cancer screening

P1.11-26 THE EPIDEMIOLOGY OF GROUND GLASS OPACITY (GGO) LUNG ADENOCARCINOMA: A NETWORK BASED CUMULATIVE META-ANALYSIS

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Background: An increasing number of early-stage NSCLC with ground glass opacity (GGO) have been detected with lung cancer screening. GGO lung cancer is considered as a low-grade adenocarcinoma with noninvasive or minimally invasive growth patterns. The long term survival for GGO lung cancer is very much better compared to the solid counterparts. In this study, we investigate the epidemiological data of GGO lung cancer and outline the variation tendency through cumulative meta-analysis. **Method:** Two individual researchers conducted the platform searches on the PubMed, Cochrane Library and Embase from the inception dates to Dec. 1st, 2018. For counting data, such as number of female and non-smoking patients, the single rate is determined along with the corresponding 95% confidence interval (CI). For measurement data, such as average diagnosis age of patients, the single mean value is determined along with the corresponding 95% confidence interval (CI). We performed cumulative meta-analysis and metatrend analysis for the epidemiology data. Data analyses was performed using the Stata version 13.0 (Stata Corp LLC, College Station, Texas, USA). **Result:** A meta-analysis from a total of 50 articles with 8565 GGO patients between 1977 and 2018 showed that the rate of female GGO lung cancer was 0.62. The average age of all GGO lung cancer patients was 62.10 and the cumulative meta-analysis showed the average age has been decreasing from 66.40 to 59.06 which variation tendency was statistically significant (p<0.05). From 21 articles included smoking status of 4262 GGO lung cancers, it showed that the total rate for non-smoking patients was 0.72 and there was a significant increasing tendency (0.65 to 0.79, p<0.05). **Conclusion:** Our analysis indicates that there are much more GGO lung cancers in females compared to males. In recent years, it showed the average age of GGO lung cancer patients has been declined prominently while the non-smoking rate significantly increased. This investigation has challenged the current criteria of lung cancer screening which excludes a huge population of younger and non- or light-smoking patients who may have GGO lung cancers. Further study has to set up a more refined model which contributes to detect early stage NSCLC with GGO manifestation, which would significantly decrease the mortality of lung cancer.

Keyword: ground glass opacity (GGO), lung adenocarcinoma, cumulative meta-analysis

P1.11-27 COMPUTED TOMOGRAPHY SCREENING FOR EARLY LUNG CANCER, COPD AND CARDIOVASCULAR DISEASE IN SHANGHAI: RATIONALE AND DESIGN OF A POPULATION-BASED COMPARATIVE STUDY

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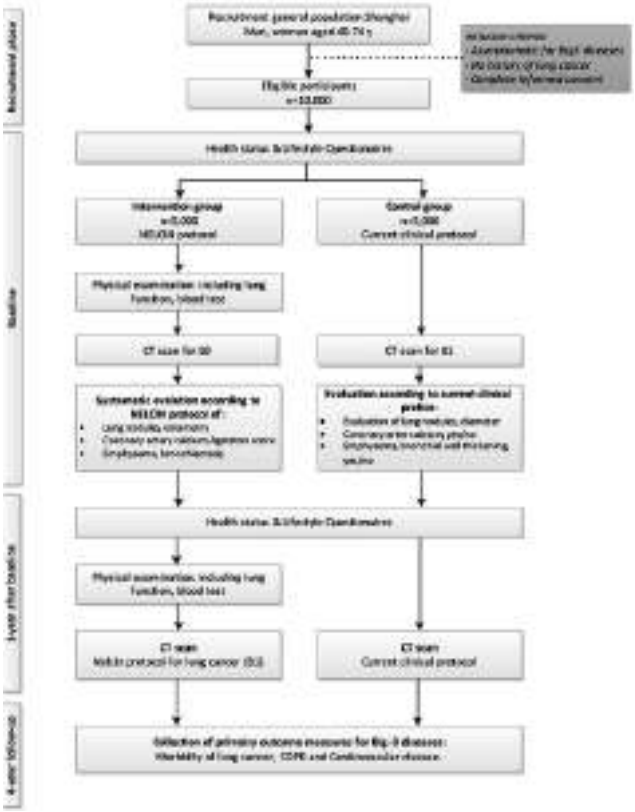
Background: Volume-based management for lung nodules is associated with a lower rate of unnecessary referral for further work up as compared to diameter-based management in European population. Screening for chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD), in addition to lung cancer, may significantly increase the benefits of lung cancer low-dose computed tomography (CT) screening. While this is unclear in Chinese population. The aim of this study is to assess the diagnostic performance of volume-based lung nodule management for lung cancer CT screening as compared to diameter-based management, and to improve the effectiveness of CT screening for COPD and CVD based on quantitative measurement of CT imaging biomarkers in a Chinese screening setting. **Method:** A comparative population-based study is ongoing, that will include 10,000 asymptomatic participants between 40 and 74 years old from Shanghai urban population in China. Participants will be randomized into the intervention and control groups and will undergo a low-dose chest CT scan at baseline and one year after baseline. NELCIN-B3 protocol will be applied in the intervention group. It recommends management of detected solid and part-solid lung nodules based on the volume and volume doubling time (VDT) of a lung nodule. The imaging biomarkers for COPD and CVD, such as emphysema score, bronchial wall thickness from inspiratory and expiratory chest CT scan, and coronary calcium score from ECG-triggered cardiac CT scan will be evaluated. In addition data on laboratory parameters and lung function test will be collected. The participants in the control group will be managed according to the standard hospital protocol based on visual assessment of the CT images. It recommends management of detected lung nodules based on the diameter according to the NCCN Clinical Practice Guideline in Oncology for Lung Cancer Screening. Epidemiological data (eg., risk factors) will be collected through questionnaires for all participants. Four years after the initial assessment the incidence of the three diseases will be evaluated. The design is shown in Figure 1.



Result: The unnecessary referral rate will be compared between the NELCIN-B3 and standard protocol for early detected lung nodules management. The effectiveness of quantitative measurement of CT imaging biomarkers for early detection of lung cancer, COPD and CVD will be evaluated. **Conclusion:** We expect that the quantitative assessment of the CT imaging biomarkers will reduce the number of unnecessary referrals for early detected lung nodules and improve the early detection of COPD and CVD in Chinese urban populations.

Keywords: chronic obstructive pulmonary disease, computed tomography screening, Lung cancer

P1.11-28 LUNG CANCER: SUSCEPTIBILITY AND SURVIVAL DIFFERENCES FOR WOMEN AND MEN

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Background: To determine the lung cancer susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer for women and men in the International Early Lung Cancer Program (I-ELCAP). **Method:** We used the prospective I-ELCAP cohort of asymptomatic men and women to identify all who were 40 years and older, had smoked at least 5 pack-years, and had low-dose CT screening in I-ELCAP between 1992 and 2018 at participating institutions in two continents, North America or Europe. Logistic regression models were used to calculate the odds ratio (OR) for lung cancer in women compared to men, adjusting for age, smoking history, and location. To account for time from baseline to lung cancer diagnosis, hazard ratio (HR) using Cox proportional hazards models were calculated for lung-cancer-specific mortality in women and men, conditioned on age, smoking history, disease stage, histology, whether resection was performed, and continent (NA or Europe). Interaction between sex and location was also evaluated. **Result:** Of the 23,438 women, 18,451 were in North America, 4987 in Europe. Of the 31,365 men, 18,451 in North America, 22,812 in Europe. Lung cancer was diagnosed in 475 women and 509 men; in NA, frequency was significantly higher in women (2.2% vs. 1.5%, p<0.0001) while in Europe, it was significantly lower (1.4% vs. 2.0%, p =0.007). As the interaction between sex and continent was significant (p<0.0001), separate multiple logistic regression analyses were performed which showed sex to be a significant independent predictor of lung cancer in North America (OR_{women}=1.7, 95% CI:1.4-2.0), but not in Europe (OR_{women}=0.8, 95% CI: 0.6-1.1). Median follow-up time of the 742 and 242 lung cancer patients in North America and Europe was 89.8 months and 67.0 months, respectively. Lung cancer deaths occurred less frequently in women than in men in North America [NA: 47/406 (11.6%) vs. 59/336 (17.6%)] and in Europe [3/69 (4.4%) vs. 17/173 (9.8%)]. In North America, the risk of death was significantly lower for women (unadjusted HR_{women} = 0.6, 95% CI: 0.4-0.9), but no longer significant when adjusted for other covariates. In Europe, unadjusted HR_{women} = 0.44 (95% CI: 0.13-1.50) was not significant. **Conclusion:** Women appear to have an increased susceptibility to tobacco carcinogens in NA but not in Europe. In both continents, however, rates of fatal outcome from lung cancer were slightly, but not significantly lower for women.

Keywords: Screening, lung cancer risk, gender differences

P1.11-29 RELATIONSHIP BETWEEN LUNG CANCER SCREENING CENTERS IN THE UNITED STATES AND HIGH-RISK INDIVIDUALS

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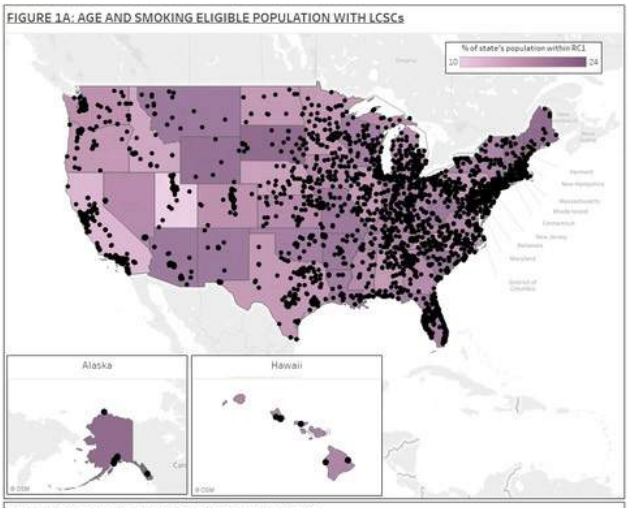
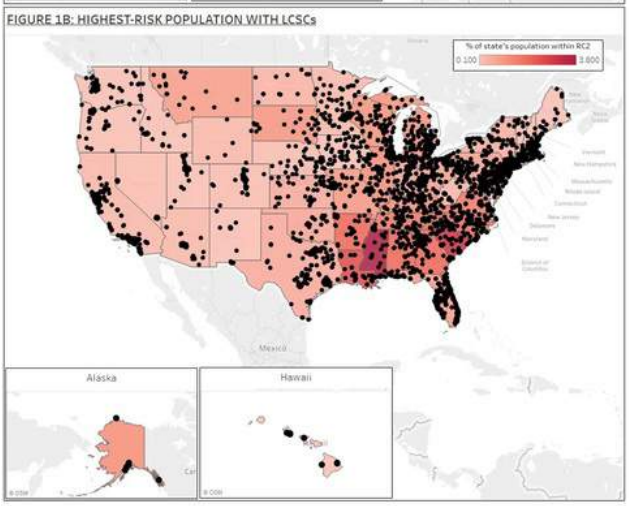
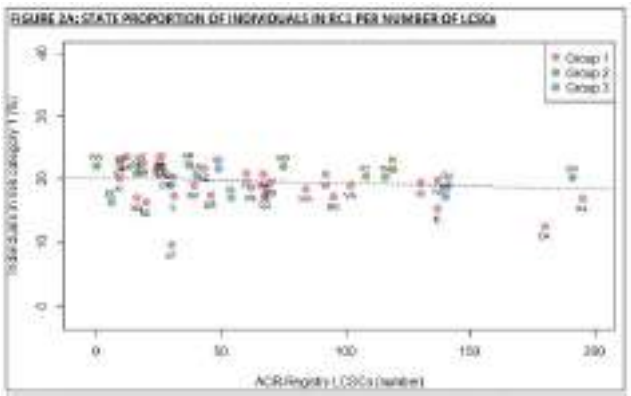
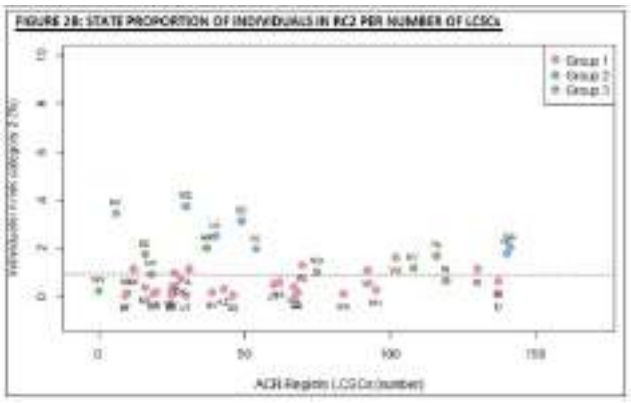
Background: Lung cancer screening center (LCSC) numbers are increasing. The location of LCSCs relative to the geographic distribution of the highest-risk lung cancer populations has not been determined. We aimed to determine the distribution of at-risk populations, and their geographic relationship to LCSCs registered with the American College of Radiology (ACR). **Method:** Population statistics datasets were obtained from the 2016 American Community Survey and Behavior Risk Factor Surveillance System. Due to differences between the two datasets, weighting and propensity matching was performed to obtain a weighted population of 477,665 individuals matched by age/race/education/income with merged smoking data. The proportion of the state population at-risk for lung cancer was calculated by two Risk Categories - RC1: 55-77 years/current-former smoker; and RC2: 55-77 years/current-former smoker/<=high school/income<$35,000/African American-American Indian. These were mapped and the 3,910 ACR-registry LCSCs superimposed. Pearson Correlation Coefficient (PCC) between at-risk populations and number of LCSCs per state was calculated. A cluster analysis based on risk characteristics categorized states into three risk groups: G1–baseline, G2 - >RC1 individuals, G3 - >RC2 individuals. Rural-Urban Continuum Codes determined metropolitan/non-metropolitan/rural status. **Result:** The national distribution of RC1 and RC2 individuals in relation to LCSCs shown in figure 1. There was no correlation between the proportion of at-risk populations and number of LCSCs [PCC for RC1=-0.23; PCC for RC2=-0.03]. Although clustering identified states with significantly different risk groups, there was no difference in the number LCSCs between the groups [median(IQR) G1=60(70), G2=75(103), G3=49(110); p=0.684] (figure 2). Of the LCSCs, 83% (3,245) were in metropolitan counties, 12% (469) in non-metropolitan and 5% (196) in rural.









Conclusion: LCSCs are not evenly distributed at the national/state/county level. There is also no significant correlation between the proportion of at-risk populations and LCSCs, even though some states have higher proportions of at-risk populations. The distribution of LCSCs may be important to LCS access.

Keyword: Lung cancer screening, High-risk populations, National Distribution

P1.11-30 VERY RAPID GROWTH OF SMALL PULMONARY NODULES PREDICTS BENIGNITY

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Background: Growth of pulmonary nodules on repeat CT is used to identify malignant lesions, although very rapid growth is thought to imply an inflammatory process. Few data exist examining the optimum threshold at which rate of growth predicts a benign aetiology. **Method:** Using an institutional CT database of small (<15mm) solid pulmonary nodules (n=784), we identified patients with antecedent (≥30 days prior) thin section (≤2mm) CT imaging and a final diagnosis of primary lung malignancy or a definite benign diagnosis based on pathology or longitudinal CT follow up data (n=137). Enlarging nodules (volume growth >25%) were identified (n=63) using semi-automated volumetry, and the volume doubling time (VDT) calculated. In cases where no nodule existed on the antecedent CT, a volume of 5mm^3 was assigned, permitting the calculation of a 'virtual' VDT. Comparison of volume doubling time between benign and malignant nodules was made using Wilcoxon signed rank test. A receiver operator curve was constructed, and the optimum threshold of nodule growth rate predictive of benignity was calculated using the methods of Miller. **Result:** The final study population consisted of 63 nodules in 57 patients [32/62 (50.8%) malignant, median age 67 years (range 34–85 years), male = 30/57 (52.6%)]. There was no difference in patient age nor in smoking status between groups, although patients with malignant diagnoses significantly more likely to be female (p < 0.001). The median time between baseline (T1) and antecedent (T0) scans was 260 days (interquartile range 343 days). At baseline (T1), benign lesions (median diameter 10mm, median volume 380 mm^3, range 10-4300mm^3) were significantly smaller than malignant nodules (median diameter 13mm, median volume 890mm^3, range 60-4250 mm^3); p = 0.001. 24/31 benign lesions and 3/32 malignant lesions were not visible on the T0 scan, and were assigned a volume of 5mm^3. The median benign lesion VDT was 70 days (interquartile range 270 days), malignant median VDT was 188 days (interquartile range 170 days); p = 0.2. The majority of lesions with very rapid growth (VDT < 90 days) were benign diagnoses (n= 17/24 [70.8%]). When examining these rapidly growing nodules, the optimal cut-point of the receiver-operator was a VDT of 50 days, AUC = 0.735. This provided 100% specificity for benign disease. **Conclusion:** Our results confirm that very rapid nodule growth predicts benignity; a VDT of <50 days was 100% specific for benignity. Further work is required to validate these findings in other cohorts.

Keywords: Volume Doubling Time, Small pulmonary nodules, Rapid growth

P1.11-31 UNDERSTANDING REFERRAL PATTERNS IN A LUNG CANCER SCREENING PROGRAM

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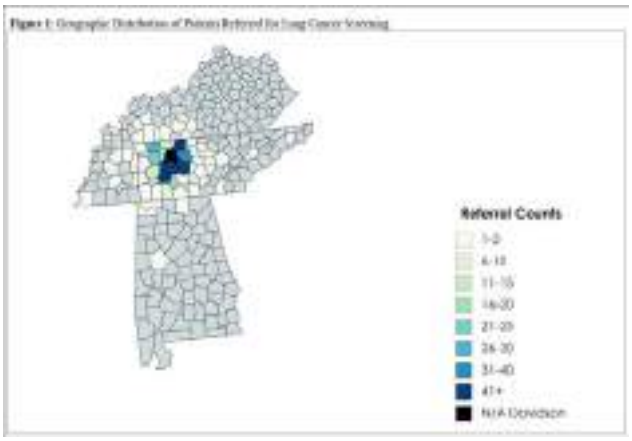
Background: Lung cancer screening (LCS) provides an important way to reduce the morbidity and mortality of lung cancer, however, the uptake of LCS has remained strikingly low, which has been attributed to both patient and provider level factors. We examined referring clinician and patient characteristics to direct interventions to promote LCS. **Method:** We examined the sociodemographic and geophysical characteristics of patients and their initial referring providers at a single institution LCS program from 1/1/2015-7/15/2018. Using data from the clinical record, we geocoded patients, generated maps, and estimated area deprivation indices, a proportional estimate of community socioeconomic status incorporating education, employment and poverty, at the census track level. We performed descriptive analysis of patient level factors such as race, insurance status, and their distribution across referring providers. **Result:** 1085 unique individuals—909 (84.0%) whites, 143 (13.2%) blacks, and 30 others (3.7%) were referred for LCS by 268 unique providers with 36 cancers detected. Approximately half (137) of providers referred one only individual and 27(10.1%) referred 52% of the patients screened. Primary care providers consisted of 76.4% of referrers, followed by pulmonologists (7.6%) and oncologists (5.3%). 211 referrers (78.7%) were affiliated with our institution. Referral of non-white patients was uniformly distributed among 170 referring providers. Referrals were geographically clustered in counties neighboring the hospital (Figure 1). Average area deprivation was 0.347 with a broad range (0.0770-0.838), with no difference between whites and blacks (0.345 vs 0.354, p=0.482), despite higher PLCO model estimated risk in blacks(7.1 vs 4.9, p<0.001).



Conclusion: A small number of physicians referred the majority of patients for LCS, however the distribution of minorities was nearly uniform across referrers. We demonstrate broad knowledge of LCS by the large number of referrers, in spite of low referral volume by most providers. These results are guiding ongoing initiatives to improve the overall uptake of LCS by targeted provider communication and community education strategies.

Keywords: lung cancer screening, underrepresented minorities, outreach initiative

POSTERS

P1.11-32 THE UKLS NODULE RISK MODEL (UKLS-NRM): UTILISING NODULE VOLUMETRY

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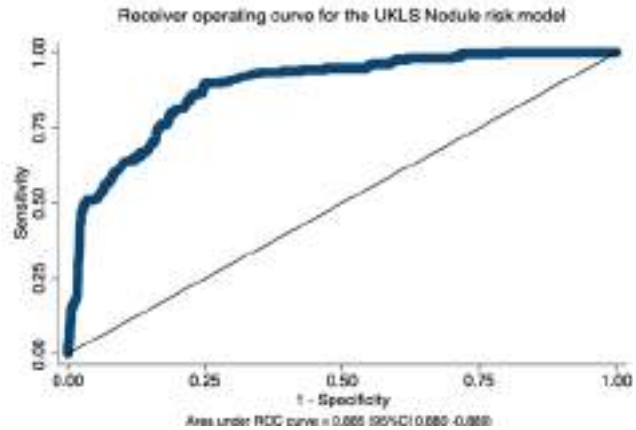
Background: Estimating the clinical probability of malignancy in patients with pulmonary nodules will facilitate early diagnosis, determine optimum patient management strategies and reduce overall costs. Currently there are two risk prediction models, which are recommended by BTS; the Brock University model, for nodules ≥300mm^3 or ≥8mm diameter, and where the risk is estimated at >10%, the Herder model after PET-CT. However, none of these models employ volumetry and all were developed for use at baseline **Method:** The UK Lung Cancer Screening (UKLS) trial data were analysed, utilising multivariable logistic regression models to identify independent predictors and develop a parsimonious model to estimate the probability of lung cancer in lung nodules detected at baseline, three month and twelve months repeat screening. **Result:**



1994 UKLS participants had a CT scan; 1013 had a total of 5063 lung nodules and 52 (2.6%) developed lung cancer during a 4 year median follow-up. Covariates that predict lung cancer included: female gender, asthma, bronchitis, asbestos exposure, history of previous cancer, early and late onset of family history of lung cancer, smoking duration, forced vital capacity, nodule type and volume. The final model had excellent discrimination; area under the receiver-operating characteristic curve (AUC [95% CI] = 0.885 [0.880 to 0.889]). Internal validation indicated that the model will discriminate well when applied to new data (optimism-corrected AUC = 0.882 [0.848-.907]). The risk model had a good calibration (goodness-of-fit χ 8.13, P = 0.42). **Conclusion:** The UKLS Nodule Risk Model (UKLS-NRM) estimates the probability of lung cancer in nodules detected at baseline, three months and twelve months from baseline. The model is based on readily available, strong, and plausible covariates that have been implicated in the aetiology of lung cancer. The application of UKLS-NRM has the potential to be used in both the research and clinical setting.

Keyword: Lung Cancer Screening: nodule risk model; volumetric analysis

P1.11-33 PROGNOSTIC VALUE OF SYMPTOMS AT LUNG CANCER DIAGNOSIS: A TWO-YEAR OBSERVATIONAL STUDY

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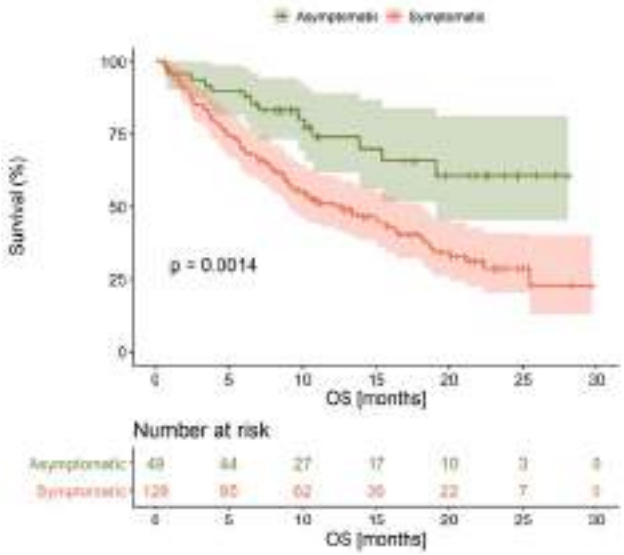
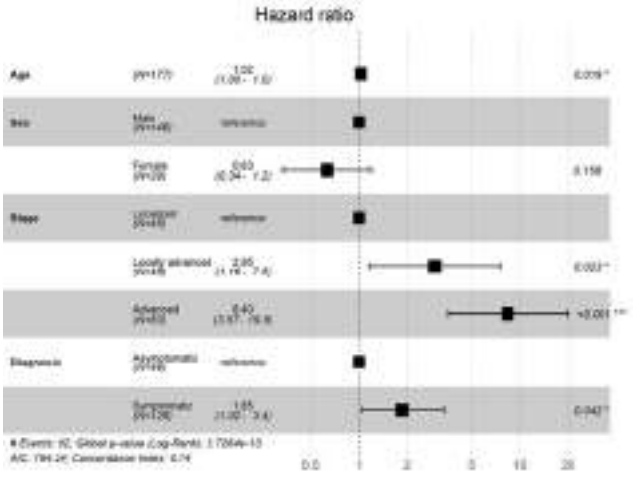
Background: Lung cancer is mainly diagnosed at advanced or locally advanced stages, usually when symptoms become evident. However, sometimes lung cancer may be diagnosed incidentally on chest imaging performed during routine care. Differences in prognosis based on symptomatic state at the time of diagnosis have been partially explored. Our aim was to analyze the prognostic value of the initial symptomatic state in a general lung cancer cohort. **Method:** Longitudinal prospective study including all patients consecutively diagnosed with primary lung cancer between January 2016 and December 2017. Patients were followed up until death or until the end of the study in July 2018. Collected data included clinical, functional, radiological and histological variables. Lung cancer symptom that led to initiation of the diagnostic process was defined as the symptom of presentation. When there were no symptoms at the identification of the lung cancer lesion it was considered an incidental diagnosis. **Result:** 177 patients were analyzed, 83.6% men, with a mean (SD) age at diagnosis of 67.9 (10.8) years. Incidental diagnosis was ascertained in 27.7% of cases. Asymptomatic patients were significantly older, diagnosed with localized stage disease and more frequently underwent surgical treatment. At the end of follow-up period survival was significantly superior in the asymptomatic group, with a 2-year OS of 60.8% versus 28.59% (p<0.001). The median OS of asymptomatic patients was not achieved during the first 24 months of follow-up, while in the symptomatic group, the median OS was 12.2 months (p = 0.0014) (Figure 1)



After performing an adjusted Cox proportional hazard model we obtained a HR (95% CI) of 1.85 (1.02 - 3.4) associated with symptomatic presentation, independent of stage at diagnosis (Figure 2).



Conclusion: Lung cancer patients who are asymptomatic at diagnosis exhibit a significantly better prognosis regardless of the stage of the disease. These findings encourage us to continue further investigations regarding early detection of and screening for lung cancer.

Keyword: Lung cancer; Prognosis; Incidental diagnosis

POSTERS

P1.11-34 THE LIVERPOOL HEALTHY LUNG PROJECT – CHAMPIONING THE IMPORTANCE OF LUNG HEALTH

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Background: Liverpool has high levels of deprivation and one of the highest rates of respiratory morbidity in England with double the incidence of lung cancer, most prevalent in the lower socioeconomic groups. To tackle this health inequality, in February 2016 in partnership with Liverpool CCG, Liverpool University, and primary care, we embarked on the 4-year Liverpool Healthy Lung Project. **Method:** Based on primary care records, individuals aged 58-75 with COPD, a history of smoking or asbestos exposure were invited to a face-to-face lung health check conducted by an experienced respiratory nurse. At this interview positive lifestyle messages were promoted and their 5-year personal lung cancer risk calculated (www.MyLungRisk.org) using the LLPv2 risk model. Those without a diagnosis of COPD underwent spirometry, and those who triggered the 5% threshold lung cancer risk threshold were offered a low dose thoracic CT scan. We now report our results to January 2019. **Result:** 8350 of 21409 (40%) patients invited to the lung health check had attended. Of these, 5501 (59%) underwent spirometry and 10% were diagnosed with COPD. A further 2947 (35%) underwent the CT scan and of these 98 (3.3%) were suspicious of malignancy. Lung cancer was ultimately diagnosed in 55 (1.9%) and 45 of these (81%) were offered radical treatment. Of the remaining 43 patients, 10 underwent an invasive test and there was 1 benign resection. 265 patients (9%) needed repeat scans for lung nodules. **Conclusion:** These early results show that this innovative project is already improving access to respiratory healthcare in a deprived area of Liverpool, has identified new COPD patients, and over time should improve outcomes for lung cancer in this disadvantaged population.

Keyword: Screening, Lung Health

P1.11-35 COMPARISON OF LUNG CANCER SCREENING TRIALS FROM EAST ASIA; SOUTH KOREA, JAPAN, AND TAIWAN

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Background: Lung cancer remains the leading cause of cancer mortality in East Asian countries. Recently, the development of the National Lung Cancer Screening Program with Low Dose Computational Tomography (LDCT) initiated by the Korean Government. To understand the possible barrier and difficulties before implementing the LDCT Lung Cancer Screening for high-risk individuals in Korea, we compared the results of recently conducted Lung Cancer Screening Trial from South Korea, Japan, Taiwan, and the NLST trial in the U.S. **Method:** We analyzed the recently reported data of LDCT based Lung Cancer Screening Trials from Korea (Pilot National Lung Cancer Screening Program in Korea conducted in 2017-2018, reported in 2019), Japan (A population-based cohort study in Hitachi city, Japan, results published in 2018), Taiwan (National Lung Screening Program in Taiwan, reported in 2018). We compared the results with the NLST trial in the U.S. **Result:**

Table 1. Comparison of Lung Cancer Screening trials from three countries from East Asia, South Korea, Japan and Taiwan.

	South Korea	Japan	Taiwan	U.S. (NLST Trial)
Design of Trial	Pilot Single Arm Trial	A population-based cohort study	Prospective single arm	Randomized Clinical Trial
Sample Size	13691	18935	10397	53454
Age (male %)	63 (77)	56 (55)	61 (26.9)	61 (59)
Smoking History	>30 pack -years	Never smoker included (24% Male, 90% in Female)	Never Smoker with one of risk factors (family history, pulmonary tuberculosis or COPD)	>30 pack -years
Screening Interval/Duration	Single Screening	LDCT screening at least once between 1998 and 2006	3 annual screening	3 annual screening
Definition of Positive Results.	>4 mm	Non calcified SPN >5-7 mm	> 6 mm or > 5mm Ground Glass Nodule	>4 mm
Screening Positive Rate (%)	15.3	26.3	Not Available	27.3 (T0)
False Positive rate (%)	14.8	Not Available	Not Avaiable	26.6
Lung cancer Detection Rate (%)	0.56	1.5	2.34	1.03
Early Stage Detection Rate (%)	68.1	Not Available	96.7	67.5
Lung Cancer Mortality RR(95% CI)	Not Available	Not Available	Not Available	0.85 (0.5-0.95)

East Asian Lung Cancer Screening Trials frequently included low-risk smokers or never smokers, along with high-risk smokers. Consequently, the results were very different compared to the NLST trial, in terms of cancer detection rate and positivity rate. Specifically, the cancer detection rate of Korean Trial was low with 0.56%, similar to that of Chest X-ray group in the NLST trial. **Conclusion:** Recently, the Korean government plans to initiate National LDCT Lung Screening. However, to date, no country has established a nationwide organized LDCT lung cancer screening program. Although evidence suggests that LDCT screening trial for lung cancer North American and European results in a favorable, however, the balance of benefit and harms was tenuous. Hasted implementation of the Western trial to Korean could have many difficulties due to low cancer detection rate. The selection of screen-eligible patients, the quality of imaging and image interpretation, the management of screen-detected findings, and the effectiveness of smoking cessation interventions need to be carefully contemplated before implementation of DLDCT screening. Additional research is needed to optimize the approach to low-dose CT screening in Korea.

Keywords: ldct, Lung Screening, East Asia

P1.11-36 A SIMPLE TOOL TO PRIORITIZE US EVER-SMOKERS FOR CT SCREENING ELIGIBILITY ASSESSMENT

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Background: CT lung cancer screening can be more efficient when risk models are used to determine eligibility. However, detailed risk assessment requires time spent by a healthcare provider and may present a barrier to screening when resources are limited. Here, we developed a tool to identify ever-smokers with low probability of risk-based eligibility. **Method:** We analyzed ever-smokers aged 50-80 in the representative 2015 US National Health Interview Survey. We defined ever-smokers with 6-year risk ≥1.3% by the 12-question PLCOm2012 model as screening-eligible. We considered that detailed risk assessment may be inefficient when the probability of eligibility is less than 5%. Accordingly, we used cross-tabulations of age, cigarettes-per-day, and quit-years to identify groups in whom risk assessment might be avoided. **Result:** There are approximately 44,140,774 U.S. ever-smokers aged 50-80 who could consider detailed risk assessment. However, a simple decision-tree tool identified 22,293,477 ever-smokers (50.5%) who are less than 5% likely to be screening-eligible (Figure). This includes all those who smoke(d) less than 5 cigarettes-per-day. Over 1 year, approximately 103,512 lung cancers were predicted among eligible ever-smokers. If our tool were used, then 1,784 of these eligible cases (1.7%) would not undergo detailed risk assessment or screening.

Conclusion: When resources are limited, a simple decision-tree tool could avoid detailed risk assessment for more than half of U.S. ever smokers aged 50-80, while still identifying 98.3% of eligible cases. Such a tool could be self-administered by patients in the waiting room or applied automatically to electronic health records to optimize use of provider time.

Keywords: low-dose CT screening, risk-based screening, screening eligibility

P1.11-37 FACE YOUR FEAR AWARENESS CAMPAIGN

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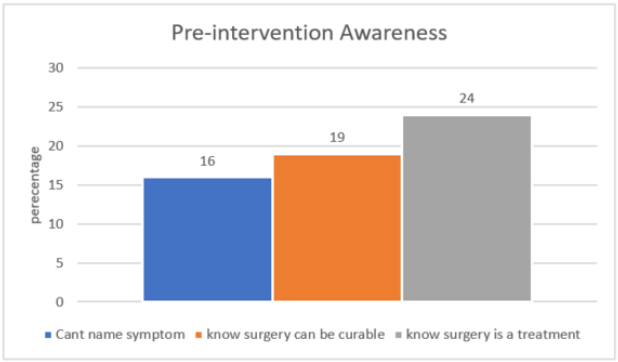
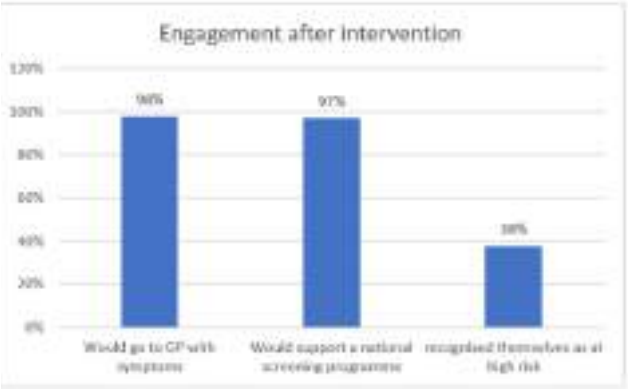
Background: Awareness of lung cancer in the UK is poor. 21% of people could not name a symptom of lung cancer. An Incisive Health study in 2018 indicated that fear stops 1in 4 people going to the doctor with potential cancer symptoms. 1year survival is 37% influenced by late stage at presentation, with 53% diagnosed at stage IV and a further 8% at stage IIIb. The Face your Fear Campaign was a multifaceted digital and community engagement campaign aimed at improving knowledge of symptoms and encouraging earlier presentation, during Awareness Month 2018.This campaign was sponsored by Astra Zeneca UK. **Method:** We filmed case studies featuring patients living well with all stages of lung cancer. We created a virtual reality film highlighting the benefits and consequences of symptom awareness and late stage presentation. A suite of materials, digital and hard copy, including an interactive quiz enabled those at risk to learn more about lung cancer and encourage action. We took an exhibition and VR film to shopping malls across the UK. The roadshow ran in locations with high incidence and poor outcomes. **Result:**

	Pre-intervention
Cant name symptom	16
know surgery can be curable	19
know surgery is a treatment	24



We had over 1.3 million views of our videos. We had an increase in 113% on web traffic and a 234% increase in views of our Signs & Symptoms page compared to the same period in 2017. Our roadshow ran across 11 locations and staff engaged with an average of 18 people per day, reaching 1008 people at risk with direct messages. We distributed over 500 Awareness Packs compared to 287 in 2017.

	After engaging:
Would go to GP with symptoms	98%
Would support a national screening programme	97%
recognised themselves as at high risk	38%



Conclusion: There is a need for accurate, patient centred information on how to diagnose lung cancer early. Public awareness in areas of poor outcomes is poorer than across the country as a whole. Targeted awareness work has a role in generating engagement with health care and increasing early detection.

Keywords: Awareness, diagnosis, Advocacy

POSTERS

P1.11-38 FREQUENCY AND PROGNOSTIC IMPACT OF CONCOMITANT MUTATIONS IN KRAS AND TP53 OR STK11 IN BRAZILIAN LUNG ADENOCARCINOMA PATIENTS

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Background: Previous studies reported that co-occurring genomic alterations in *KRAS* and *STK11/LKB1* or *TP53* tumor suppressor genes define subgroups of *KRAS*-mutant lung adenocarcinomas (LADC) with distinct biology, therapeutic vulnerabilities, and immune profiles. The impact of concomitant *STK11, TP53 and KRAS* mutations in Brazilian lung cancer patients remains poorly explored. Aims: In our preliminary study, we investigated the frequency of *STK11* and *TP53* in *KRAS* mutant or wild-type LADC. *STK11* and *TP53* mutational status was correlated with clinico-pathological characteristics and overall survival (OS). **Method:** This is a retrospective analysis which included 27 consecutive LADC patients treated with platinum-based chemotherapy and/or immunotherapy. Mutational status analysis was performed using the Illumina TruSight Tumor 26™ panel based on multiplex-PCR. This customized multiple genes panel covers 26 critical oncogenes or tumor supressor genes including: exons 2–4 of *KRAS*, exons 1–9 of *STK11* and 1–11 of *TP53,* specifically considered in the current study. Kaplan-Meier method was used to calculate overall survival and the univariate Cox model was used to compare survival. **Result:** Among the 27 patients included, 23 (85%) were *KRAS* mutant (*KRAS*mut), 15 (55.6%) were *TP53* mutant (*TP53*mut) and 5 (18%) harbored a *STK11* mutation (*STK11*mut). From all mutant cases, 10 (37%) were *KRAS*mut only; 4 (14.8%) *TP53*mut only; 2 (7.4%) *KRAS+STK11;* 8 (29.6%) *KRAS+TP53;* 3 (11%) *KRAS+TP53+STK11.* No associations were observed between *KRAS, TP53* and *STK11* status and clinico-pathological variables. OS was shorter for *TP53mut* compared with wild-type patients in Cox univariate analysis (p=0.006). *KRAS* and *STK11* status did not impact OS and progression-free survival. The co-occurrence of *KRAS* and *TP53* mutations appears to have a detrimental effect in OS (p=0.064). **Conclusion:** In this cohort, *KRAS, TP53,* and *STK11* mutations were not associated with clinico-pathological features. *TP53* mutations may identify a more aggressive molecular subtype of LADC.

Keyword: STK11, P53, KRAS, Lung Adenocarcinoma, molecular diagnosis, overall survival

P1.11-39 LOW-DOSE CT LUNG SCREENING: DATA ANALYSIS OF LUNG CANCER PATIENTS WITH ABOVE 40 YEARS OLD

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Background: LDCT lung cancer screening now being implemented in US and some European countries. However, LDCT lung cancer screening is still under consideration in China due to the epidemiological characteristics, medical system and patient compliance. This study aims of 1) to explore the application value of LDCT lung cancer screening in different age groups in China through analysis the data of clinical, pathology and radiology for LDCT participants, 2) to improve the effectiveness of LDCT lung cancer screening. **Method:** 10033 participants had LDCT lung cancer screening in *Cancer Hospital, Chinese Academy of Medical Sciences* were involved and divided into three groups by age (40-49, 50-59 and ≥ 60years old group). The detection rate was calculated for overall and individual groups. Clinical, pathology and radiology data were also collected and analyzed for group differences. **Result:** Lung cancer detection rate: The overall lung cancer detection rate with LDCT was 0.6% (64 cases) and the detection rate for 40-49, 50-59 and ≥60 years old group was 0.4%, 0.6%, 1.2% respectively. The difference of lung cancer detection rate between age groups was significant (*P*=0.001), and increased with age (*P*=0.002). Stage: In 64 lung cancer cases, the proportion of stage I, II, III, IV were 88%,5%, 5%, 2% respectively, with more advanced lung cancers (stage III or IV) were oberserved in ≥60 years old group than other groups(*P*=0.031). Pathological type: Adenocarcinoma was 61 cases (61/64, 95.3%), and squamous-cell carcinoma, small cell carcinoma and carcinoid was 1 case respectively, no significant differences of pathological types were found among three groups (*P*=0.134). Tumor markers: 9 cases had CEA increase (9/53,17.0%), among which 7 cases were in ≥60 years old group (7/24, 29.2%), higher than other age groups, and the difference was statistically significant (P=0.03). In addition, The odds ratio of CEA abnormally increased in ≥60 years old group was 2.059 (95% CI:0.36-11.91) compared with the 40-49 years old group. Other clinical parameters for all age groups showed no significant difference (*P*>0.05).

Table 1 The clinical, pathology and radiology data of lung cancers detected by LDCT

Characteristics	Number of cases
Age group	
40-49 years old group	15 (23.4%)
50-59 years old group	23 (35.9%)
≥60 years old group	26 (40.6%)
Sex	
Male	29 (45.3%)
Female	35 (54.7%)
History of Smoking	
Yes	18 (28.1%)
No	45 (70.3%)
Unknown	1 (1.6%)
History of Secondhand Smoking	
Yes	61 (95.3%)
No	2 (3.1%)
Unknown	1 (1.6%)
Family history of lung cancer	
Yes	15 (23.4%)
No	40 (62.5%)
Unknown	9 (14.1%)
Lung cancer stage	
Stage I	50 (87.7%)
Stage II	3 (5.3%)
Stage III	3 (5.3%)
Stage IV	1 (1.7%)
Histology	
Adenocarcinoma	61 (95.3%)
Squamous-cell carcinoma	1 (1.6%)
Carcinoid tumour	1 (1.6%)
Small-cell carcinoma	1 (1.6%)
Location	
Right lung	39 (60.9%)
Left lung	25 (39.1%)
CT consistency of lung cancer	
Solid	36 (56.3%)
Part-solid	23 (35.9%)
Non-solid	5 (7.8%)

Conclusion: The LDCT lung cancer detection rate increased significantly with age. 40-49years old group detection rate is lower than overall. ≥60years old group had the highest detection rate but stage III or IV patients proportion rised. Thus, we recommended it LDCT lung cancer screening for ≥50 years old to guarantee more early stage lung cancer cases being detected. LDCT lung cancer screening for ≥60years old could combine with CEA. This study detected 88% stage I lung cancers.

Keywords: lung cancer screening, ldct, age

P1.11-40 SYSTEMATIC DEVELOPMENT AND MULTI-COHORT VALIDATION OF A SERUM MIRNA BIOMARKER PANEL FOR DETECTION OF EARLY STAGE NON-SMALL CELL LUNG CANCER

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Background: High mortality from lung cancer is related to the late manifestation of its symptoms. The incidence of non-small cell lung cancer (NSCLC) has been rising over the past several decades. A blood-based biomarker with the ability to detect early stages of NSCLC could significantly improve patient outcomes. Previous attempts have shown promising results of circulating miRNA as potential non-invasive NSCLC biomarker. However, concerns have been raised on several pre-analytical and analytical variables which could confound the performance of these miRNA biomarkers. In this study, we aimed to systematically evaluate and develop a serum miRNA biomarker panel for early detection of NSCLC through a multi-cohort study with well-controlled pre-analytical and analytical parameters. **Method:** This study included a total of 768 NSCLC

and 948 matched control subjects from Singaporean, Chinese and European Cohorts to develop a multi-target miRNA panel. Serum specimen from these subjects were collected and stored with a stringently controlled sample collection and processing protocol that minimized hemolysis, variations in clotting and platelet activation. Using high-throughput, single-plex RT-qPCR, we quantified the absolute expressions of 520 high confidence circulating miRNAs in a discovery cohort of 204 Stage 1 and 2 NSCLC patients, with 220 age, gender, ethnicity and smoking history matched controls. The regulation of candidate miRNA biomarkers in NSCLC patients was then verified in two additional cohorts of 432 Chinese and 218 Caucasians subjects. A panel of miRNA biomarkers was then constructed through multi-variant data analysis. The results were generated with the use of a logistic-regression algorithm. We subsequently validated the performance of this multi-miR panel in three independent Singaporean and Chinese cohorts comprising of 642 Subjects. All participants underwent LDCT independent of the miRNA results. **Result:** Among the 520 high confidence miRNA quantified, 29 were significantly dysregulated in the discovery cohort of 424 subjects. These miRNAs were also found to be scarcely influenced by pre-analytical and analytical variables. We were able to verify the dysregulation of 18 miRNAs in two additional Chinese and Caucasian cohorts and developed a final panel 5-miR biomarkers through a two-fold cross-validation procedure that incorporated a feature selection algorithm and a logistic regression predictive model. This 5-miR panel demonstrated an Area-Under-Curve (AUC) of 0.936 to 0.984 in the discovery cohorts. When validated in the 3 independent cohorts, the 5-miR panel with a fixed algorithm showed AUC of 0.973 (95% CI, 0.950 to 0.986), 0.916 (95% CI, 0.852 to 0.949), and 0.911 (95% CI, 0.822 to 0.963) respectively. We estimated an overall sensitivity of 81.3% (95% CI, 78.2% to 84.1%) at a specificity of 90.7% (95% CI, 88.3% to 92.8%) in the 3 validation cohorts. **Conclusion:** We have systematically evaluated the absolute expression of circulating miRNAs in NSCLC patients and matched controls of both Asian and Caucasian ethnicity. We developed a 5-miR serum miRNA panel that is minimally confounded by pre-analytical and analytical factors and validated its performance in 3 independent cohorts. These biomarkers have the potential to be a useful, non-invasive assay for early detection of NSCLC.

Keywords: blood biomarker, microRNA, early detection

P1.11-41 THE IMPLEMENTATION OF THE LUNG-RADS ™ IN PILOT SILESIAN STUDY WITH LDCT - AN OPPORTUNITY FOR BETTER CONTROL OF OVERDIAGNOSIS

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Background: A high percentage of false positive results observed in lung cancer screening (LCS) studies with LDCT was the reason for the modification of radiological assesement methods. Originally, all non-calcified nodules with a dimension ≥ 4 mm were considered as positive, whereas the implementation of the Lung-RADS ™ recommends additional testing only for nodules ≥ 6 mm in categories 3 and 4. This allowed for the reduction of false positive results and avoiding the effect of "overdiagnosis" (unnecessary interventions). **Method:** We retrospectively analyzed 601 of first round LDCT scans, performed in 2010-2012 in asymptomatic volunteers of Pilot Silesian Study of Early Lung Cancer Detection with Low-Dose CT, with a smoking history of at least 20 pack-years, who actively smoked tobacco or quit smoking in the last 15 years. The analysis of non-invasive (additional examinations with contrast CT) and invasive interventions (bronchoscopy, EBUS, biopsies, surgery) done in screening participants was performed, followed by assessment of nodules according to the Lung-RADS ™ system, grouping them to 2, 3, 4A and 4B categories. Then the percentage of interventions that could be avoided using the ACR LungRADS ™ criteria was estimated. **Result:** In total, 1016 nodules of solid, partial-solid and non-solid morphology were identified in 265 participants. In the entire screening cohort 87 interventions were performed, including 58 (66.6%) non-invasive and 29 (33.3%) invasive. Among nodules belonging to category 4A and B, 8 invasive lung cancers were identified, 1lung cancer was overlooked (false negative) and in 1 case metastases from colorectal cancer were diagnosed. With the using of LungRADS ™ criteria, 34.4% of non-invasive and 8% of invasive interventions in categories 2 and 3 could be avoided. **Conclusion:** The LungRADS ACR classification system proved to be a practical tool for assessing lung nodules, which allowed to significantly reduce the effect of "overdiagnosis" especially in category 2 where the probability of lung cancer is low (<1%).

Keywords: lung cancer screening, Lung-RADS, LDCT (low dose computed tomography)

P1.12 SMALL CELL LUNG CANCER/NET
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.12-01 CD81-HOTTIP REGULATING LOOP ENHANCES MYC-MEDIATED CHEMORESISTANCE IN SMALL CELL LUNG CANCER VIA ERK SIGNALING PATHWAY

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Background: The majority of small cell lung cancer (SCLC) patients who are treated with platinum-based chemotherapy will eventually develops into drug resistance. Currently, there are no effective durable therapies for patients with resistant recurrent SCLC. High expression of CD81 is associated with SCLC chemoresistance and poor clinical outcome. Here, our goal is to study the underlying mechanism and define a novel signaling pathway controlled by CD81 -modulating SCLC chemotherapy resistance. **Method:** The expression of CD81, HOTTIP, and MYCBP were examined in human SCLC tissues, patient-derived xenograft (PDX) models, cell lines derived xenograft tumor model, and SCLC cell lines. The correlations between CD81 and HOTTIP were also confirmed by RNA immunoprecipitation and luciferase reporter assay. Functional analysis of HOTTIP, MYCBP, and ERK signaling was investigated in SCLC cell lines and xenografts. **Result:** Knockdown CD81 enhanced cell responsiveness to chemotherapeutic drugs in SCLC and decreased the expression of HOTTIP, as well as inhibited the intra-nuclear translocation of MYCBP/MYC complex. Conversely, overexpression of CD81 decreased the chemotherapeutic reactivity and increased the expression of HOTTIP and promoting nuclear translocation of MYCBP/MYC complex. CD81 upregulation of HOTTIP requires the transcription factor TCF4. Further analysis demonstrated that CD81-mediated activation of ERK signaling pathway and inhibition of β-catenin degradation leads to promotion of β-catenin transfer to the nucleus. Nuclear β-catenin enhances transcriptional activity of TCF4 and then promotes the transcription of HOTTIP. Synergistically, HOTTIP could bind and increase the nucleus transduction of the MYCBP, form a HOTTIP/MYCBP/MYC complex in nucleus, resulting in increased MYC levels in nucleus. Nuclear MYC further mediates chemoresistance and promotes CD81 expression, forming a positive feedback regulatory pathway in SCLC. In addition, in vivo experiments showed that inhibitors that target the CD81-HOTTIP feedback regulatory loop combined with chemotherapeutic drugs can reverse the chemotherapeutic resistance of SCLC. **Conclusion:** Our findings suggest a novel feedback regulatory pathway dominated by CD81 and HOTTIP controlling SCLC chemotherapeutic resistance, which could serve as a new therapeutic targets for this devastating disease.

Keywords: chemoresistance, small cell lung cancer (SCLC), CD81-HOTTIP

P1.12-02 NATIONWIDE ASSESSMENT OF THE ROLE OF ADJUVANT SYSTEMIC THERAPY IN HIGH-RISK LUNG CARCINOIDS

M. Kamel, A. Sholi, A. Naik, S. Harrison, B. Lee, B. Stiles, N. Altorki, J. Port

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Background: Carcinoid tumors are often considered indolent tumors. However, a subset of patients develop recurrence after resection, and some even develop disseminated disease. To date, little data exists regarding the role of adjuvant therapy in high-risk carcinoid patients. We sought to assess whether adjuvant systemic therapy provides survival benefit for patients with these tumors. **Method:** The National Cancer Database was queried for patients undergoing resection for carcinoids (2004–2014). Adjusted mortality hazard ratios (aHR) (adjusted for age, gender and stage) were estimated for typical vs. atypical carcinoids and also for node

negative vs. node positive atypical carcinoids. Patients with node positive atypical carcinoids were divided into two groups; adjuvant chemotherapy vs. no adjuvant chemotherapy. Balance between the two groups was obtained by propensity matching (controlling for age, gender, comorbidity, pStage, and number of positive nodes). **Result:** 21820 patients had carcinoid tumors (19560 typical, and 2260 atypical). Carcinoids had a lower mortality (aHR 0.35, CI:0.31-0.39) compared to adenocarcinoma (reference) and squamous cell carcinoma (aHR 1.17, CI:1.14-1.20). Among patients with carcinoid tumors, atypical carcinoids had higher mortality compared to typical carcinoids (aHR 2.16 CI:1.55-3). Among atypical carcinoids only, those with node positive disease had worse survival (aHR 2.42 CI:1.63-3.58). Patients with atypical carcinoids who had lymph node positive disease were propensity matched (1:1, caliper 0.1, n=250) to those who received adjuvant chemotherapy and those who had no adjuvant therapy (Table). There was no difference in 5-year survival between the two groups (67% vs 62%, P=0.67).

	Adjuvant CTH (n=125)	No CTH (n=125)	P value
Age	60 (50.5-69)	61 (52.5-71)	0.389
Gender (M)	90 (72%)	91 (72.8%)	0.887
Charlson Comorbidity Index			
0	80 (64%)	78 (62.4%)	0.963
1	31 (24.8%)	32 (25.6%)	
≥2	14 (11.2%)	15 (12%)	
Path stage			
Stage II	59 (47.2%)	56 (44.8%)	0.703
Stage III	66 (52.8%)	69 (55.2%)	
Number positive nodes	2 (1-3)	2 (1-3)	0.554

CTH, Chemotherapy

Conclusion: Patients with node positive, atypical carcinoid tumors, have a significantly reduced survival compared to other carcinoid patients. However, adjuvant therapy did not confer an improvement in outcome. Novel adjuvant treatments are required for these higher risk patients.

Keywords: carcinoid, adjuvant chemotherapy, Lung cancer

P1.12-03 ANTITUMOR ACTIVITY OF SINGLE AGENT LURBINECTEDIN IN PATIENTS WITH RELAPSED SCLC OCCURRING ≥30 DAYS AFTER LAST PLATINUM DOSE

J.M. Trigo Perez[1], V. Subbiah[2], B. Besse[3], V. Moreno[4], R. López[5], M.A. Sala[6], S. Ponce[7], C. Fernendez[8], A. Nieto[8], C. Kahatt[8], A. Zeaiter[8], K. Zaman[9], V. Boni[10], J. Arrondeau[11], M. Martinez[12], J. Delord[13], A. Awada[14], R. Kristeleit[15], F. Longo[16], J. Sarantopoulos[17], M. Rubio[18], A. Anton[19], L. Wannesson[20], J. Valdivia[21], G. Shappiro[22], V. Villalobos[23], A. Santoro[24], M. D'Arcangelo[25], L. Aparicio[26], L. Paz-Ares[7]

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Background: Lurbinectedin (L) inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. **Method:** This multicenter, single agent, phase II Basket trial treated a cohort of 105 SCLC patients (pts) with ECOG PS 0-2 who had received one prior chemotherapy line. L 3.2 mg/m^2 was administered as a 1-hour i.v. infusion on Day 1 q3wk. Primary endpoint, confirmed overall response rate (ORR) by RECIST v.1.1 according to investigator assessment, was met (ORR=35.2%; 95% CI, 26.2-45.2%). A sub-analysis excluding the 21 pts with disease relapse < 30 days after last platinum dose is reported here. **Result:** Median age of 84 evaluated pts was 60 years (range, 41-83), 58.3% were male, ECOG PS 0-1/2 in 96/4%, liver metastasis in 36.9%, history of CNS involvement in 4.8%, prior platinum in 100%, median chemotherapy-free interval (CTFI)=3.9 months (1.1-16.1); prior immunotherapy in 8.3%. A median of 5.5 cycles (range, 1-24) was administered.

ORR, % (95% CI) (confirmed responses) (n=84)	40.5 (29.9-51.7)*
CTFI≥90d (n=60)	45.0 (32.1-58.4)
CTFI 30-89d (n=24)	29.2 (12.6-51.1)
Disease Control Rate at 6 months, % (n=84)	48.8
Median duration of response (months) (95% CI) (n=34)	5.3 (3.5-6.4)
CTFI≥90d (n=27)	6.2 (3.5-7.3)
CTFI 30-89d (n=7)	4.1 (2.6-5.3)
Median overall survival (months) (95% CI) (n=84)**	10.9 (7.8-14.9)
CTFI≥90d (n=60)**	11.9 (9.7-16.2)
CTFI 30-89d (n=24)**	(4.1-7.6)
*4 of 7 pts who failed prior immunotherapy had confirmed response **Preliminary data	

L was well tolerated. Neutropenia was the most common adverse event (AE) (G3:21.5% and G4:25%), whereas febrile neutropenia was reported in 2.4%. Most common non-hematological AEs included fatigue (G3: 7.1%), nausea and vomiting (all G1-2: 32.1% and 16.7%) and transaminase increase (G3:7.2%). There was no death due to treatment related AE. **Conclusion:** L is an active agent for second-line treatment of SCLC. The highest ORR (45.0%) was reported for pts with CTFI≥90d. Notable antitumor activity (ORR=29.2%) was also observed in pts with CTFI 30-89d, for whom no therapy is currently approved. Hence, L is a valuable therapeutic option for SCLC pts with disease relapse after first-line platinum-based therapy. Updated trial results will be presented at the conference.

Keywords: second line, Lurbinectedin, SCLC

P1.12-04 A PHASE I STUDY OF THE ^{177}LU-DOTA^0-TYR^3-OCTREOTATE IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER

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Background: Despite initial sensitivity to systemic treatment, most patients with extensive-stage small cell lung cancer (ES-SCLC) relapse. It has been shown that somatostatin receptors are expressed in SCLC. Lutathera is a ^{177}Lutetium-labeled somatostatin analog approved for treatment of gastroenteropancreatic neuroendocrine tumors (NETs). Nivolumab, an anti-PD-1 antibody, in combination with lutathera may act synergistically to generate anti-tumor immunity. Here we report the final results of the phase I study of this combination in patients with ES-SCLC. **Method:** This is a phase I/II trial of lutathera and nivolumab in patients with ES-SCLC (NCT03325816). For phase I, patients with either relapsed/refractory ES-SCLC or non-progressing ES-SCLC after first-line platinum-based chemotherapy, or advanced grade I-II pulmonary NETs were eligible. The primary objective was to determine the recommended phase 2 dose (RP2D). The phase I portion followed the standard 3+3 design, assessing two dose levels (dose level 1: Lutathera 3.7 GBq Q8W for 4 doses with nivolumab 240 mg Q2W; dose level 2: Lutathera 7.4 GBq Q8W for 4 doses with nivolumab 240 mg Q2W). The DLT period was defined as first 8 weeks after treatment initiation. Adverse events (AEs) were assessed per CTCAE

4.03. **Result:** A total of 9 patients were enrolled. Three patients with ES-SCLC (2 relapsed ES-SCLC, 1 non-progressing ES-SCLC after first-line chemotherapy) were enrolled at dose level 1 and no DLTs were observed. At dose level 2, six patients (3 relapsed/refractory ES-SCLC, 2 metastatic atypical carcinoid, and 1 high-grade NET) were enrolled. One patient with refractory ES-SCLC developed a DLT (grade 3 rash). The most common treatment-related AEs (trAEs) were lymphopenia (n=7), thrombocytopenia (n=4), anemia (n=3), and nausea (n=3). 5 (55.5%) of 9 patients had grade 3 trAEs, but the most common grade 3 trAE was lymphopenia (n=4). Grade 3 anemia, thrombocytopenia, pneumonitis, and rash occurred in one patient each. No grade 4/5 trAEs were reported. Among 7 patients with measurable disease, 1 patient with non-progressing ES-SCLC had a confirmed partial response and 2 patients with metastatic atypical carcinoid had stable disease lasting 6 months. The RP2D was lutathera 7.4 GBq Q8W for 4 doses with nivolumab 240 mg Q2W. **Conclusion:** Evidence from this phase I study of lutathera and nivolumab suggests that the combination has a manageable safety profile and showed initial signs of antitumor activity. The safety and efficacy of the combination may be further explored in phase II as maintenance therapy in patients with ES-SCLC.

Keywords: SCLC, Lutathera, nivolumab

P1.12-05 MICROENVIRONMENT CHARACTERIZATION OF SMALL CELL LUNG CANCER XENOGRAFTS IMPLANTED IN HEMATOPOIETIC HUMANIZED MICE

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Background: With the high mutational burden seen in small cell lung cancer (SCLC) there is the theoretical potential to improve SCLC outcome through immunotherapy. Recent immunotherapeutic clinical trials in SCLC have demonstrated promising results. However, to better understand the immune response and the potential role of immunotherapy in SCLC, immunocompetent models are needed. To this end, we have applied a hematopoietic humanized mouse model, Hu-CB-BRGS to investigate the mechanisms underlying SCLC immunotherapy and develop novel strategies to improve therapeutic efficacy. **Method:** BALB/c-Rag2nullllll2rynullSIRPαNOD (BRGS) pups were humanized through transplantation of cord blood (CB)-derived CD34+ cells. SCLC flank tumors were initiated in BRGS mice using two characterized SCLC cell lines (CDX) and 1 patient derived xenograft (PDX). Upon verification of human T-cell chimerism in the Hu-CB-BRGS mice, SCLC tumors grown in BRGS mice were engrafted into the flanks of Hu-CB-BRGS mice by trocar transfer. Tumor growth was quantified by twice weekly measurement and harvested on reaching 1200 mm3. At harvest, tumor tissue as well as host immune organs (lymph node, spleen) were collected for immunological assessment. Humanized immune system and tumor were evaluated by flow cytometry and immunohistochemistry (IHC). **Result:** Flank tumors from two CDX tumors (H82 and H187) and one PDX tumor (LX-95) were successfully developed in the Hu-CB-BRGS mice with take rates averaging 82%. SCLC tumor growth rate in Hu-CB-BRGS mice was comparable to that seen in BRGS mice. Although human T cells were well represented in the lymph nodes and spleens of the Hu-CB-BRGS mice, we detected very few tumor infiltrating immune cells in the engrafted SCLC tumors by IHC and flow cytometry as defined by CD45 and CD3, which is consistent with the observations in SCLC patient tumor tissue. Tumor cells, identified by EpCAM expression, expressed low levels of MHC class I, II and PD-L1. PD-1 was expressed by human T cells found in the lymph nodes and spleen of Hu-CB-BRGS mice, while the SCLC xenografts expressed varying levels. **Conclusion:** We demonstrate that both SCLC PDX and CDX tumors can be grown in the context of a humanized immune system within mouse recipients. SCLC Hu-CB-BRGS mice demonstrate persistence of human immune cells, including T cells and B cells in the immune organs. The xenograft tumor microenvironment included variable human immune infiltrates. The SCLC Hu-CB-BRGS mouse model may be a valuable preclinical platform for testing human specific immune-oncology therapeutics for SCLC patients.

Keywords: SCLC, hematopoietic humanized mouse model, Microenvironment

P1.12-06 OZONE-PRIMED NEUTROPHILS PROMOTE EARLY STEPS OF TUMOR CELL METASTASIS TO LUNGS BY ENHANCING THEIR NETS PRODUCTION

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Background: Air pollution is becoming a major health problem since it is responsible for millions of deaths related to cardiovascular and lung diseases. Particulate matter and gazes such as ozone produced have been shown to increase lung cancer morbidity in industrialized countries. However, no clear link between air quality levels and cancer cell dissemination to lung tissue has yet been established. **Method:** A reliable murine model of concomitant pulmonary O_3 exposure and tumor cell injection was used to evaluate metastatic burden in the lungs after pulmonary ozone exposure. The implication of neutrophils in this process was studied by using anti-Ly6G antibodies to prevent recruitment of neutrophils to the lungs. Additionally, the implication of neutrophil extracellular traps (NETs) in metastatic processes was evaluated using *MRP8cre-Pad4lox/lox* mice or by treating mice with DNase I. **Result:** Pulmonary ozone exposure induces 1) a strong inflammatory response in lung tissues characterized by the recruitment of neutrophils and, 2) colonization of lung tissues by cancer cells and this already at early steps of the metastatic dissemination process. Additionally, an increased production of NETs by ozone-primed neutrophils was observed. Interestingly, neutrophil depletion and inhibition of NET formation greatly diminished the metastatic burden in lungs of mice exposed to ozone. The ability of O_3-primed neutrophils to enhance lung colonization by tumor cells was further confirmed after their adoptive transfer in Balb/c mice unexposed to O_3. **Conclusion:** Pulmonary neutrophils induced by O_3 promote metastatic dissemination to lungs by producing NETs. These findings open new perspectives to improve treatment and prevention strategies in patients affected by metastatic diseases.

Keywords: NETs, metastasis, ozone pollution

P1.12-07 NEAR INFRARED PHOTOIMMUNOTHERAPY TARGETING DLL3 AGAINST SMALL CELL LUNG CANCER

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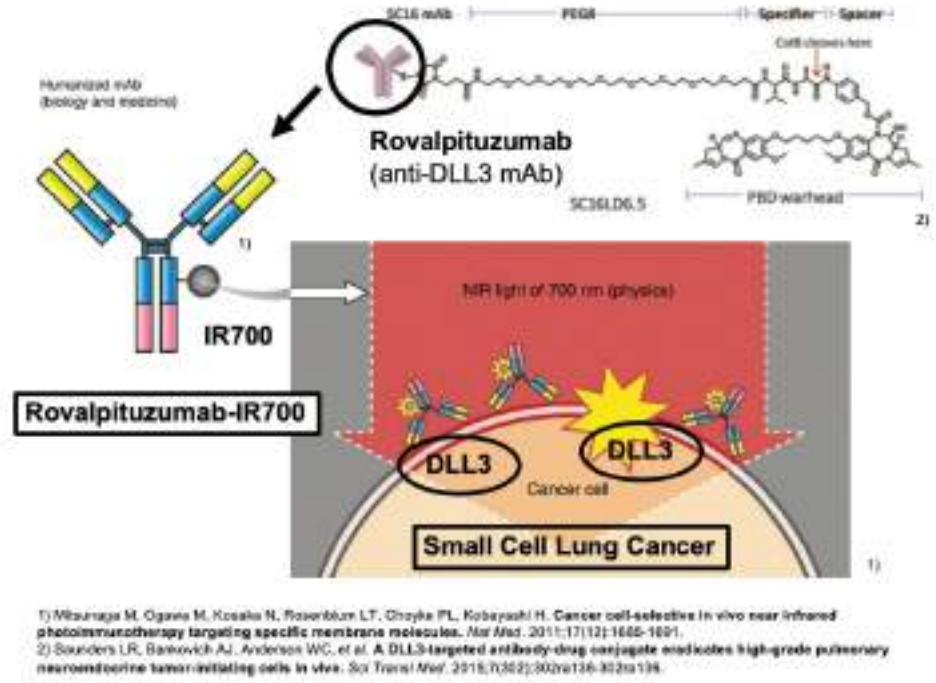
Background: Small cell lung cancer (SCLC) has poor prognosis, and its treatment options are limited. Delta-like protein 3 (DLL3) is a promising treatment target for SCLC, and Rovalpituzumab tesirine (Rova-T) is the first antibody drug conjugate targeting DLL3, which is currently in clinical trials. Although DLL3 is ideal target for SCLC, the result of clinical studies has not reached its primary object. Thus, new approaches are still needed. Near infrared photoimmunotherapy (NIR-PIT) is a new cancer treatment that combines the specificity of intravenously injected antibodies for targeting tumor with the toxicity induced by photosensitizers after exposure to near infrared (NIR) light. This new therapy is now in international Phase III clinical trial against locoregional, recurrent head and neck squamous cell cancer (LUZERA-301). Herein, we exploited NIR-PIT to develop new therapy for SCLC with DLL3 antibody. We preclinically evaluates the efficacy of DLL3-targeted-NIR-PIT.



1) Mitsunaga M, Ogawa M, Kosaka N, Rosenblum LT, Choyke PL, Kobayashi H. **Cancer cell-selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules.** *Nat Med.* 2011;17(12):1685-1691.
2) Saunders LR, Bankovich AJ, Anderson WC, et al. **A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo.** *Sci Transl Med.* 2015;7(302):302ra136-302ra136.

Method: *In vitro* and *in vivo* experiments were conducted with DLL3, GFP, and luciferase-expressing SCLC cell line and/or mouse fibroblast cell line (SBC5-DLL3-luc-GFP and 3T3-DLL3-luc-GFP). An antibody-photosensitizer conjugate consisting of rovalpituzumab (anti-DLL3 humanized monoclonal antibody) and a phthalocyanine dye, IRDye-700DX, was synthesized (rova-IR700) and cells or tumors were exposed to NIR-light. Serial fluorescence microscopic observation was done before and after NIR-PIT. *In vitro* NIR-PIT cytotoxicity was assessed with dead cell staining by flow cytometry and luciferase activity. *In vivo* NIR-PIT was performed in mice with tumors implanted in the flank and these were assessed by tumor volume, bioluminescence and overall survival. **Result:** After exposure to NIR-light, cellular swelling, bleb formation, rupture of the lysosome and dead cell staining were observed in fluorescence microscope. *In vitro* cytotoxicity of NIR-PIT was light dose dependent. *In vivo* the antitumor effects of NIR-PIT were confirmed by significant reductions in tumor volume ($p < 0.05$), luciferase activity ($p < 0.01$) and overall survival ($p = 0.023$). **Conclusion:** These results suggest that DLL3-targeting-NIR-PIT could be a new promising treatment for SCLC.

Keywords: small cell lung cancer, DLL3, Photoimmunotherapy

P1.12-08 THE IMPACT OF PATIENT AGE AND SOCIOECONOMIC FACTORS ON CLINICAL OUTCOMES IN SMALL CELL LUNG CANCER (SCLC): A NATIONAL STUDY

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Background: SCLC represents one of the most aggressive cancers with limited treatment options. Chemotherapy with or without radiation therapy remain the backbone treatment for this challenging disease. The impact of age and other socioeconomic factors on treatment modalities and clinical outcomes remain largely unknown. This study investigates the demographic, clinical, socioeconomic, and treatment modalities in each age group and the impact of patients' age on survival. **Method:** The National Cancer Database with NSCLC incident cases between 2004-2014 was used. Clinical factors including Charlson-Deyo comorbidity score, TNM staging, tumor histology, and type of treatment, demographic features, socioeconomic status and overall survival (OS) were analyzed by age of diagnosis, accounting for multivariate factors in NCDB. **Result:** A total of 214,096 SCLC patients were included in the analysis. Median age at diagnosis was 67 years old (y/o). OS including all stages is 10.97 months for <60 y/o; 9.43 months for 60-69 y/o; 7.20 months for 70-79 y/o and 3.42 months for ≥ 80 y/o respectively ($p<0.0001$). The impact of age on survival is more prominent in stage I, II and III patients than those in stage IV patients. Patients ≥ 80 y/o are associated with significant smaller tumor size (41 mm vs 50 mm, $p<0.0001$) and more stage I cancer at diagnosis (3.8% vs 6.9%, $p<0.0001$) compared to patients <60 y/o respectively. Patients ≥ 80 y/o are associated with high income, high education and Pacific geographic region. Hispanics, Asians, females, and patients younger than 60 y/o are independently associated with improved OS. Despite comparable comorbidity, patients with ≥ 80 y/o are treated differently and received much less aggressive therapy including radiation therapy and/or chemotherapy at each stage ($p<0.0001$). **Conclusion:** The overall survival of SCLC is significantly impacted by patient's age and socioeconomic factors. In particular, elderly patients are associated with significantly smaller tumor size, more stage I at diagnosis, however, they are under-treated and have worse survival compared to younger patients.

Keywords: Socioeconomic factors, small cell lung cancer, age

P1.12-09 RNA SEQUENCING IN SMALL CELL LUNG CARCINOMA REVEALS CHANGE IN NEUROENDOCRINE PATTERN IN PRIMARY TUMOR VERSUS LYMPH NODE METASTASES

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Background: Recent preclinical cell line data presented at World Conference on Lung Cancer 2018 suggest that neuroendocrine (NE) pattern of small cell lung cancer (SCLC) has strong therapeutic relevance. NE high tumors are associated with immune desert and NE low tumors are considered immune oasis phenotype. **Method:** Targeted RNA-sequencing of 2560 genes was performed on 32 matched surgically resected SCLC patients primary tumors and lymph node (LN) metastases. We performed a cluster analysis and heat map to divide patients into NE high and NE low subtypes by using the top NE associated genes. **Result:** Cluster analysis clearly identified SCLC NE subtypes according to primary tumor (NE high vs. low, 20 vs. 12, respectively) and LNs (NE high vs. low, 23 vs. 9, respectively). In case of five patients, a change in NE pattern was observed, suggesting a possible inter-tumor heterogeneity regarding NE differentiation. Moreover, a significant downregulation of NE associated genes CAV1, CAV2 and ANXA3 was found in LN metastases compared to primary tumor. A lower expression of NE associated key RNA genes REST and Myc, and the higher expression of DLL3 in NE high subtype are in accordance with the preclinical findings, and confirms the accuracy of the cluster analysis performed. **Conclusion:** Our data confirm the results of preclinical studies and show NE low and high differentiation clusters in SCLC. NE pattern of the LN metastatic lesions might not reflect the NE phenotype of the primary tumor, consequently, treatment decisions including immunotherapy administration needs to be further investigated.

Keyword: Small cell lung cancer, neuroendocrine tumor, RNA sequencing

P1.12-10 THE GENOMIC PROFILES OF SMALL CELL LUNG CANCER IN EAST ASIAN

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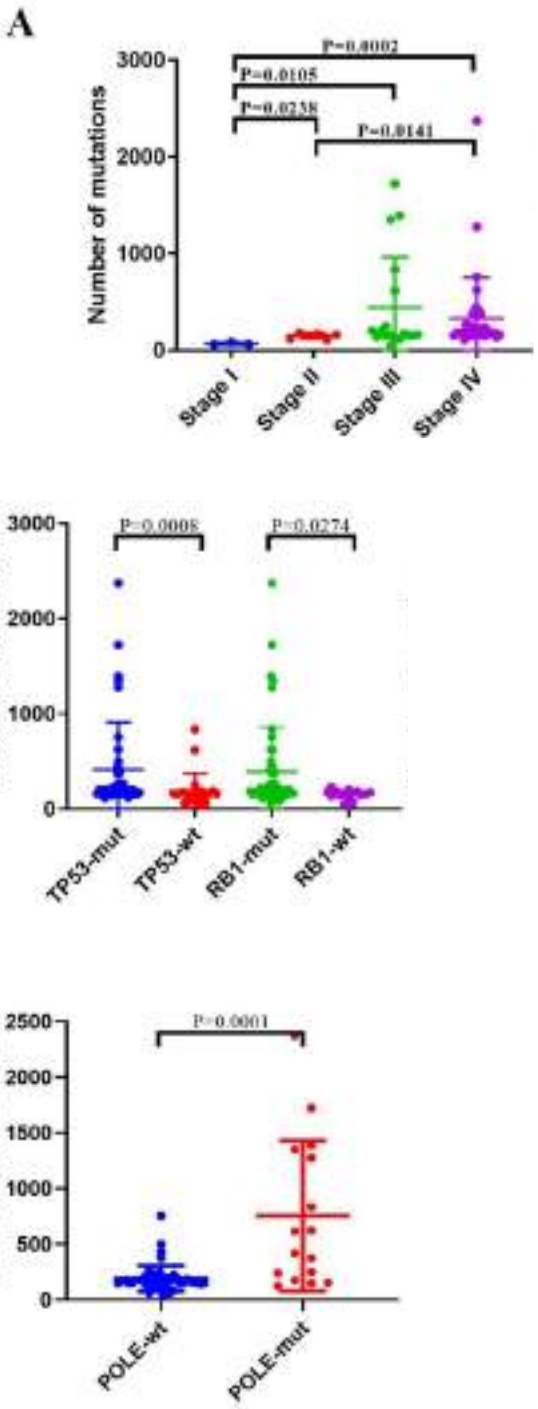
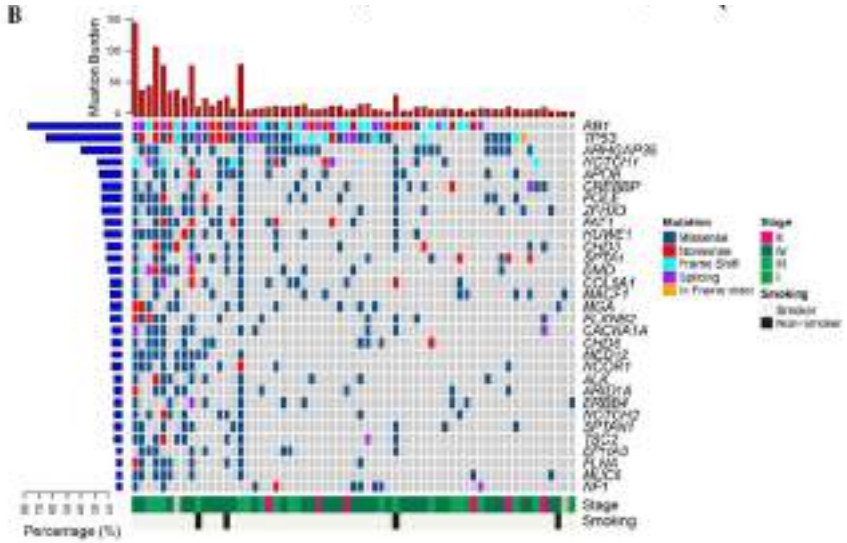
Background: Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy with poor survival, which is initially effective treated by chemotherapy and relapses rapidly. Comprehensive genomic analysis of SCLC contribute to the understanding of drug resistance mechanisms and discerning patients who respond to treatments, especially immunotherapy that has been proved to be efficient in SCLCs harboring high tumor mutational burden (TMB). This study was initiated to investigate the genomic profiles of SCLC in Chinese. **Method:** SCLC specimens were obtained by surgery or biopsy from 64 patients. Whole-exome sequencing (WES) was performed on tumor samples without paired PBMCs. Alterations were confirmed with VAF between 5% and 90%, subsequently filtered by mutated genes above 5% in J.Geroge's and LY. Jiang's researches. Tumor mutational burden was calculated by the number of non-synonymous mutations. The mutations of highly mutated driver genes in SCLC was also determined based on MH. Bailey's study. **Result:** TP53 and RB1 were the most frequently mutated genes in SCLCs, occurred in 87.5% (56/64) tumors, and furthermore related to a higher mutational burden (P = 0.0008 and 0.0274, respectively). Tumor mutational burden after filtered by highly mutated genes in SCLC was 333 non-synonymous mutations per tumor, with high mutation rates exhibited in advanced stage of SCLCs, while the smoking history did not correlate with the number of mutations. Driver genes mutation in high frequency was detected almost in all tumors (63/64), with 17.4 mutations on average (0-144). Tumors with POLE mutation tended to harbor a higher driver genes mutation rates, as well as a higher TMB. Pathway analysis using altered driver genes showed enrichment of PI3K-Akt (adj. P = 8.38e-07), MAPK (adj. P = 1.63e-05), mismatch repair (adj. P = 4.55e-05), cell cycle (adj. P= 0.0016), and Wnt (adj. P= 0.0047) signaling pathways. We did not observe significant correlation of mutations in Wnt signaling pathway with survival, though it has proved to be a mechanism of chemoresistance in SCLCs.





Conclusion: SCLCs exhibited complex genomic features with extensive mutational burden and high numbers of altered driver genes. Various sorts of cancer-related pathways were enriched, highlighted the complicacy of SCLCs.

Keywords: TMB, driver gene, SCLC

P1.12-11 EXPLORING SEX DIFFERENCES IN SMALL CELL LUNG CANCER: IS THIS A HORMONAL ISSUE?

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Background: Small cell lung cancer (SCLC) accounts for about 10% to 15% of lung cancers among women and men. Though heavily associated with smoking, its incidence in women is rapidly increasing despite a decline in cigarette exposure. Given the changing demographics of SCLC and hormonal factors associated with other forms of lung cancer, we studied differences between sexes in SCLC. **Method:** Utilizing the National Cancer Database, we identified all incident SCLC cases from 2004 to 2014. Patients were classified as limited (LS) or extensive stage (ES). Women were stratified by menopausal status (≥55 years = postmenopausal). Kaplan-Meier method and Cox regression were used for overall survival (OS) and multivariable analysis. **Result:** 161,978 patients were identified. No significant sociodemographic differences were observed between sexes. The majority of patients were non-Hispanic whites (89.1%), followed by non-Hispanic blacks (7.5%). Men were more likely to be diagnosed with ES disease than women (63% vs. 56%). Both sexes initiated treatment within a similar time frame from diagnosis (chemotherapy, median 18 days, IQR 8-32). Women had better median OS compared to men in both LS (15.2 vs. 12.7 months, HR: 0.85, 95% CI 0.83-0.86, p < 0.0001) and ES (6.4 vs. 5.7 months, HR: 0.88, 95% CI 0.87-0.90, p < 0.0001). No racial or ethnic disparities in OS were observed, overall and when examined within sex and disease stage groups. Differences between sexes in OS were also observed when comparing patients within the same racial/ethnic group (women having better OS). When divided by menopausal status, postmenopausal women with LS and ES had worse OS than premenopausal women (14.7 vs. 22 months, HR: 1.50, 95% CI 1.44-1.56; 6.1 vs. 9.8 months, HR: 1.41, 95% CI: 1.37-1.46, respectively). We also observed worse OS in older men when divided by age (<55 years and ≥55 years). In multivariable analysis, older age, postmenopausal status, and Medicaid as primary insurance were associated with worse OS for both LS and ES. **Conclusion:** In this large cohort, women with SCLC had better OS compared to men. Post-menopausal women had worse OS compared to pre-menopausal women. Since older men had a similar trend of worse survival compared to younger men, age might exert a more significant influence on survival than hormonal status in SCLC. Further studies with data on sexual hormone levels are necessary to better understand their role in women with SCLC.

Keywords: small cell lung cancer, hormones, women with lung cancer

P1.12-12 FACTORS AFFECTING THE RISK OF BRAIN METASTASIS IN LIMITED-STAGE SMALL CELL LUNG CANCER AFTER PROPHYLACTIC CRANIAL IRRADIATION

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Background: Prophylactic cranial irradiation (PCI) can reduce brain metastases (BM) and improve overall survival (OS) in patients with limited-stage small cell lung cancer (LS-SCLC) after complete response to primary therapy. However, some SCLC patients still suffer from BM after PCI with unknown risk factors.This study conducted to assess the factors affecting the risk of BM in patients with LS-SCLC after PCI and identify characteristics of patients who may not benefit from PCI. **Method:** We identified 550 patients who received chemoradiotherapy at Zhejiang Cancer Hospital in 2002–2017. All patients received PCI. Kaplan–Meier analyses and Cox regression analyses were used to identify factors influencing OS and BM. **Result:** The median survival time for this patient population was 27.9 months, and the 5-year overall survival rate was 31%. Pathologic stage not only correlated with overall survival but also significantly affected the risk of BM. For the whole group, 15.6% (86/550) of the patients had evidence of metastases to brain. The frequency of BM in patients with pathologic stages I, II, and III were 9.3% (4/43), 13.4% (7/52), and 16.5% (75/455), (P=0.026), Having tumors ≥5 cm increased the risk of BM (HR: 1.781 95%CI:1.044-3.039, P=0.034) but not death (HR:1.126 95%CI:0.925-1.663, P=0.182). The median survival time among patients <60 years were significantly higher than patients ≥60 years (34.9 months VS. 24.6 months,P=0.001),however, the difference of the BM risk in two group was not statistically significant. **Conclusion:** PCI remains standard therapy after complete response to chemoradiotherapy for LS-SCLC. However, patients with tumors ≥5 cm may have a higher risk of developing brain metastases after PCI. Further work is warranted to identify patients who may not benefit from PCI.

Keywords: prophylactic cranial irradiation, brain metastasis, small cell lung cancer

P1.12-13 THE PAST, PRESENT, AND FUTURE OF SCLC AND NSCLC INCIDENCE, MORTALITY, AND PREVALENCE IN DENMARK DURING 2006 THROUGH 2030

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Background: Information on the epidemiology of lung cancer and its main subtypes, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), is needed to assess the impact of lung cancer subtypes on the current and future health care system. **Method:** Data from Danish nationwide registers were used to describe trends in lung cancer incidence, mortality, and prevalence in Denmark during the study period January 1, 2006 to December 31, 2015. Annual forecast on prevalence of lung cancer in Denmark up till 2030 was developed using projections of incidence rates from NORDCAN (http://www-dep.iarc.fr/NORDCAN/english/frame.asp) combined with forecasted mortality rates in the study patient population. **Result:** A total of 44,291 lung cancer patients were identified in the Danish Cancer Registry during the study period, of which 6,353 (14.3%) had pathologically verified SCLC. Among the remaining cases 'NSCLC+other'; 33,747 (89.0%) had verified NSCLC, 4,038 (10.6%) lacked pathology, and 153 (0.4%) had other pathology than indexed lung cancer. Among SCLC, the annual numbers of new cases and deaths were stable, and at similar levels (Figure 1). As a result, the SCLC prevalence was projected to remain at same stable level until 2030. Among NSCLC+other, the annual numbers of new cases increased gradually. The gap between new cases and deaths became greater during the study period due to slowly steadying number of deaths. Hereby, the observed prevalence of NSCLC +others grew exponentially and was projected to continue so. **Conclusion:** The current and future epidemiological profiles differ according to lung cancer subtype. This finding should be considered when prioritizing and planning for future lung cancer care, particularly in the context of new treatment strategies, where personalized medicine and treatment modalities such as immunotherapy may result in improved prognosis. Further and continuous epidemiological monitoring is recommended to assess the impact of such improvements.

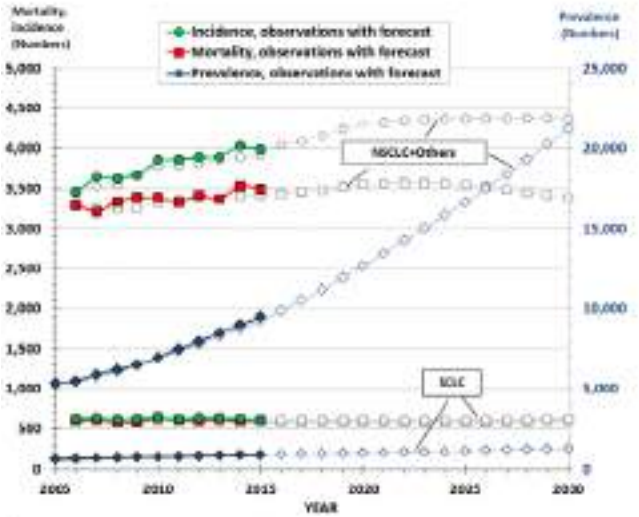

Figure 1 Numbers of annual incidence, mortality, and prevalence in lung cancer stratified by subtypes. Observed during 2005-2015 and predicted during 2016-2030

Keywords: SCLC, NSCLC, Epidemiology profile

P1.12-14 PHASE II TRIAL OF APATINIB PLUS CHEMOTHERAPY FOR SECOND-LINE AND ABOVE TREATMENT OF ADVANCED SCLC: FOCUS ON EFFICACY AND SAFETY

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Background: Small-cell lung cancer (SCLC), which accounts for ~15% of all lung cancers, is characterised by its rapid proliferation. The clinical outcomes of second-line and above treatments are unsatisfactory, resulting in a median progression-free survival (PFS) of less than 3 months. There is currently none targeted drugs or new chemotherapeutic drugs that can achieve breakthroughs in advanced SCLC. This study aims to observe whether apatinib in combination with chemotherapy can be a new choice for second-line and above treatment of advanced SCLC. **Method:** This is a prospective, single-center, single-arm clinical study designed to evaluate the efficacy and safety of apatinib plus chemotherapy for second-line and above treatment of advanced SCLC (ClinicalTrials.gov NCT03547804). Patients received 500mg apatinib qd orally, if the patient has a grade 3/4 adverse reaction during the treatment, it can be reduced to apatinib 250mg qd orally. Chemotherapeutic agents are limited to irinotecan or docetaxel alone. The primary endpoint was the progression-free survival (PFS). The secondary endpoints included overall survival (OS), disease control rate (DCR), objective response rate (ORR), and adverse events (AEs). **Result:** Twenty patients were enrolled from March 2018 to March 2019. Fifteen patients were available for response evaluation. The ORR and DCR were 33.33% (5/15) and 93.33% (14/15), respectively. The predicted median PFS time was 5.8 months (95% confidence interval [CI] 5.1-6.5 months) (SPSS 20.0 software). The most common treatment-related AEs were neutropenia (45.0%), leucopenia(35.0%), abnormal liver function (20%), nausea and vomiting (20%) and thrombocytopenia (20.0%), without any treatment-related deaths. It is worth noting, 12 patients underwent apatinib reduction due to grade 3/4 adverse reactions.

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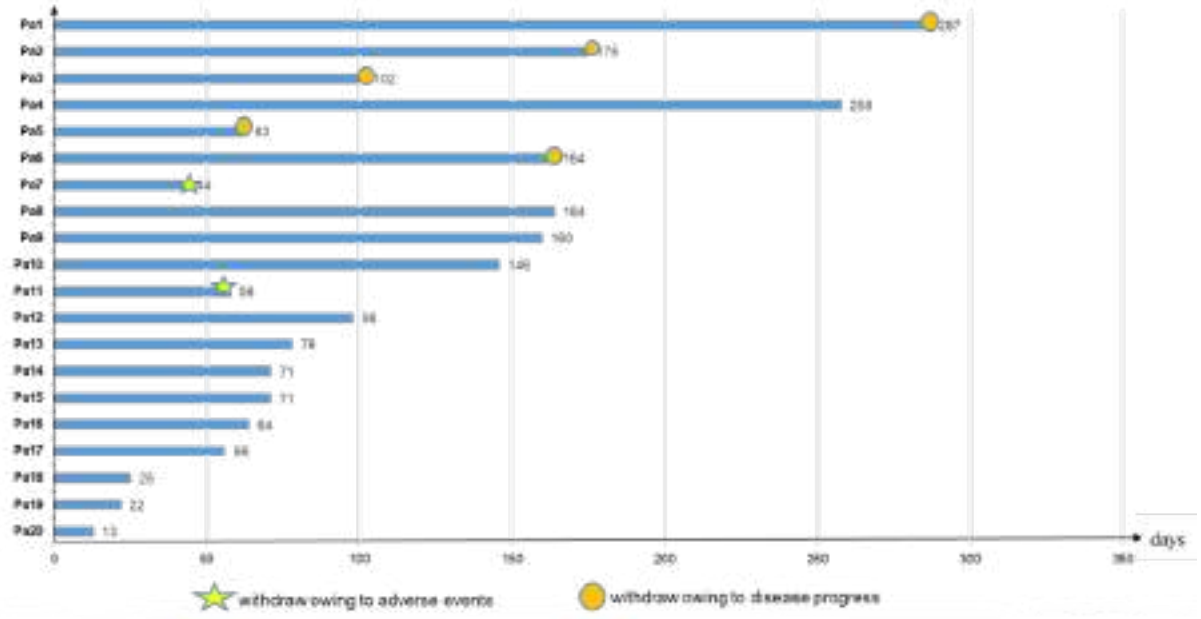

Figure 1. Survival analysis of enrolled patients.

Conclusion: Apatinib plus single agent chemotherapy showed promising efficacy in a patients with advanced SCLC who had failed chemotherapy. And the recommended phase II dose of apatinib as combination therapy was 250 mg qd.

Keywords: small-cell lung cancer, apatinib, phase II

P1.12-15 PET IMAGING OF [^{18}F]PARP INHIBITOR AS A PHARMACODYNAMIC BIOMARKER OF TALAZOPARIB IN SMALL CELL LUNG CANCER PDXS

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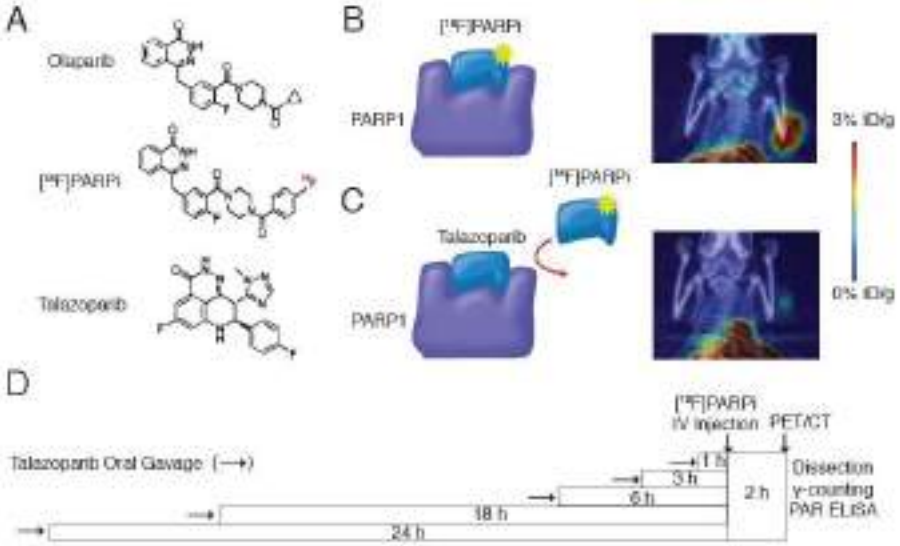
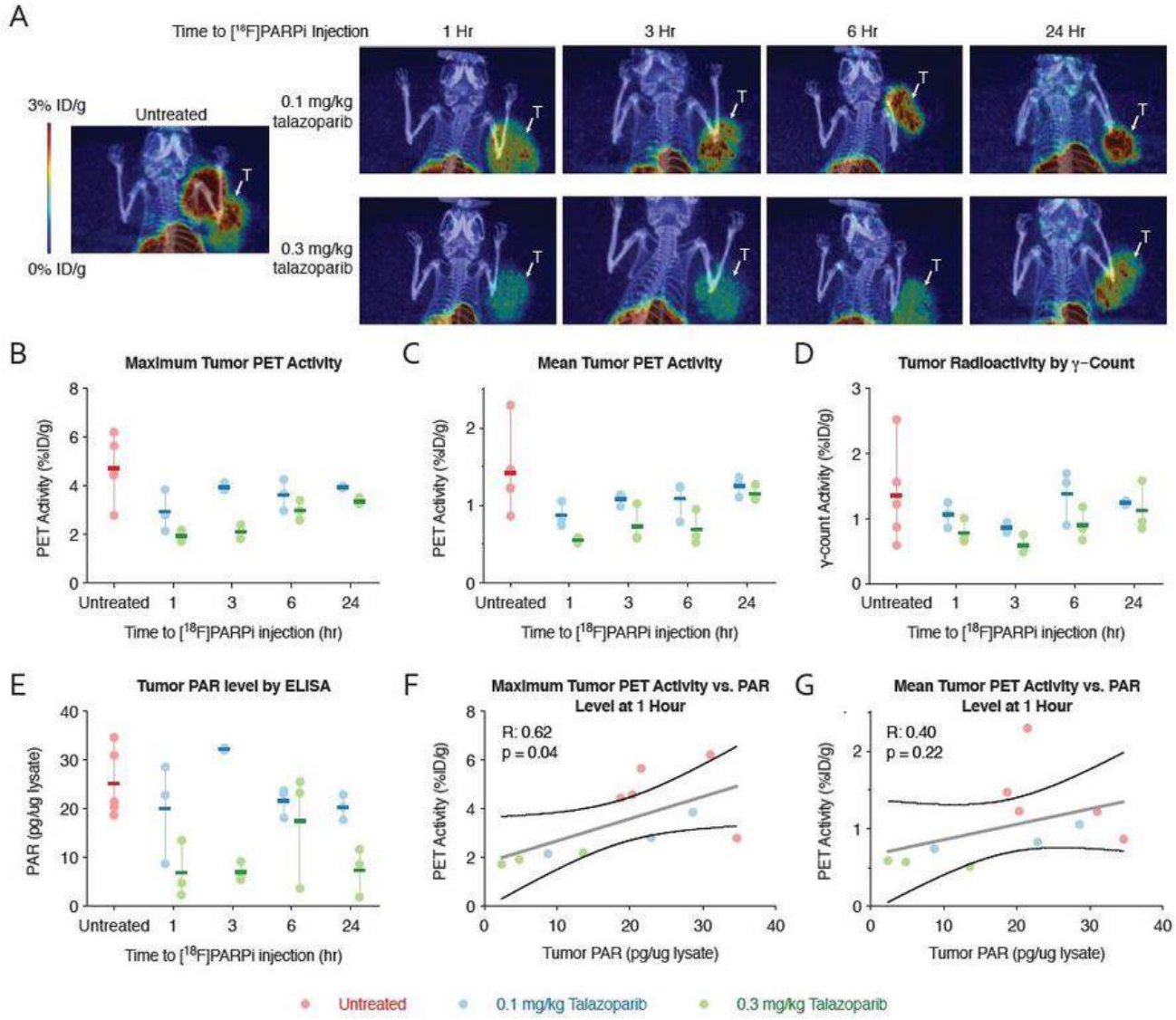
Background: Inhibitors of poly-(ADP)-ribose polymerase (PARP) are promising therapeutics for small cell lung cancer (SCLC). We tested whether PARP inhibitor (PARPi) target engagement as measured by a radiolabeled PARP inhibitor ([^{18}F]PARPi) has the potential to predict drug efficacy *in vivo.* **Method:** Tumor growth inhibition during daily talazoparib treatment was evaluated in mice engrafted with SCLC patient-derived xenografts to evaluate talazoparib efficacy at multiple doses. Mice were intravenously injected with [^{18}F]PARPi radiotracer at multiple time points after single doses of oral talazoparib to quantitatively assess the extent to which talazoparib could reduce tumor radiotracer uptake and PET/CT activity.

Result: A dose range of talazoparib with differential therapeutic efficacy was established, with significant delay in time to reach 1000 mm^3 for tumors treated with 0.3 mg/kg (p=0.02) but not 0.1 mg/kg talazoparib. On PET/CT with [^{18}F]PARPi tumor was among the tissues with the highest radioactivity per gram (1.37 ± 0.15 %ID/g), significantly higher than surrounding lung (0.24 ± 0.05 %ID/g, p = 0.007), bone (0.27 ± 0.05 %ID/g, p = 0.007), and muscle (0.24 ± 0.15 %ID/g, p < 0.002). A reduction in [^{18}F]PARPi uptake after talazoparib dosing was consistent with talazoparib clearance, with reduction in PET activity attenuating over 24 hours. Talazoparib target engagement, measured by maximum tumor PET uptake, increased in a dose dependent manner (3.9% vs. 2.1% ID/g for 0.1 and 0.3 mg/kg at 3 hours post-talazoparib, p=0.003) and correlated with PARP enzymatic activity among individual tumors as measured by total tumor PAR (p=0.04, R=0.62 at 1 hour post-talazoparib).





Conclusion: [18F]PARPi PET imaging appears to model PARP inhibitor pharmacokinetics, correlates with PARP inhibitor pharmacodynamics as measured by tumor PAR levels, and differs significantly between therapeutic and subtherapeutic doses of talazoparib. PET imaging using [18F]PARPi has the potential to be a powerful tool in treatment monitoring by assessing PARP inhibitor target engagement in real-time.

Keywords: PARP Inhibitor, [18F]PARPi PET, small cell lung cancer

P1.12-16 LMW HEPARIN ADHERENCE AND EFFECTS ON SURVIVAL WITHIN A RANDOMIZED PHASE III LUNG CANCER TRIAL (RASTEN)

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Background: Coagulation activation is a hallmark of cancer, and anticoagulants have shown tumor-inhibiting properties. However, recent trials have failed to demonstrate improved survival with low-molecular-weight heparin (LMWH) in cancer populations. This has raised the question of suboptimal adherence as a possible explanation of the lack of benefit. Still, there is no standardized method to directly monitor LMWH in patient plasma. Here, we directly determine LMWH levels in patients using the Heparin Red assay and the anti-factor Xa activity (anti-FXa) assay to objectively assess adherence and how this associates with patient outcome in the RASTEN trial. **Method:** RASTEN is a multi-center, randomized phase-III trial investigating if the addition of LMWH to standard therapy can improve survival in small-cell lung cancer (SCLC). LMWH was measured in plasma (*N*=258) by the Heparin Red assay, and compared with the anti-FXa assay. **Result:** Both methods could differentiate patients in the LMWH from the control arm, and patients receiving therapeutic LMWH due to thrombosis, respectively. ROC analyses yielded adherence rates of 85% for anti-FXa and 68% for Heparin Red. No survival benefits were found in the adherent subgroup compared to the control arm (HR: 1.26; 95% confidence interval (CI) 0.95-1.67; *P*=0.105 and HR: 1.19; 95% CI 0.89-1.60; *P*=0.248 for anti-FXa and Heparin Red, respectively). **Conclusion:** Heparin Red could define patients with high probability of adherence to LMWH treatment, which warrants prospective studies for further validation. Our finding that the LMWH adherent subpopulation did not show improved survival as compared with control patients, excludes that the negative outcome of RASTEN was due to poor adherence. We conclude that LMWH cannot be recommended in the general management of patients with SCLC.

Keywords: Anticoagulant therapy adherence, Heparin assays, small cell lung cancer

P1.12-17 ASSOCIATION BETWEEN THE PHARMACOKINETICS AND CLINICAL OUTCOME OF AMRUBICIN TREATMENT

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Background: Amrubicin (AMR) is a key agent for small cell lung cancer (SCLC) but involves a high frequency of severe neutropenia. However, the influence of AMR pharmacokinetics (PK) on the clinical outcomes has not been fully elucidated. It was reported that organic cation transporter6 (OCT6) is one of influx transporters, and that single nucleotide polymorphism (SNP) of OCT6 effects clinical outcome of doxorubicin. In this study, we examined the PK parameters of AMR and its active metabolite, amrubicinol (AMR-OH), and whether OCT6 SNP is related to clinical outcome of AMR treatment. **Method:** Seventy-eight lung cancer patients treated with AMR from March 2009 to March 2017 at Nagoya City University hospital were enrolled in this study. Of these 78 patients, 62 were male, 58 were SCLC and 20 were non-small cell lung cancer, and in 35 the dose of AMR were 40mg/m^2 and in 43 were 30 or 35mg/m^2. In 21 patients, blood samples were obtained seven times in a 24-hour after the first AMR administration, and we quantified AMR and AMR-OH concentration by a high-performance liquid chromatography assay and calculated area under curve (AUC) of AMR and AMR-OH by the liner trapezoidal rule from 0 to 24-hour. In 78 all patients, grade of neutropenia and the percent decrease in the absolute neutrophil count (ANC)* in first course of AMR treatment were investigated, and OCT6 SNP (A146G) was genotyped using Taqman genotyping assay. *%decrease ANC= pretreatment ANC – nadir ANC/ pretreatment ANC×100. **Result:** The %decrease ANC was significantly related to the AUC of AMR-OH (r=0.5873, p=0.0051). The AUC of AMR-OH was significantly higher in the patients with grade4 neutropenia (608.9±47.92 ml/min) than in without grade4 neutropenia (383.8±33.75 ml/min) (p=0.0008). Of all 78 patients, classified into OCT6 SNP A146G genotype group, 26 had AA, 43 had AG, and 9 had GG. Among 21 patients examined the PK parameters, 8 had AA and 13 had AG+GG, the AUC of AMR-OH was significantly higher in AA (615.0±51.83 ml/min) than in AG+GG (397.3±35.01 ml/min) (p=0.0019). These results were same as in AMR. The incidence of grade4 neutropenia was significantly higher in patients with AA (15/26) than in patients with AG+GG (12/52) (p=0.0048). **Conclusion:** OCT6 SNP A146G is associated with the AUC of AMR and AMR-OH, as well as affects the emergence of severe neutropenia.

Keywords: OCT6, single nucleotide polymorphism, Amurubicin

P1.12-18 NONCLINICAL SAFETY ASSESSMENT OF AMG 757, A DLL3 BISPECIFIC T CELL ENGAGER, IN THE CYNOMOLGUS MONKEY

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Background: Bispecific T-cell engager (BiTE®) antibody constructs, which direct T cell killing of tumor cells by bridging the T cell receptor CD3 subunit and a tumor-associated antigen, are a clinically validated therapeutic modality in hematologic malignancies and have the potential to be effective in solid tumors. Delta-like 3 (DLL3) is overexpressed in small cell lung cancer (SCLC), an aggressive neuroendocrine tumor with a poor prognosis and limited therapeutic options. AMG 757 is a half-life extended BiTE® molecule that binds DLL3 and is in clinical development for the treatment of SCLC. The nonclinical safety assessment of AMG 757 included an evaluation of DLL3 expression and a repeat dose toxicology study in the cynomolgus monkey. **Method:** DLL3 mRNA and protein expression were evaluated in an extensive set of normal cynomolgus monkey and human tissues using RNA sequencing, in situ hybridization, quantitative polymerase chain reaction, Western blot, and immunohistochemistry. In the cynomolgus monkey toxicology study, 3 animals/sex/group received AMG 757 weekly by intravenous infusion at 0, 50, 500, or 4500 μg/kg for 28 days during the dosing phase. An additional 2 animals/sex/group received 0 or 500 μg/kg weekly during the dosing phase and were retained for a 28-day recovery phase. **Result:** The expression data indicate that DLL3 is expressed at low levels only in the pituitary, pancreas, and brain. In an immunohistochemistry assay, immunoreactivity with an anti-DLL3 antibody was cytoplasmic and generally weak in intensity. In the 28-day toxicology study, there were no AMG 757-related changes in clinical signs, body weight, food consumption, ophthalmic examinations, respiration rates, body temperature, neurologic examinations, clinical pathology parameters, cytokines, organ weights, or macroscopic tissue observations. AMG 757-related changes were limited to a transient, slightly higher heart rate at ≥500 μg/kg, a transient, minor decrease in lymphocyte populations at 4500 μg/kg, and a minimal to mild mixed cell infiltrate comprised of lymphocytes and eosinophils in the pituitary at 50 and 500 μg/kg. These changes were considered reversible and the highest non-severely toxic dose was determined to be 4500 μg/kg. **Conclusion:** DLL3 is expressed at low levels in the cytoplasm of a few normal tissues, where it would not be accessible to AMG 757. The nonclinical safety profile of AMG 757 was consistent with this expression pattern and the drug's mechanism of action. These results suggest that limited on-target, off-tumor toxicity is anticipated, and that it may be possible to achieve high clinical exposures that maximize T cell-redirected responses in patients.

Keywords: DLL3, small cell lung cancer, Immunotherapy

P1.12-19 IDENTIFICATION AND POTENTIAL APPLICATION OF HUMAN BLOOD EXOSOMAL RNA IN SMALL CELL LUNG CANCER

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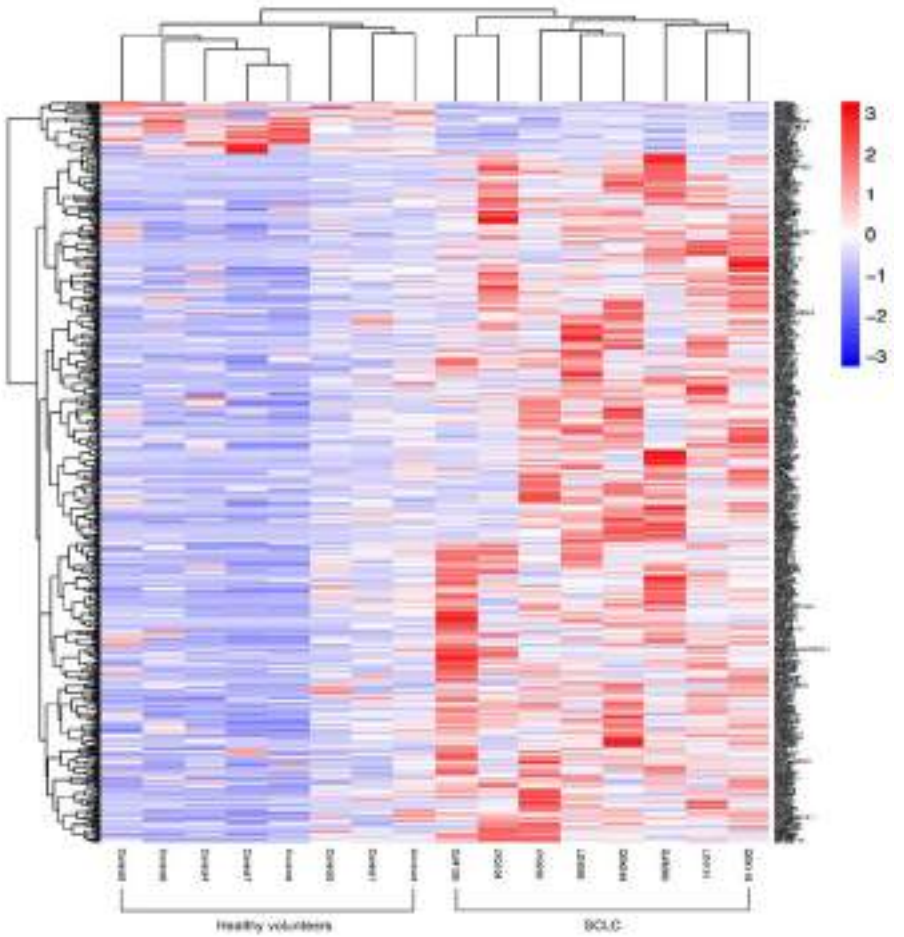
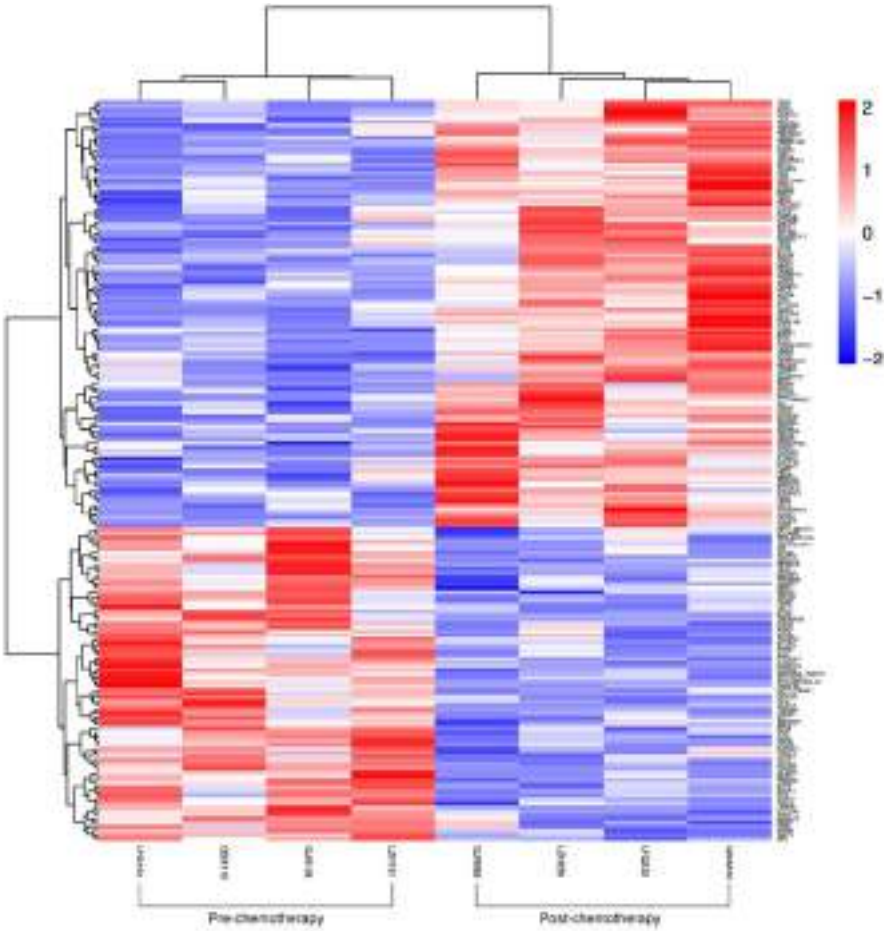
Background: Plasma exosomes, which are nanosized endocytic vesicles that have been implicated as non-invasive diagnostic, prognostic sources, contain an abundant cargo of different RNA species that may be used as biomarkers for human cancers. Little research has been done on small cell lung cancer (SCLC) blood exosomal RNA. The aim of this study is to explore SCLC exosomal specific transcriptional profiles and to further predict efficacy of first-line chemotherapy. **Method:** Pre-chemotherapy and paired post-chemotherapy plasma samples (8ml whole blood) from patients with limited or extensive disease SCLC and healthy volunteers were prospectively collected. We used exoRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany) to purify exosomes and isolate total exosomal RNAs. Exosomal RNA profiling was performed using RNA-seq. RNA-seq libraries were generated using SMART technology (Clontech). We conducted pre-experimental analysis of 8 samples from healthy volunteers and 8 samples of 4 SCLC patients before and after chemotherapy. **Result:** The heat map showed that the exosomal mRNA expression profile of SCLC was significantly up-regulated compared to healthy volunteers and that the mRNA profiles before and after chemotherapy were also significantly different. Compared with healthy volunteers, SCLC had a significant up-regulation of 499 genes including the most differential gene ZNF805 (p=2.82E-05), COPS8 (p=3.20E-05), LRRC47 (p=3.54E-05), FANCE (p=1.02E-04), PGM3 (p=1.47E-04). Before and after chemotherapy, up-regulated genes with the greatest difference included KCNN4, HBB, TRAK2, TMUB2, ELF3; down-regulated genes with the greatest difference included ZBTB7C, LHFP, WNT11, VPS33B, STON1.





Conclusion: This preliminary analysis firstly identified blood exosomal RNA profiles in SCLC and highlighted the potential application of exosomal RNA based non-invasive liquid biopsy in SCLC.

Keywords: exosomes, RNA, small cell lung cancer

P1.12-20 SURGICAL RESECTION VERSUS STEREOTACTIC BODY RADIATION THERAPY FOR T1-2 N0 TYPICAL BRONCHOPULMONARY CARCINOID TUMORS

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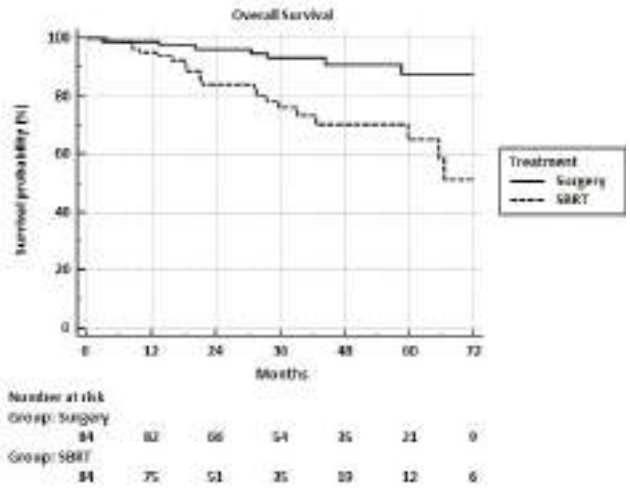
Background: There is an ongoing debate of surgical resection versus stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer. However, no study to date has compared these modalities for early-stage bronchopulmonary carcinoid tumors. **Method:** The National Cancer Database was queried for histologically-confirmed T1-2N0M0 typical carcinoid tumors. Additional exclusion criteria were lack of treatment, conventionally-fractionated radiotherapy, or postoperative radiotherapy. Multivariable logistic regression ascertained factors associated with SBRT delivery. Cox proportional hazards modeling examined factors associated with overall survival (OS). Kaplan-Meier OS analysis was performed following propensity matching. **Result:** Of 6,276 patients, 98.7% underwent resection (most commonly bi/lobectomy (67%) or sublobar resection (31%)) and 1.3% underwent SBRT (median dose/fractionation of 50 Gy in 4 fractions). Patients receiving SBRT were older, had greater comorbidities, and lower income (p<0.05 for all). Median follow-up had not been reached. SBRT was associated with poorer OS on Cox multivariate analysis (p<0.001). Following propensity matching, median OS was not reached in either group; respective mean and 5-year OS were 95.6 months and 87%, versus 68.8 months and 79% (p<0.001). Differences between cohorts persisted when removing patients who underwent SBRT specifically owing to surgical contraindications (p<0.001).



Conclusion: Surgical resection should remain the cornerstone of therapy for early-stage bronchopulmonary carcinoid tumors. For inoperable cases, SBRT also produces acceptable survival and should be preferred over conventionally-fractionated radiotherapy. However, because causation cannot be implied in any retrospective comparison of surgery versus SBRT, investigations evaluating cancer-related endpoints are required to corroborate these results.

Keywords: stereotactic body radiation therapy, lobectomy, carcinoid tumor

P1.12-21 IMPACT OF TREATMENT MODALITY ON LONG-TERM SURVIVAL OF SMALL-CELL LUNG CANCER WITH IA STAGE: A COHORT STUDY OF THE US SEER DATABASE

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Background: The purpose of this study is to identify the optimal treatment modality for small-cell lung cancer (SCLC) patients with IA stage (T1N0M0 status). **Method:** The Surveilance, Epidemiology and End Results database was used to identify SCLC patients with IA stage who received surgical resection or chemo-radiotherapy (CRT) between January 2004 and December 2014. Propensity score match analysis is utilized to balance the baseline characteristics. **Result:**

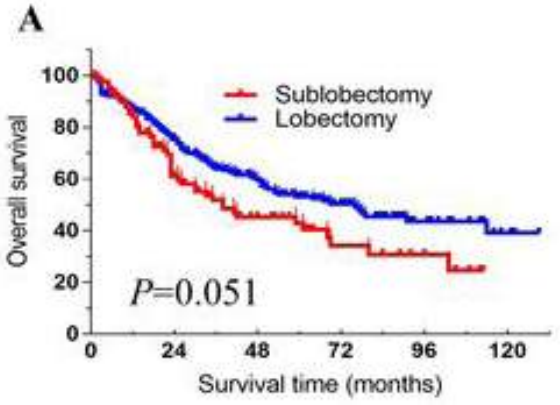
TABLE 1. Patient characteristics of small-cell lung cancer with IA stage.

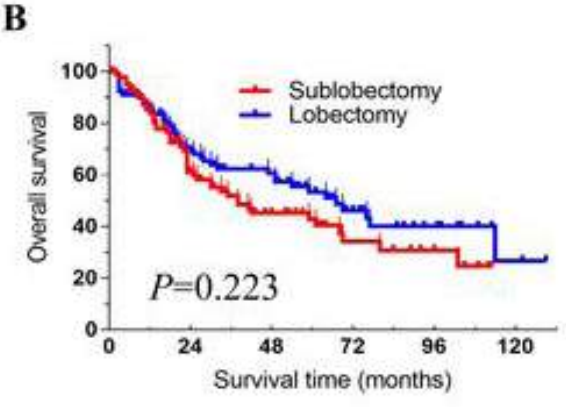
		5-year OS		Multivariate analysis		
Variables	Case	(%)	P^a	HR	95% CI	P^b
Age						
≤65	221 (32.2)	49.5	<0.001	Reference		<0.001
>65	465 (67.8)	31.1		1.656	1.312-2.089	
Gender						
Male	312 (45.5)	34.7	0.060	Reference		0.209
Female	374 (54.5)	39.1		0.878	0.716-1.07	
Location						
Upper	430 (62.7)	36.9	0.984			
Middle	54 (7.9)	38.8				
Lower	202 (29.4)	38.5				
Lateral						
Left	282 (41.1)	39.6	0.851			
Right	404 (58.9)	35.5				
T status						
T1a	68 (9.9)	47.3	0.039	Reference		0.213
T1b	327 (47.7)	34.4		1.385	0.925-2.074	
T1c	291 (42.4)	39.3		1.229	0.813-1.856	
Therapy						
CRT alone	349 (50.9)	24.7	<0.001	Reference		<0.001
Surgery	337 (49.1)	50.0		0.495	0.401-0.611	

TABLE 2. Impact of treatment on overall survival in patients with resected SCLC with T1N0M0 status

	Univariate analysis				Multivariate analysis			
	HR	95%CI	P^a	$P_{trend}{}^a$	HR	95%CI	P^b	$P_{trend}{}^b$
Treatment group								
Sublobectomy	Reference			0.011	Reference			0.047
Lobectomy	1.060	0.641-1.752	0.822		1.095	0.662-1.811	0.725	
Sublob+chemo/radio	1.274	0.664-2.443	0.467		1.304	0.680-2.501	0.425	
Lob+chemo/radio	0.750	0.439-1.282	0.293		0.851	0.494-1.465	0.561	
Sublob+chemo+radio	1.049	0.480-2.293	0.904		1.220	0.554-2.687	0.621	
Lob+chemo+radio	0.377	0.189-0.754	0.006		0.438	0.217-0.882	0.021	

Abbreviation: SCLC, small cell lung cancer; HR, hazard ratio; CI, confidence interval; Sublob+chemo/radio, sublobectomy + chemotherapy/radiotherapy; lob+chemo/radio, lobectomy + chemotherapy/radiotherapy; Sublob+chemo+radio, sublobectomy + chemotherapy + radiotherapy Lob+chemo+radio, lobectomy + chemotherapy + radiotherapy.
[a] Univariate Cox analysis; [b] Multivariate Cox analysis.





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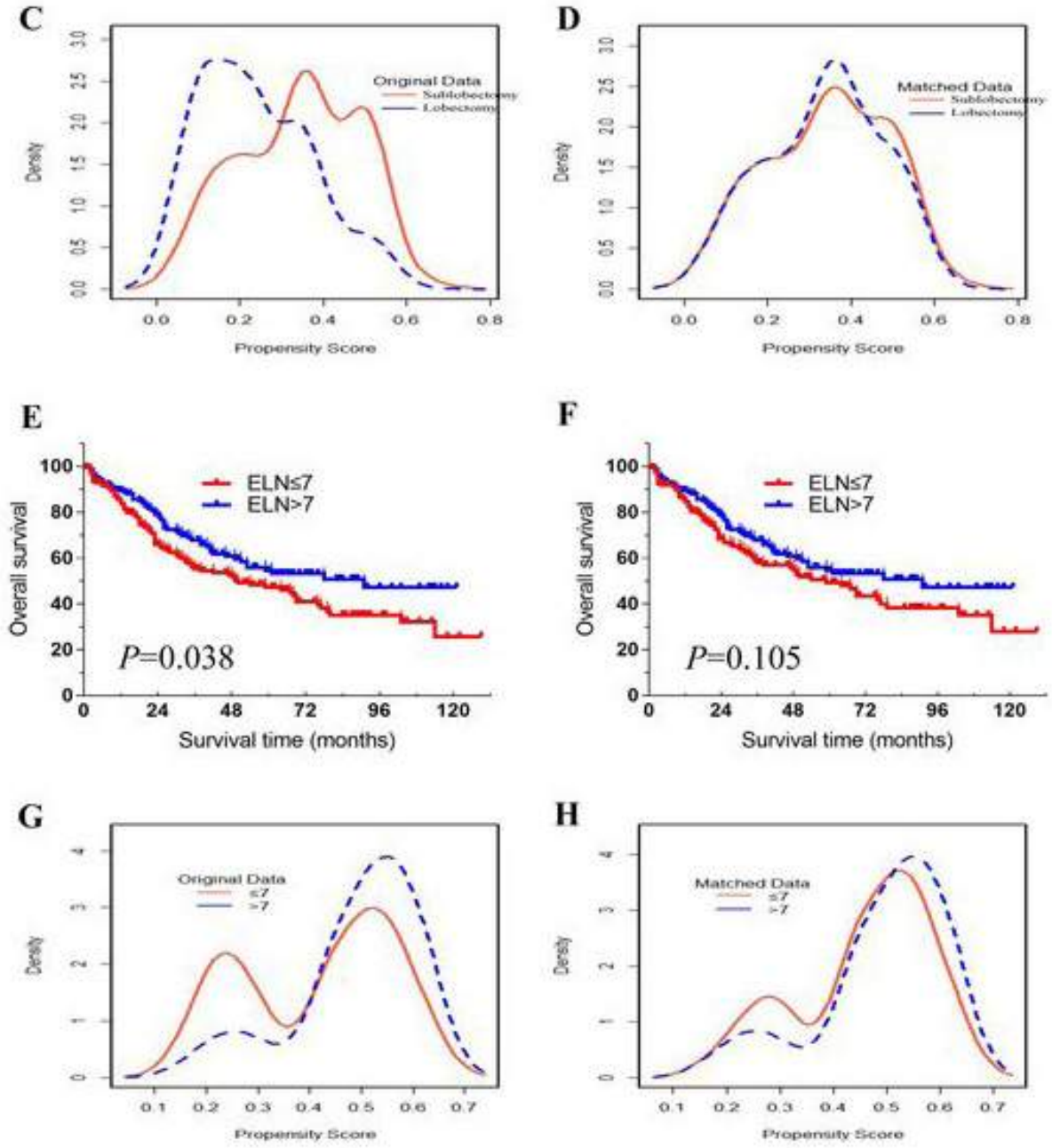

A total of 686 SCLC with IA stage were included (Table 1). Surgery lead to better outcome than CRT alone, with the adjusted hazard ratio (HR) of 0.495. Patients received lobectomy presented longer overall survival (OS) than sublobectomy (crude cohort, median OS, 69 months vs. 38 months; match cohort, median OS, 67 months vs. 38 months); patients with examined lymph nodes (ELN) >7 present longer OS than ELN ≤7 (crude cohort, median OS, 91 months vs. 49 months,; matched cohort, median OS, 91 months vs. 54 months) (Figure 1). The best prognosis was observed in lobectomy plus CRT cohort, with the 5-year survival rate of 73.5% (Table 2). **Conclusion:** Lobectomy plus chemo-radiotherapy as a component of treatment is associated with longer survival and should be considered in the management of IA stage patients with SCLC.

Keywords: small-cell lung cancer, IA stage, surgery

P1.12-22 A PHASE 1B/2 STUDY OF NIRAPARIB PLUS TEMOZOLOMIDE VERSUS STANDARD CARE AS MAINTENANCE THERAPY IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER PATIENTS

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Background: Maintenance therapy is a promising therapeutic approach for extensive-stage small cell lung cancer (ES-SCLC), especially in light of IMpower 133 (Horn NEJM 2018). SCLC models of poly (ADP-ribose) polymerase (PARP) protein 1 and 2 inhibition suggested synergy with temozolomide (TMZ) (Wainberg AACR 2016). Combining PARP inhibition with TMZ after first-line therapy for ES-SCLC may improve disease control. **Method:** This is a phase 1b/2, randomized, open-label study of TMZ plus niraparib, a PARP inhibitor, versus best supportive care (BSC) as maintenance therapy in adult patients with ES-SCLC after completion of platinum-based first-line chemotherapy. The primary outcome for phase 1b is the RP2D of TMZ in combination with niraparib, and for phase 2, progression-free survival (PFS). Secondary endpoints include safety and overall survival. Exploratory endpoints include patient-reported outcomes on health-related quality of life and adverse events which will be collected electronically through a patient portal. Phase 1b participants are required to have an advanced and incurable solid malignancy. An accelerated lead-in of 12 participants will be treated in cohorts of 6 with an initial dose level of niraparib 200 mg po daily in 28-day cycles in addition to low-dose TMZ 40 mg po daily on days 1-5 of each cycle. For phase 2, participants are required to have ES- SCLC with a complete response or partial response per RECIST 1.1 following 4 to 6 cycles of platinum-based chemotherapy and ability to proceed to randomization within 7 weeks after day 1 of the last cycle of prior chemotherapy. Prophylactic WBRT is allowed prior to study. 52 participants will be stratified by a history of brain metastases and randomized 1:1 to RP2D niraparib plus TMZ versus BSC. There will be no cross-over between arms. **Result:** Section not applicable. **Conclusion:** Section not applicable.

Keywords: clinical trial, Extensive-Stage Small Cell Lung Cancer, maintenance therapy

P1.12-23 DLL3 IS A PREDICTIVE MARKER OF SENSITIVITY TO ADJUVANT CHEMOTHERAPY FOR HIGH-GRADE NEUROENDOCRINE TUMORS

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Background: High-grade neuroendocrine carcinomas (HGNECs) include Large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC), which represent ~18% of primary lung cancer. The mammalian Notch family ligands delta-like 3 (DLL3) is considered to be a potential therapeutic target for HGNECs. The clinicopathological significance of DLL3 for HGNEC was still unclear. **Method:** We used the prospectively maintained database of Hyogo Cancer Center (Akashi, Japan), and reviewed the medical records of patients who underwent tumor resection and were diagnosed with HGNEC between January 2001 and December 2009. We performed immunohistochemistry for DLL3(E3J5R, monoclonal, 1:300 dilution, CST), and all samples were evaluated by an expert pathologist without knowledge of the patient's outcome. The results were reported as negative (no positive cell) or positive (more than 1% positive cells). We investigated the correlation between the sensitivity of HGNEC to adjuvant chemotherapy and the results of immunohistochemical staining for DLL3. Overall survival (OS) and recurrence-free survival (RFS) was estimated by the Kaplan–Meier method, and differences in distribution were evaluated using the log-rank test. **Result:** We identified 58 patients who underwent complete resection of the primary tumor and who were diagnosed with HGNEC(LCNEC n=39, SCLC n=19). The mean follow-up period was 50.9months. Twenty-one patients (LCNEC n=12, SCLC n=9) received adjuvant chemotherapy. All of them received platinum-based anticancer drugs. DLL3 was positive in 16 (51.7%) LCNEC patients and 14 (73.7 %) SCLC patients. The distribution of pathologic stage in DLL 3 positive and negative patients was stage I in 17 and 14 patients, stage II in 5 and 9 patients, and stage III in 8 and 5 patients. There was no significant difference in OS and RFS between DLL3 positive and negative patients (DLL3 positive vs. negative, 5-year OS: 40.0% vs. 39.3% p=0.79, 5-year RFS: 46.4% vs. 41.5% p=0.87). Amon patients with DLL3 positive tumors, no difference was found in 5-year OS and RFS between patients with adjuvant chemotherapy and those without adjuvant chemotherapy (Adjuvant chemotherapy vs. Surgery alone, 5-year OS: 57.1% vs. 25.0% p=0.28, 5-year RFS: 42.9% vs. 36.5% p=0.92). In contrast, when the tumors were negative for DLL3, a significantly greater 5-year OS and RFS was observed for the patients with adjuvant chemotherapy than for those without adjuvant chemotherapy (Adjuvant chemotherapy vs. Surgery alone: 5-year OS: 100.0% vs. 19.1% p<0.01, 5-year RFS: 85.8% vs. 33.3% p=0.02). **Conclusion:** DLL3 might be a predictive marker of sensitivity to adjuvant chemotherapy for HGNEC.

Keywords: high grade neuroendocrine tumor, adjuvant chemotherapy, surgery

P1.12-24 COMPARISON OF FOUR PROGNOSTIC SCORES FOR PATIENTS WITH BRAIN METASTASES FROM SMALL-CELL LUNG CANCER

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Background: Prognostic indexes are useful to guide tailored treatment strategies for cancer patients with brain metastases(BMs). Primary tumors have different biological behavior justifying separate scoring systems for different tumors. The purpose of this study was to compare four prognostic scores [recursive partitioning analysis(RPA), graded prognostic assessment(GPA), score index for radiosurgery(SIR), and basic score for brain metastases(BSBM)] for patients with BMs from small-cell lung cancer(SCLC). **Method:** Pathological diagnosis of SCLC patients with radiologically confirmed BMs were enrolled except those who received surgery of primary lesion. Clinical data, including age, KPS, primary tumor control, extracranial disease status, number of BMs, systemic disease status, and the largest lesion volume were recorded. The score of RPA, GPA, SIR and BSBM were calculated separately. Overall Survival(OS) was calculated from the date of diagnosis of BMs to the date of death from any case, or the last follow-up. OS was estimated by the Kaplan-Meier method. Cox's regression analysis was performed using a backward elimination approach to determine the best model predicting survival. $P<0.05$ was considered statistically significant. **Result:** From Jan 2011 to Oct 2014, 224 patients were eligible for the study. For the entire cohort, median OS was 9 months (95%CI, 7.7-10.3). The median survival was 10 months for RPA Class I, 9 months for RPA Class II, and 4 months for RPA Class III($P=0.039$). Using the SIR, the median survival was 11, 9, and 6 months for a score of 8-10, 4-7, and 0-3, respectively($P=0.008$). In addition, the median survival was 10 months for GPA Class I, 12 months for GPA Class II, 8 months for GPA Class III, and 6 months for GPA Class IV($P=0.136$). Using the BSBM, the median survival was 10, 8, 9, and 4 months for a score of 3, 2, 1, and 0, respectively($P=0.099$). The backward elimination model in multivariate Cox analysis identified SIR as the only variable significantly associated with survival($P=0.012$).

	Number of patients	OS	P
RPA I	31	10±1.4	
RPA II	184	9±0.7	0.039
RPA III	9	4±0.4	
GPA I	22	10±1.4	
GPA II	30	12±2.2	0.136
GPA III	136	8±0.8	
GPA IV	36	6±1.3	
BSBM 0	6	4±1.2	
BSBM 1	85	9±1.3	
BSBM 2 88		8±0.7	0.099
BSBM 3	45	10±0.7	
SIR I	14	11±2.5	
SIR II	182	9±0.7	0.008
SIR III	28	6±1.3	

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Conclusion: The SIR score was more prognostic than the RPA, GPA, and BSBM scores. For patients with BMs from SCLC, SIR was the most accurate for estimating survival. As it was mainly used for radiosurgery in BMs, maybe a new disease-specific prognostic score should be generated in this particular population.

Keywords: small-cell lung cancer, Brain metastases, prognostic scores

P1.13 STAGING
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.13-01 THE IMPORTANCE OF STAGING OF LUNG CANCERS, 30 MM OR LESS, SEPARATELY FOR SUBSOLID AND SOLID NODULES

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Background: To determine pathologic results on non-small-cell lung cancers (NSCLCs), 30 mm or less in maximum diameter, separately by tumor consistency (solid, subsolid) on CT scans as we had shown that long-term survival was significantly different by tumor consistency and by type of parenchymal invasion. **Method:** We reviewed all patients enrolled in the Initiative for Early Lung Cancer Research on Treatment (IELCART), a prospective cohort study of patients with first primary T1a-T1c NSCLC between 2016 and 2018 who had surgical resection. Short-axis diameter of N1-N3 lymph node on CT and SUVmax uptake on FDG-PET, if performed, were documented with values ≥ 2.5 defined as PET positive. Pathology reports were reviewed for N1-N3 lymph nodes (LNs) metastases and parenchymal invasion. **Result:**

Table 1

CT tumor size	Total	LN Metastases *		Parenchymal/Pleural Invasion		
		N2	N1	Angiolymphatic	Pleural	Major vascular
≤ 10 mm (n=75)						
Solid	42	0 (0.0%)	0 (0.0%)	9 (21.4%)	1 (2.4%)	0 (0.0%)
Subsolid	33	0 (0.0%)	0 (0.0%)	4 (9.5%)	0 (0.0%)	0 (0.0%)
11-20 mm (n=173)						
Solid	148	3 (2.0%)	6 (4.1%)	54 (36.5%)	18 (12.2%)	13 (8.8%)
Subsolid	25	0 (0.0%)	0 (0.0%)	8 (32.0%)	3 (12.0%)	0 (0.0%)
21-30 mm (n=100)						
Solid	90	2 (2.2%)	8 (8.9%)	41 (45.6%)	21 (23.3%)	9 (10.0%)
Subsolid	11	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (9.1%)	0 (0.0%)
Total						
Solid	280	5 (1.8%)	14 (5.0%)	104 (37.1%)	40 (14.3%)	22 (7.9%)
Subsolid	67	0 (0.0%)	0 (0.0%)	13 (19.4%)	4 (6.0%)	0 (0.0%)

*N1: lymph node metastases in ipsilateral peribronchial, and/or ipsilateral hilar lymph nodes, and/or intrapulmonary nodes.
N2: lymph node metastases in ipsilateral mediastinal and/or subcarinal lymph nodes.

Among 347 patients, 280 (80.7%) and 67 (19.3%) had solid and subsolid NSCLCs, respectively; all subsolid NSCLCs were adenocarcinoma. There was FDG-PET uptake in 253 (93.3%) with solid NSCLCs and in 55 (91.7%) with subsolid NSCLCs. None of the 67 subsolid NSCLCs had N1 or N2 LN metastases (Table 1). Among the 280 solid NSCLCs, none of the 42 NSCLCs≤ 10 mm had N1 or N2 metastases, while 5 of the 238 solid NSCLCs greater than 10 mm had N2 and 14 had N1 LN metastases. None of the N2 LNs were positive on FDG-PET and only 4(28.6%) of the 14 N1 LNs were positive on FDG-PET. Angiolymphatic invasion was most frequently, followed by pleural and major vascular invasion (Table 1). For solid NSCLCs, invasion increased with increasing tumor diameter. **Conclusion:** No N1-N3 LN metastases were identified in solid NSCLCs ≤ 10 mm; none in subsolid NSCLCs ≤ 30 mm. None with N2 LN metastases were positive on FDG-PET. This suggests that for NSCLCs, 30 mm or less, clinical staging be based on solely tumor size. For pathologic staging, we recommend differentiating staging classification by tumor consistency in line with the latest recommendations for pathologic assessment.

Keywords: TNM staging, PET, nodule consistency

P1.13-02 SHOULD AORTIC LYMPH NODES BE CONSIDERED HILAR LYMPH NODES IN PATIENTS WITH COMPLETELY RESECTED NSCLC? A MULTICENTER STUDY

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Background: It has been suggested that aortic lymph nodes (stations #5 and #6, aortic-LNs) may have a similar prognostic significance as hilar-LNs (stations #10 and #11). Therefore we compared survival of lung cancer patients with aortic-LNs metastasis to those with N1 disease at the hilar-LNs. **Method:** Between 2008 and 2017, 865 patients with left upper lobe (LUL) lung cancer underwent complete resection in three centers. Overall survival was assessed retrospectively and compared in four groups according to pN status: N0 (n=429, 49.6%), N1 (n=259, 29.9%), $N2^{5,6+}$ (only metastasized to stations 5 and/or 6 with/without N1 disease, n=126, 14.6%), and $N2^{7+}$ (only metastasized to station 7 with/without N1 disease, n=51, 5.9%). pN1 was divided two subgroups according to location; $N1^{peripheral}$ (n=124), $N1^{hilar}$ (n=135). **Result:** Five-year survival rate was significantly better for $N2^{5,6+}$ than $N2^{7+}$ patients (32.7% vs 22.1%) (p=0.05) (Figure 1). Skip metastasis for aortic-LNs (n=39) was a factor of better prognosis as compared to non-skip metastasis (n=87) (42.5% vs. 26.3%) (p=0.03) although five year survival rates were similar for $N2^{single\ (5+\ or\ 6+)}$ (n=96) and $N2^{multiple\ (both\ 5+\ and\ 6+)}$ (n=30) patients (32.8% vs 32.3%, p=0.8). There was no statistically significant difference between the $N2^{5,6+}$ and $N1^{hilar}$ (p=0.4), although $N1^{peripheral}$ had a significantly better survival than $N2^{5,6+}$ (p<0.0001) (Figure 2).

Figure 1. The survival curves of $N2^{5,6+}$ and N^{7+}

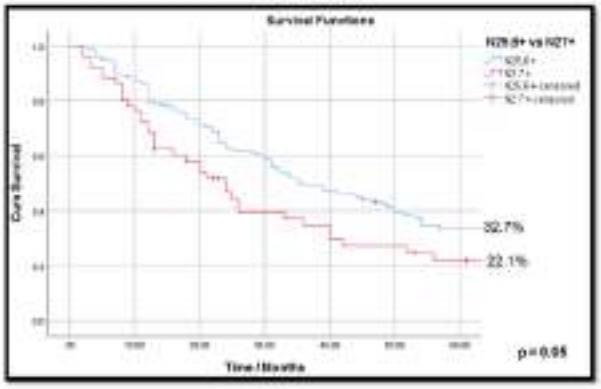
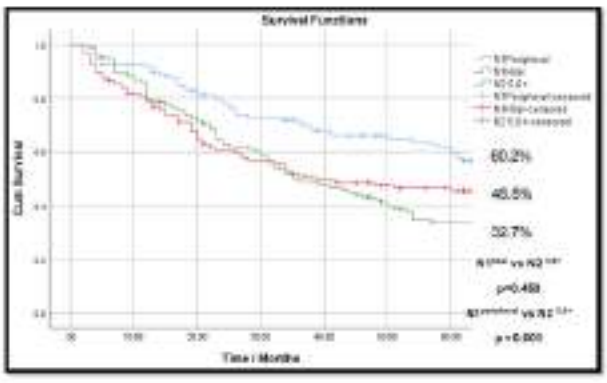


Figure 2. Survival Comparison of $N1^{peripheral}$, $N1^{hilar}$ and $N2^{5,6+}$



In multivariate analysis, age (p<0.0001), N2 versus N0/1 (p<0.0001), $N1^{hilar}$ versus $N1^{peripheral}$ (p=0.006), $N2^{5,6+}$ versus $N1^{peripheral}$ (p=0.0001), $N2^{7+}$ vs $N2^{5,6+}$ (p=0.05), and $N2^{non\text{-}skip\ 5\ and/or\ 6+}$ vs $N2^{skip\ 5\ and/or\ 6+}$ (p=0.01) were significant independent negative prognostic factors (Table 1).

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N status	No	5-year survival rate (%)	Median survival (months)	Comparison	p value	Hazard Ratio	Multivariate analysis
N0	429	68.5%	113				
N1	259	52.5%	66	N0 vs N1	<0.0001	1.614	0.0006
N2	177	29.7	33	N1 vs N2	<0.0001	1.587	<0.0001
N1-subgroup							
$N1^{Peripheral}$	124	60.2%	98				
$N1^{Hilar}$	135	45.5%	39	$N1^{Peripheral\ vs}\ N1^{Hilar}$	0.005	1.652	0.006
N2-subgroup							
$N2^{5,6+}$	126	32.7%	36	N1 vs $N2^{5,6+}$	0.008	1.442	0.01
				$N1^{Peripheral}$ vs $N2^{5,6+}$	<0.0001	2.037	0.0001
				$N1^{Hilar}$ vs $N2^{5,6+}$	0.450	1.126	
$N2^{7+}$	51	22.1%	24	$N2^{5,6+}$ vs $N2^{7+}$	0.05	1.443	0.05
T status							
T1	202	65.7%	113				
T2	335	54.9%	83	T1 vs T2	0.02	1.456	0.219
T3	181	49.8%	58	T2 vs T3	0.05	1.321	0.02
T4	147	40.1%	47	T3 vs T4	0.272	1.102	
Age <65 Age >65	595 270	60.2% 39.3%	98 41	<65 vs >65	<0.0001	1.946	<0.0001
Lobectomy Pneumonectomy	498 367	58.5% 48.5%	94 58	Lob vs Pnmc	0.008	1.326	0.275
Female Male	133 732	61.6% 53.2%	118 68	Female vs Male	0.09	1.367	
Hystologic Type Squamous Adeno Others	478 305 82	55.9% 53.0% 49.9%	87 83 59	Squam. vs Adeno	0.665	1.201	

Conclusion: The prognostic significance of aortic-LNs is similar to hilar-LNs even if LUL tumors with hilar-LNs metastasis is associated with statistically not significant prognosis than aortic-LNs metastasis. In order to generalize this result, it needs to be validated in a bigger database.

Keywords: Aortic Lymph nodes, Nonsmall cell lung cancer, Mediastinal Lymph nodes

P1.13-03 LUNG ADENOCARCINOMAS MANIFESTING AS RADIOLOGICAL PART-SOLID NODULES DEFINE A SPECIAL CLINICAL SUBTYPE

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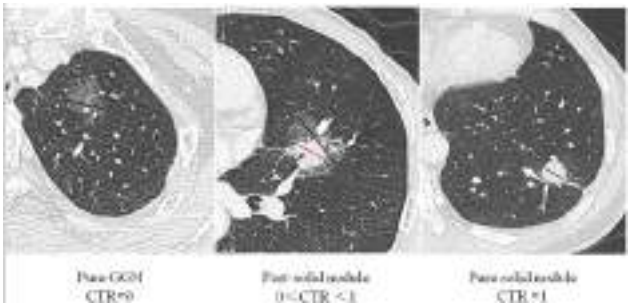
Background: According to guidelines from the Fleischner Society in 2017, subsolid nodules are categorized into pure ground glass nodules (pGGNs) having only a GGO component and part-solid nodules having both GGO and solid components on thin-section computed tomography (TS-CT). Persistent part-solid nodules with solid components ≥ 6mm should be considered highly suspicious. Clinicopathologic features and prognostic predictors of radiological part-solid lung adenocarcinomas were unclear. **Method:** We retrospectively compared clinicopathologic features and survivals of part-solid tumors with those of pure ground glass nodules (pGGNs) and pure solid tumors receiving surgery at Fudan University Shanghai Cancer Center, and evaluated prognostic implications of consolidation-to-tumor ratio (CTR), solid component size and tumor size for part-solid lung adenocarcinomas.



Result: 911 patients and 988 pulmonary nodules (including 329 part-solid nodules (PSNs), 501 pGGNs & 158 pure solid nodules) were analyzed. More female patients (P=0.015) and non-smokers (P=0.003) were seen in PSNs than those in pure solid nodules. Prevalence of lymphatic metastasis was lower in PSNs than that in pure solid tumors (2.2% vs 27%, P=0.000). 5-year lung cancer specific recurrence free survival (LCS-RFS) and overall survival (OS) of PSNs were worse than those of pGGNs (P<0.001; P=0.042), but better than those of pure solid tumors (P<0.001; P<0.0001), respectively. CTR (OR: 12.90; 95% CI: 1.85-90.04), solid component size (OR: 1.45; 95% CI: 1.28-1.64) and tumor size (OR: 1.23; 95% CI: 1.15-1.31) could predict pathologic invasive adenocarcinoma for PSNs. None of them could predict the prognosis. Patients receiving sublobar resection had comparable prognoses with those receiving lobectomy (5-year LCS-RFS: P=0.178; 5-year LCS-OS: P=0.319). Prognostic differences between patients with systemic lymph node dissection (sLND) and those without sLND were statistically insignificant.

Table 1 Baseline clinicopathologic characteristics of objects in this study

	All N=988	Part Solid nodule N=329	Pure Ground Glass nodule N=501	Pure Solid nodule N=158	P value
Age (Mean±SD)	56.49±10.83	58.89±9.71	53.64±10.86	60.54±10.52	0.000
Gender					0.015
Male	277(30.4)	91 (28.9)	124 (28.2)	62 (39.5)	
Female	634(69.6)	224 (71.1)	315 (71.8)	95 (60.5)	
Smoking status					0.003
Smoker	153(16.8)	52 (16.5)	62(14.1)	39(24.8)	
Non-smoker	758(83.2)	263(83.5)	377(85.9)	118(75.2)	
Tumor size(mm)	15.14±7.38	20.51±7.18	10.22±3.84	19.54±5.58	0.000
Location					0.009
RUL	364 (36.8)	126 (38.3)	197 (39.3)	41 (25.9)	
RML	67 (6.8)	21 (6.4)	29 (5.8)	17 (10.7)	
RLL	181 (18.3)	48(14.6)	93 (18.6)	40 (25.3)	
LUL	266 (26.9)	98 (29.8)	130 (25.9)	38 (24)	
LLL	110 (11.2)	36 (10.9)	52 (10.4)	22 (14.1)	
Surgery					0.000
Wedge resection	456(46.2)	72(21.9)	370(73.8)	14(8.9)	
Segmentectomy	97(9.8)	33(10.0)	58(11.6)	6(3.8)	
Lobectomy	435(44.0)	224(68.1)	73(14.6)	138(87.3)	
Pathology					0.000
AIS/MIA	509(51.5)	56(17.0)	447(89.2)	6(3.8)	
IAD	479(48.5)	273(83.0)	54(10.8)	152(96.2)	
Lepidic predominant	154(32.6)	104(38.8)	30(55.5)	30(55.5)	0.000
Solid/Micropapillary predominant	21(4.5)	4(1.5)	1(1.9)	16(3.4)	0.000
Acinar/Papillary predominant	290(61.4)	157(58.6)	22(40.7)	111(74.0)	0.000
Mucinous adenocarcinoma	7(1.5)	3(1.1)	1(1.9)	3(2.0)	0.753
Pathologic N status					0.000
N0	904 (94.9)	305(97.8)	488 (100)	111(73)	
N1/2	48(5.1)	7(2.2)	0 (0)	41 (27)	

Conclusion: Part-solid lung adenocarcinoma showed different clinicopathologic features compared with pure solid tumor. CTR, solid component size and tumor size could not predict the prognosis. Part-solid lung adenocarcinomas define one special clinical subtype.

Keywords: part-solid nodule, lung adenocarcinoma, prognosis

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P1.13-04 IMPACT OF THE PRESENCE AND PROPORTION OF GGO ON SURVIVAL AND PATHOLOGICAL CHARACTERISTICS IN CLINICAL STAGE I LUNG ADENOCARCINOMA

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Background: The aim of this study was to investigate a prognostic and clinicopathological impact of ground-glass opacity (GGO) on existing clinical T classification. **Method:** We analyzed 1228 patients with lung adenocarcinoma classified as clinical stage I who underwent complete resection by lobectomy or pneumonectomy from 2003 to 2013. We divided patients into four groups based on the presence and proportion of GGO by using consolidation-to-tumor ratio (CTR), calculated with the maximum solid component diameter divided by the maximum tumor diameter including GGO area on thin-slice computed tomography; A, CTR ≤0.5; B, 0.5< CTR ≤0.75; C, 0.75< CTR ≤1.0 including GGO; D, GGO negative (pure solid). We compared them on overall survival, pathological findings and histological subtypes in each clinical stage of IA1 to IB. **Result:** In all clinical stage, we found no significant differences among group A-C on prognosis and pathological findings. The prognosis of each group of A-C was significantly more favorable than that of group D in clinical stage IA2 and IA3. With respect to the pathological findings, group D had significantly larger positive number of N/ly/v in stage IA2 and that of N/pl/v/STAS in stage IA3 than each group of A-C. Group D had significantly less proportion of lepidic component and consisted with more percentile of solid component than each group of A-C in clinical stage IA2-IB. **Conclusion:** Not proportion but presence of GGO had great impact on prognosis and pathological characteristics. The presence of GGO might as well be included in the next T classification.

Keywords: lung adenocarcinoma, ground-glass opacity, consolidation-to-tumor ratio

P1.13-05 EVALUATION OF PET/CT SCANS TO PREDICT PATHOLOGIC LUNG CANCER STAGING

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Background: PET/CT scan use prior to biopsy of lesions suspicious for lung cancer is not recommended due to a lack of supporting data. We hypothesize that a PET/CT Scan provides critical information that directly impacts biopsy strategy. **Method:** We retrospectively analyzed all patients referred to the Pulmonary service at the Miami VA Medical Center for abnormal chest imaging concerning for lung cancer from February 12, 2013 to October 1, 2018. **Result:** Of 481 patients, 400(83.2%) underwent PET/CT scanning and 225(46.8%) had lung cancer. Based on PET/CT findings, 74(18.5%) only had a Solitary Pulmonary Nodule(SPN) and went directly to definitive treatment. 51(68.9%) patients underwent surgical resection. However, 1(1.3%) had stage IV pleural disease found during surgery. 3(4%) had invasive disease and 5(6.7%) had lymph node involvement requiring post-operative chemotherapy. 14(18.9%) had stereotactic body radiation therapy, 2(2.7%) had small cell lung cancer without lymph node involvement and 3(4%) were considered inoperable based on comorbidities and were treated with XRT and chemotherapy due to large tumor size. 3(4%) were lost to follow-up. Only one patient (1.3%) was found to have metastatic disease not identified by PET/CT Scan. Of 61(15.2%) patients with a CT scan revealing only an SPN, 30(49.1%) had FDG avid mediastinal lymph nodes positive for cancer in 25 cases (83.3%). 2 were downstaged as the mediastinal lymph nodes were negative on biopsy. One(3.3%) patient was lost to follow-up, 1(3.3%) treated as possible mediastinal disease even though biopsy was negative and 1(3.3%) was stage 4 due to contralateral lung disease. Among the 25 patients, PET/CT missed bone metastasis in 1. Thirty one(50.9%) had extrathoracic lesions on PET/CT with 14(45.1%) proven to have metastatic disease, 11(35.4%) were assumed to have metastatic disease based on imaging, 2(6.4%) had oropharyngeal cancer, 1(3.2%) had a hepatoma and 1(3.2%) had lymphoma. 2 patients (6.4%) were false positives. Among 90 patients with multiple pulmonary nodules on CT, PET/CT found 35(38.8%) had activity in the nodules without mediastinal/extra-thoracic involvement. In these patients, 3(8.6%) had positive mediastinal nodes on biopsy, 21(65.6%) underwent surgery (2 were found to have positive mediastinal lymph nodes at surgery), 7(21.8%) were treated with SBRT, 1(3.1%) had SCLC, 1(3.1%) was treated with chemotherapy/radiation due to size, 1(3.1%) had pleural disease and 1(3.1%) was treated with chemotherapy/radiation for suspected mediastinal disease. Of the remaining 55 patients, 20 had extra thoracic disease, 16 had mediastinal disease and 19 had multiple hypermetabolic nodules with congruence between PET/CT and biopsy in 18(90%), 14(87.5%) and 16(84.3%), respectively. In 225 lung cancer patients, PET/CT accurately predicted pathological stage in 194 patients (86.2%). Compared to CT, PET/CT identified an alternative biopsy location in 16.2% of the patients. Analysis showed SPNs greater than 8mm have 8.2% and 6.5% risk of mediastinal and extra-thoracic disease, respectively. **Conclusion:** Based on our data, we believe use of PET/CT prior to biopsy in patients with chest imaging suspicious for lung cancer will direct a single biopsy that produces the highest stage by least invasive route.

Keywords: PET CT, Lung cancer, Biopsy

P1.13-06 IMPACT OF LYMPH NODE INVOLVEMENT AND TUMOR LOCATION ON SURVIVAL FOLLOWING RESECTION FOR PN1/PN2 NON-SMALL CELL LUNG CANCER

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Background: The aim of this analysis is to validate the proposal for the new N staging system for non-small cell lung cancer and evaluate the impact of cancer location on N disease **Method:** Between January 2011 and December 2015 2,531 anatomical lung cancer resections were performed. Retrospective analysis of the database identified 449 patients with pathological N1 / N2 disease. Patients with N0 disease, carcinoid, small cell lung cancer or secondary cancer were excluded. Patients with M1a (n=5) were excluded as well. **Result:** 449 patients were enrolled in the analysis. Median age was 68 years (range 37 - 87). There were 197(43.9%) female patients. 63.3% (n=284) of the patients were dead at the time of the analysis. Median overall survival of the population was 36.4 months (range 0.4 – 116 months). N1 disease had a median OS of 41.8 months (range 33 -50 months) and N2 26.9 months (range 19 - 34 months) (p=0.004). Dividing single N1 (N1a), multiple N1 (N1b), single N2 with skip metastases (N2a1), single N2 metastasis with N1 disease (N2a2) and multiple N2 (N2b) there was a statistical significant difference in survival (p=0.048): 41.7 months (range 32 - 51), 39.2 months (range 17 - 61), 33.3 months (range 14 - 52), 25 months (range 10 - 39) and 24.6 motnhs (range 19 -30) respectively. Analyzing multiple N2 disease (N2b) with single N1 station involved vs multiple N2 the OS was 18.9 months (range 12-25) vs 31.8 months (range 13-49) respectively. Seventy one patients had skip metastasis, the presence or not of skip metastasis alone did not correlate with OS: 32.2 months (range 16 - 47) vs 37.3 mo (range 32.5 – 42 mo) (p=0.7). Analyzing factors related to the N subclassification sex (p=0.24), side (p=0.17) and histology (p=0.26) were not correlated with the N status. The tumor location was instead related with N status (p=0.05)

Lymph node involvement per tumor location for N1/N2 subgroups

	N1a	N1b	N2a1 ('skip')	N2a2	N2b	Total
Left Hilum	24	0	2	4	5	35
Left upper lobe	63	2	20	23	10	118
Left lower lobe	30	3	6	12	5	56
Right hilum	32	3	2	3	11	51
Right upper lobe	59	6	10	22	15	113
Middle lobe	6	0	3	4	3	16
Right lower lobe	25	4	13	9	9	60

Conclusion: N staging has a significant impact on survival. The new proposed N staging system better stratifies the survival of lung cancer patients with lymph node involvement. Within the N2 category single or multiple N1 and skip N2 metastasis do not have a statistically significant impact on survival.

Keywords: Lung cancer, N2 disease, staging

P1.13-07 COMPARISON OF THE 7TH AND 8TH EDITION OF TNM STAGING FOR NSCLC IN PATIENTS UNDERGOING PULMONARY RESECTION AFTER NEOADJUVANT/ INDUCTION TREATMENT

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Background: The new staging system for lung cancer (8thTNM) has been defined and in use since 2017. The aim of this study was to confirm the novel staging system's distinctive ability and prognostic performance in patients with clinic local advanced NSCLC undergoing Neoadjuvant/Induction (N/I) treatment followed by pulmonary resection. **Method:** The patients with locally advanced NSCLC who underwent segmentectomy or larger lung resection after N/I treatment between 2000 and 2017 were prospectively recorded and retrospectively analyzed. ypTNM stages of the patients were recorded using the 7th and 8th TNM staging system. The results were analyzed. **Result:** The study included 449 patients with a mean age of 58.92 ± 8.47, 30 were female and 419 male. Chemotherapy as an N/I was the treatment of choice for 321 (71.5%) patients and chemoradiation in 128 (28.5%) patients. The type of lung resection was segmentectomy in 22 (4.9%), lobectomy in 345 (76.8%) and pneumonectomy in 82 (18.3%). According to the 7th TNM classification; complete response, T0N0, was observed in 78, stage 1a in 83, Ib in 53, IIa in 66, IIb in 45, IIIa in 90, IIIb in 5 and stage IV in 29 patients. However, according to the 8th TNM classification; complete response, T0N0, was observed in 78, Ia1 in 18, Ia2 in 24, Ia3 in 42 patients, Ib in 35, IIa in 21, IIb in 98, IIIa in 88, IIIb in 16, and stage IV in 29 patients. When the long-term survival was analyzed for the 7th and 8th TNM Staging System, significant differences were observed in stages for each edition respectively ($p < 0.001$, $p < 0.001$). **Conclusion:** In patients undergoing surgery after neoadjuvant/induction treatment, a significant number of stage migration was detected between the 7th and 8th staging system. The 8th TNM classification showed no improvement in the ability to differentiate between subgroups compared to the older version, especially for ypStage1. To prove that the 8th TNM classification is a superior method for staging patients with N/I, further studies with larger databases are needed for this group.

Keyword: staging, neoadjuvant treatment, induction treatment, TNM, surgery

P1.13-08 THE MAXIMUM STANDARDIZED UPTAKE VALUES ON POSITRON EMISSION TOMOGRAPHY PREDICT PATHOLOGICAL CHARACTERISTICS OF NON-SMALL CELL LUNG CANCER

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Background: ^{8}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is widely used in the preoperative staging of non-small cell lung cancer (NSCLC). In this study, we sought to assess the predictive value of maximum standardised uptake value (SUV_{max}) on PET-CT for postoperative pathological metastasis and involvement in clinical stage IA NSCLC patients undergoing curative intent surgical resection. **Method:** In July 2015, FDG-PET/CT was introduced to our institution. We retrospectively reviewed patients with c-stage IA NSCLC diagnosed by FDG-PET/CT at our institution who underwent macroscopic complete pulmonary resection. The pathological metastasis and/or involvement was defined that positive pleural effusion or lavage cytology, pleural involvement, pulmonary metastasis, lymph node metastasis, and/or lymphovascular involvement were identified on pathological examination. To identify predictors for the pathological metastasis and/or involvement, preoperative clinical and radiologic factors (age, sex, smoking index, tumor markers, whole tumor size, solid component size, consolidation/tumor ratio, diseased side, tumor location, tumor histology, and SUV_{max} on FDG-PET/CT) were analyzed by a univariate analysis and multivariate logistic regression analysis. For the significant factors by the multivariate analysis, optimal cutoff points were determined with a receiver operating characteristic (ROC) analysis. **Result:** Of the 179 eligible patients, 103 were male and 76 were female. The median age was 70 years. The median whole tumor size, solid component size, and consolidation/tumor ratio on CT were 2.1 cm (range, 0.3-5.8 cm),1.7 cm (range, 0-3.0 cm),and 87% (range, 0-100%),respectively. The median SUV_{max} on FDG-PET/CT was 4.20 (range, 0.78-28.07). According to the postoperative pathological examination, 147 patients (82%) had adenocarcinoma, 25 (14%) had squamous cell carcinoma, and 7 (4%) had other types of NSCLC. Pleural involvement, pulmonary metastasis, lymph node metastasis, lymphatic permeation, and vascular invasion were identified in 26 (15%), 6 (3%), 15 (8%), 11 (6%), and 19 patients (11%), respectively, and in total, 46 patients (26%) developed the pathological metastasis and/or involvement. The univariate analysis identified SUV_{max}, sex, carcinoembryonic antigen, Sialyl Lewis^{x}-1, whole tumor size, solid component size, consolidation/tumor ratio, diseased side, tumor location, and tumor histology as significant predictors. A multivariate analysis revealed SUV_{max} (OR: 1.197, $p<0.001$) and consolidation/tumor ratio (OR: 1.052, $p = 0.001$) as significant independent predictors. The solid component size and whole tumor size were not identified as significant independent predictors. By the ROC analysis, the optimal cutoff point for SUV_{max} was determined as 6.10. Thirty-seven of the 67 patients (55%) with $\geq$6.10 of SUV_{max} developed the pathological metastasis and/or involvement whereas 9 of the 112 patients (8%) with <6.10 of SUV_{max} developed pathological metastasis and/or involvement. **Conclusion:** Our results suggested the predictive effect of high SUV_{max} on pathological metastasis and involvement in clinical stage IA NSCLC patients. Thus, FDG-PET/CT should be utilized for the preoperative precise evaluation of early stage NSCLC, and we may consider SUV_{max} on FDG-PET/CT to decide surgical procedure for these patients, such as the extent of pulmonary resection and lymphadenectomy.

Keywords: Non-Small Cell Lung Cancer, 18F-fluorodeoxyglucose positron emission tomography/computed tomography, FDG-PET

P1.13-09 UTILITY OF ARTIFICIAL INTELLIGENCE IN ESTIMATION OF THE HISTOLOGIC TYPE OF LUNG CANCER

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Background: With the development of artificial intelligence (AI), various activities using AI have become able to be performed without specialized knowledge. Computer-aided diagnosis systems using AI have also made great strides in decades. We examined the qualitative diagnostic ability to estimate the histologic type of lung cancer using an image recognition system that can be used online. **Method:** We used 316 computed tomography (CT) images of lung cancer with solid component diameter less than 3 cm resected at our hospital. All images were trimmed at the tumor edge to increase the accuracy of machine learning by AI. Prepared images were classified by pathological diagnosis into adenocarcinoma (AD) group and non-adenocarcinoma (non-AD) group. 159 images were assigned to the training set and 157 were assigned to the test set. IBM watson studio; visual recognition app developed for image recognition was used for machine learning and judgment. The established algorithm by the training set was applied to the test set. The histologic type of which possibility calculated by AI was over 0.5 was defined as the AI answer. **Result:** There were 93 AD and 66 non-AD in the training set and 92 AD and 65 non-AD in the test set. In the AD group, the median of the solid component diameter was 1.5 cm (0 - 2.9 cm). 21 images were pure ground-glass nodules, 122 images were part-solid ground-glass nodules and 42 images were consisted of solid component. In the non-AD group, the median of the solid component diameter was 2.0 cm (0.5 - 3.0 cm) and all images were consisted of solid component. Of the 65 non-AD images in the test set, the AI answer was correct in all images (100%). However, of the 92 AD images in the test set, the AI answer was correct only in 49 images (53%). When the 47 AD images with dominant ground-glass opacity were analyzed, the AI answer was correct in 33 images (70%). **Conclusion:** Although the CT image recognition using AI could accurately estimate the histologic type of lung cancer in tumors with dominant ground-glass

opacity, it was difficult to distinguish solid AD from solid non-AD. The multimodal image analysis including enhanced CT and FDG-PET seems necessary.

Keyword: AI, image recognition, NSCLC

P1.13-10 INCIDENCE OF HIDDEN EXTRATHORACIC METASTASES AND UNEXPECTED SECOND MALIGNANCIES DETECTED BY PET IN PATIENTS WITH LUNG CANCER

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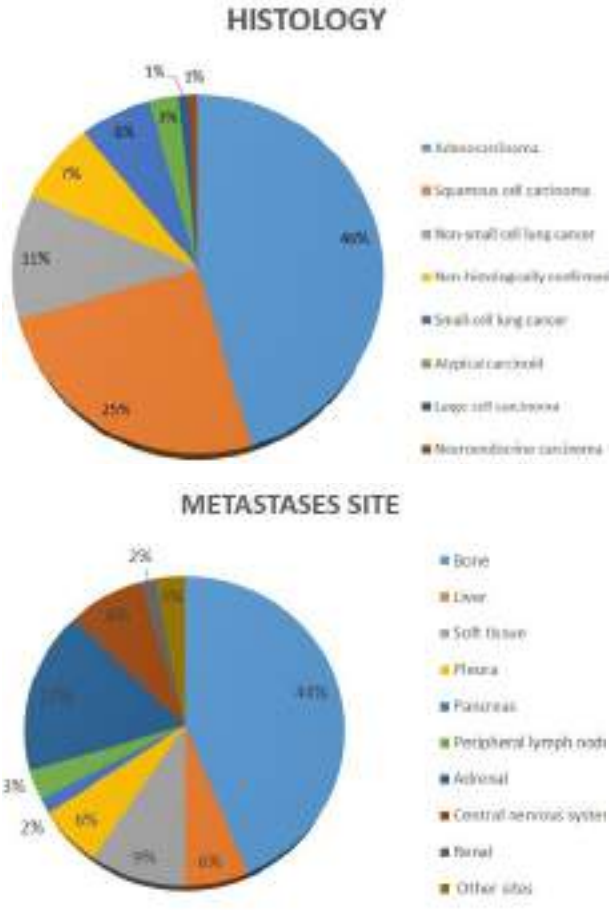
Background: Recent staging guidelines for lung cancer (LC) staging recommend invasive mediastinal staging regardless of the findings of positron emission tomography (PET). Thus, the role of PET in the staging of LC seems to be increasingly relegated to the detection of hidden extrathoracic metastases. The aim of the study was to determine the incidence of hidden metastasis and second malignancies diagnosed by PET in a cohort of patients with LC and without extrathoracic metastases identified in the initial radiologic work up. **Method:** This is a retrospective study that included patients with a final diagnosis of LC without extrathoracic metastases identified in the initial radiologic work up (thorax and upper abdomen computer tomography). The incidence of hidden metastases and unexpected second malignancies detected by PET were recorded. **Result:** From 2006 to 2018, 343 patients were included (81% male, mean age 68.2 ± 9.6 years) (Table 1). PET detected hidden metastases in 57 (16.6%) patients (Table 2). Fifty-two patients had a single metastasis and 5 had multiple metastases. A total of 64 metastases were detected, the most frequent location was bone (28). Five (1.4%) patients presented an unexpected second malignancy: 2 head and neck, 2 colorectal and one lymphoma.



Conclusion: PET detects hidden metastases in 16% of patients with LC and without extrathoracic metastases identified in the initial radiologic work up. 1.4% patients presented an unexpected second malignancy.

Keywords: Lung cancer, Metastases, positron emission tomography

P1.13-11 AN AUDIT ON IASLC COMPLIANCE OF LYMPH NODES DISSECTION AND IMPACT ON SURVIVAL AFTER SURGERY FOR NON-SMALL CELL LUNG CANCER

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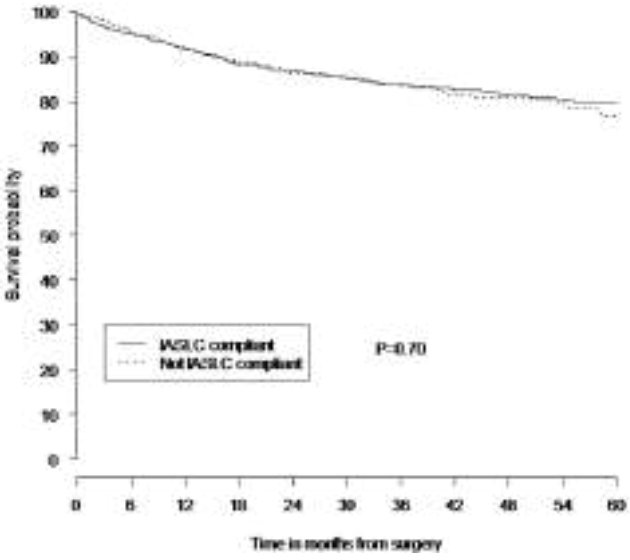
Background: The IASLC proposed minimal criteria for 6 nodes / stations to ascertain certainty status of complete (R0) resection after lung cancer surgery and in 2017, Edwards et al presented that failure of compliance leading to R0 (un) status was associated with poorer survival. The aims of this audit are to assess compliance of the IASLC recommendations on lymph node staging and determine the impact of R0 (un) status on prognosis in an independent cohort. **Method:** We included patients who underwent lobectomy or pneumonectomy for primary lung cancer. Data was obtained from electronic records and survival status obtained from NHS Spine. **Result:** From January 2010 to December 2017, 2,521 patients underwent lung resection for primary lung cancer staged using TNM7. The mean age (SD) was 67 (10) and 1,235 (49%) were men, the primary diagnoses were either adenocarcinoma or squamous carcinoma in 2,057 (82%). The IASLC compliance with 6 node / stations was 627 (25%) and when sub-carinal station was mandatory it was 608 (24%). After exclusions, we were left with 1,859 patients and on adjustment of T and N category, there was no difference between IASLC non-compliance R0 (un) on overall survival with a hazard ratio of 0.95 (95% CI 0.74 to 1.21; P=0.657) compared to R0 compliant. After adjusting for T and N category there was no significant difference in total lymph nodes stations harvested with a HR 1.01 (0.97 to 1.04, P=0.712) or number of positive stations HR 1.04 (0.92 to 1.16; P=0.543) in survival.



Conclusion: Independent validation of R0 (un) status did not concur with poorer survival. The designation carries uncertainty and likely to be influenced by the extent of N2 dissection. When adjusted for stage, there was no difference on number of stations harvested nor the total number of positive stations on survival.

Keywords: Lung cancer, surgery, lymph node

P1.13-12 THE INVASION OF MEDIASTINAL FAT TISSUE SHOULD BE CONSIDERED FOR T4 DESCRIPTION IN THE NEXT TNM CLASSIFICATION OF NSCLC

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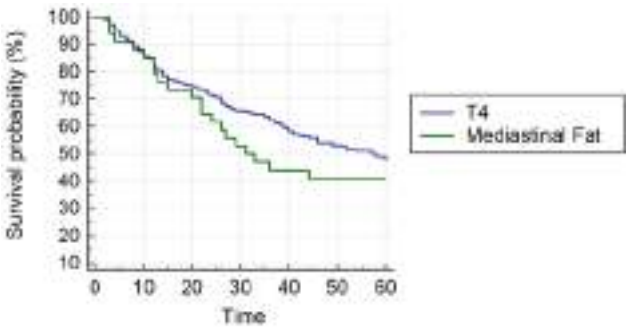
Background: Mediastinal fat tissue invasion is not included for the T description in the 8th edition of the TNM classification of NSCLC. The present study aimed to compare survival of patients who have

mediastinal fat tissue invasion with patients who are determined as T4 according to the 8th classification of lung cancer. **Method:** Between 2006 and 2016, 2052 patients undergoing pulmonary resection for NSCLC were evaluated. The present study analyzed of 284 cases; of which 36 patients who had been found mediastinal fat tissue invasion by pathological evaluation (Mediastinal Fat group) and 248 cases who had been determined as T4 according to the 8th classification of NSCLC (T4 group; invasion of structures in 78 patients, ipsilateral different lobe satellite pulmonary nodule in 32 patients, and tumor diameter > 7 cm in 138 patients). **Result:** Complete resection (R0) was possible in 255 patients (89.7%). The overall 5-year survival rate was 46.5% (median 54 months). Five-year survival rates for T4 subcategories (invasion of other structures, ipsilateral different lobe pulmonary nodule, and tumor diameter > 7 cm) were 39.4%, 41.9%, and 50.3%, respectively (p=0.109). Mediastinal Fat group survival was found worse better than T4 group (37.6% vs 47.3%, median 31 months vs 57 months), although this difference was not statistically significant (p=0.205, HR=1.325) (Figure 1).



By multivariate analysis, three factors significantly and independently influenced survival: nodal status (N0/1 vs N2; p=0.0001, HR=2.162), complete resection (R0 vs R1; p<0.0001, HR=2.948), and age (<65 vs ≥65; p<0.0001, HR=2.201). As though only N0/1 analyzed for to eliminate the effect of pN2 disease on survival, we observed that the survival of Mediastinal Fat group was worse than T4 group (39.7% vs. 50.8%; p=0.419, HR=1.245). Also, we found that survival of T4 group was better than Mediastinal Fat group when only R0 patients was analyzed (50.9% vs 41.3%, p=0.418, HR=1.237). **Conclusion:** There was no significant difference in survival between patients with mediastinal fat invasion and patients on T4 category for lung cancer. Mediastinal fat invasion should be inclueded as one of a descriptor of T4 in new classification of NSCLC.

Keywords: Nonsmall cell lung cancer, Mediastinal fat invasion, T4 descriptor

P1.13-13 HIGH-RISK CLINICAL STAGE I NON-SMALL CELL LUNG CANCER BASED ON HIGH-RESOLUTION COMPUTED TOMOGRAPHY FINDINGS

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Background: Perioperative systemic therapy for stage I non-small cell lung cancer (NSCLC) has not been established. The purpose of this study was to identify the high-risk patients for recurrence in clinical stage I NSCLC who were potentially candidates for systemic therapy in addition to standard lobectomy. **Method:** After excluding patients who underwent sublobar resection, 397 patients with clinical stage I NSCLC who underwent lobectomy with systematic lymph node dissection between April 2007 and March 2016 were analyzed. Solid component size on high-resolution computed tomography (HRCT) was used as tumor size on the basis of the 8th edition of TNM classification. Relapse-free survival (RFS) was estimated using Kaplan-Meier method, and multivariable Cox proportional hazards model was used to identify independent prognostic factors for RFS. **Result:** Five-year RFS of all patients was 73.6%. Multivariable Cox analysis revealed that age (hazard ratio [HR], 1.04 (95% confidence interval [CI], 1.01– 1.06; P = 0.005), solid component size (mm) (HR, 1.06 (95% CI, 1.04–1.09; P <0.001), and pure solid type (HR, 1.79 (95% CI, 1.10–2.91; P = 0.02) were independent prognostic factors for RFS. When patients were divided into high-risk group for recurrence (solid component size of >2 cm or pure solid type) and low-risk group (solid component size of <2 cm and part solid type), there was a significant difference in RFS between high-risk group (n = 298; 5-y RFS, 65.0%) and low-risk group (n = 129; 5-y RFS, 91.0%; P <0.001). Lymphatic invasion (29.5% vs. 9.3%, P <0.001), vascular invasion (36.6% vs. 7.8%, P <0.001), pleural invasion (28.4% vs. 9.3%, P <0.001), and lymph node metastasis (17.9% vs. 1.6%, P <0.001) were more frequent in high-risk group than in low-risk group. **Conclusion:** In clinical stage I NSCLC, patients with solid component size of >2 cm or pure solid type on HRCT were high-risk group for recurrence. These patients may be potential candidates for systemic therapy such as neoadjuvant immunotherapy.

Keyword: non-small cell lung cancer, recurrence, lobectomy

P1.13-14 PROGNOSIS AND CLINICOPATHOLOGIC CHARACTERISTICS OF SKIP N2 METASTASIS IN COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER

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Background: In our daily practice of non-small cell lung cancer (NSCLC) surgery, we sometimes encounter cases of pathological stage was up because of unexpected lymph node metastasis. If single-station N2 metastasis without N1 (skip-N2) of the tumor ≤ 5cm was noted postoperatively, it becomes stage IIIA like other N2 disease, and is to be poor prognosis in the current TNM staging system. The aim of this study is to analyze the impact for prognosis and clinicopathologic characteristics of skip-N2 disease. **Method:** We identified 415 patients with <T3 N1-2 NSCLC who underwent anatomical lung resection completely between January 2000 and December 2018. The degree of lymph node metastasis was classified into three; N1, skip-N2 and the other N2 (N2). The prognosis and clinicopathologic characteristics of patients were analyzed comparing skip-N2 with N1 and N2. **Result:** The median follow-up time was 45.7 months. Cases with N1 was 215 (51.8%), skip-N2 was 48 (11.6%) and N2 was 152 (36.6%). Among 48 cases of skip-N2, only 8 cases (16.7%) was diagnosed as N2 preoperatively. 5-year overall survival rate (5y-OS) for N1, Skip-N2 and N2 were 70.9%, 65.7% and 45.3% respectively. 5-year recurrence free survival rate (5y-RFS) for N1, Skip-N2 and N2 were 69.8%, 60.4% and 36.0% respectively. Prognosis of Skip-N2 had similar N1 (5y-OS; p=0.476, 5y-RFS; p=0.534) and had a tendency of better prognosis than N2 (5y-OS; p=0.08, 5y-RFS; p=0.01). As for clinicopathologic characteristics (patients characteristics, tumor marker, tumor size, tumor location, clinical stage and pathological characteristics), there were no significant differences between Skip-N2 disease and the other N1-2 disease. In skip-N2, 98% of cases were found within the extent of lobe specific lymph-node dissection. **Conclusion:** From clinicopathologic factors which can be obtained preoperatively, it is difficult to predict skip-N2. But the possibility of skip N2 among clinical N0 is not high, almost of skip N2 were detectable during surgery; lobe specific lymph node dissection is appropriate for clinical N0. The prognosis of skip N2 showed similar outcome of N1 rather than N2, but the prognosis is not enough; adjuvant chemotherapy is necessary for this population.

Keywords: NSCLC, skip N2, Lymph node metastasis

P1.14-01 ARE PRETREATMENT INFLAMMATION-BASED PROGNOSTIC SCORES USEFUL IN PREDICTING THE OUTCOMES OF PATIENTS WITH ALK-POSITIVE NSCLC?

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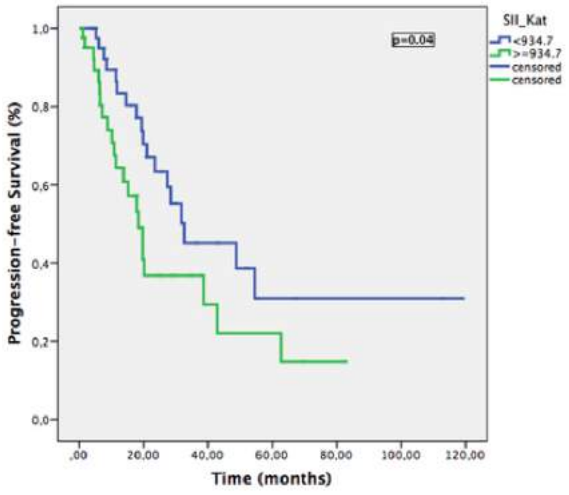
Background: Approximately 5% of all diagnosed non-small cell lung cancer (NSCLC) patients harbor a genetic rearrangement between the ALK and EML4 genes, representing a specific molecular and clinical subgroup (ALK+ NSCLC). To date, upfront treatment with ALK-tyrosine-kinase inhibitors (ALK-TKIs) has replaced chemotherapy in the first line setting for this subset of patients with excellent results, but reliable prognostic markers are lacking. An increased systemic inflammatory response has been shown to be associated with a poor prognosis, and some of the parameters used to characterize this response can easily be measured in clinical practice in several tumor types, but have not been analyzed extensively in ALK+ lung cancer in the era of crizotinib. **Method:** We reviewed the medical records of all patients with previously treated advanced ALK-positive NSCLC who received crizotinib between January 2013 and March 2018 outside of a clinical trial. Pre-treatment modified Glasgow prognostic score (mGPS), Prognostic Nutritional Index (PNI) and Systemic immune-inflammation index (SII) were calculated. Multivariable logistic regression and Cox proportional hazards models were used to assess the impact of pretreatment mGPS, PNI and SII on overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). **Result:** 82 patients were treated. Median age was 52.5 years (range; 20–77 years); 42.7% were female. Eighty-four point two percent of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥1; 17.1% had received ≥2 prior systemic therapies. The objective response rate was 77.2% (CR+PR).The optimal cutoff levels were 0.09 for mGPS and PNI, 934.7 for SII by ROC curves analysis. Patients in the SII ≥ 934.7 grous was significantly correlated with worse PFS and OS by univariate analysis (Figure 1).In multivariate analyses, pretreatment prognostic nutritional index (PNI) ≥ 0.09 was independently associated with inferior OS (1 year OS rates, 90.2% vs. 73.7%; HR 2.46, 95% CI 0.88-4.85; p = 0.035). Additionally, we evaluated the effects of these markers on response prediction. The logistic regression analysis of the predictive factors for the response to crizotinib demonstrated that the mGPS and PNI were associated with inferior ORR (OR: 0.1, 95% CI 0.16-1.04; p = 0.009 and OR: 0.16, 95% CI 0.02-0.55; p = 0.035, respectively).



Conclusion: In a cohort of patients with ALK positive NSCLC treated with crizotinib in routine practice,elevated pre-treatment SII was associated with shorter OS and PFS in univariate analysisand PNI was associated with shorter OS in multivariate analyses. Moreover the mGPS and PNI were associated with lower response rates.

Keywords: Inflammation-based prognostic scores, Non small cell lung cancer, Anaplastic lymphoma kinase

P1.14-02 SURVEY OF EGFR MOLECULAR TESTING OF NSCLC IN THE ASIA-PACIFIC REGION

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Background: Around 1 million new lung cancer cases occur annually in the Southeast Asian and Western Pacific regions combined, comprising more than half the global new cases each year. In recent years several key oncogenic driver alterations have been identified in non-small cell lung cancer (NSCLC), including epidermal growth factor receptor (*EGFR*) gene mutations, which are detected in up to 60% of adenocarcinoma in Asian patients. *EGFR* mutation testing to optimise therapy and outcomes has become the standard of care in advanced NSCLC. This study aimed to survey the practice of *EGFR* mutation testing in NSCLC across countries in the Asia-Pacific region. **Method:** The survey was circulated as a web-based electronic online survey questionnaire (www.surveymonkey.com) from 18 August to 3 October 2018 to members of the Asian Pacific Society of Respirology. Survey questions sought information on the following aspects of *EGFR* molecular testing: prevalence, methods of testing, funding and cost, type of tissue or sample, time frame for test results, retesting after progression, prevalence of *T790M* testing and use of liquid biopsy. **Result:** Of 121 respondents from 16 countries who treated lung cancer patients, 71 (58.7%) treated <10 lung cancer patients per week, 38 (31.4%) treated 10-30 lung cancer patients per week, and 7 (5.8%) treated >30 lung cancer patients per week. A significantly higher percentage of NSCLC patients was tested for *EGFR* mutation in academic/tertiary centres and public hospitals than in private hospitals [96 of 99 (97.0%)] vs [18 of 22 (81.8%)] (OR, 7.11; 95% CI, 1.47–34.50; p=0.02). The percentage of *EGFR* mutation testing for ≥50% of cases was significantly higher when the number of lung cancer patients treated in the practice was ≥10 per week [40 of 45 (88.9%)] vs [49 of 71 (69.0%)] (OR, 3.56; 95% CI, 1.13–11.17; p=0.023). Testing for molecular aberrations in the initial biopsy was more commonly physician initiated [89 of 121 respondents (73.5%)] than reflex (i.e., ordered by the reporting pathologist based on histopatholgy) [32 respondents (26.4%)]. The percentage of *EGFR* mutation testing for ≥50% of cases was significantly higher when the test was fully reimbursed [46 of 51 (90.2%) compared to otherwise [47 of 70 (67.1%)] (OR, 1.63; 95% CI, 1.25–2.12; p=0.003). The turnaround time (days) was <7 (35.5% of the practices), 7-14 (47.9%) and >14 (12.4%). A significantly higher percentage of respondents would perform tissue rebiopsy in ≥50% of the cases with disease progression while on treatment with 1st- or 2nd-generation *EGFR*-TKIs if osimertinib was accessible for use, 34 of 72 (47.2%) compared to 7 of 49 (14.3%) if otherwise (OR, 5.37; 95% CI, 2.13-13.53; *p*<0.0001). Liquid biopsy for *T790M* mutation detection was performed more frequently in practices where there was access to osimertinib (91.6% vs 28.6%; OR, 27.50, 95% CI, 9.72-77.84; *p*<0.0001). **Conclusion:** It was more likely for ≥50% of NSCLC patients to be tested for *EGFR* mutation by respondents who treated ≥10 lung cancer patients per week and if the test was fully reimbursed. Tissue rebiopsy and liquid biopsy for *T790M* mutation detection was more frequently performed in practices with access to osimertinib.

Keywords: EGFR mutation testing, Asia-Pacific, Rebiopsy

POSTERS

P1.14-03 MOLECULAR DETERMINANTS FOR LORLATINIB ACTIVITY IN ROS1 POSITIVE NSCLC: RESULTS OF THE PROSPECTIVE PFROST TRIAL

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Background: Lorlatinib, an ALK/ROS1 inhibitor, demonstrated activity in *ROS1+* NSCLC pretreated with crizotinib. However, molecular events predictive for tumor response during lorlatinib treatment are largely unknown. **Method:** PFROST was a prospective phase II trial designed to include *ROS1+* NSCLC refractory to crizotinib. Eligible patients were treated with lorlatinib at the daily dose of 100 mg until disease progression. Primary end point was response rate (RR). For all included patients pre-lorlatinib tumor tissue or blood sample collection was mandatory. At the time of lorlatinib failure liquid biopsy was recommended. The samples were then run with the NEOliquid assay, specifically designed for liquid biopsies, or NEOselect, a panel optimized for formalin-fixed paraffin-embedded (FFPE) tumor tissue, covering 39 cancer related genes. **Result:** From June 2017 to April 2019, 22 *ROS1+* crizotinib refractory lung adenocarcinoma patients were included in 10 Institutions. Median age was 56 years (range 39-82); male/female: 8/14; ECOG PS 0 (N=8; 36.4%), PS1 (N=14; 63,6%); The majority had brain metastases at baseline (N=15; 68.1%), were never smokers (N=13; 59.1%) and received lorlatinib as third line therapy (N=16; 72.7%). In all cases crizotinib was the last therapy line before lorlatinib. At the time of the present analysis, trial completed its accrual and 13 patients are still receiving therapy. A total of 18 patients were evaluable for response and 7 had confirmed complete (N=1) or partial (N=6) responses for an overall RR of 38.8%. In 4 patients, response to therapy was not yet evaluated. A total of 10 tissue biopsies and 20 blood samples obtained after crizotinib and before lorlatinib therapy were collected. For 7 samples analyses are ongoing. Among responders, no patient harbored a secondary *ROS1* mutation. Conversely, no response was observed among patients with secondary *ROS1* mutations (N= 1 *ROS1*^{S1861I}, *N=1 ROS1* ^{V2054A}, N=3 *ROS1*^{G2032R}). All patients harboring the *ROS1*^{G2032R} mutation rapidly progressed and maintained this aberration in liquid biopsy at the time of radiological evidence of lorlatinib failure. **Conclusion:** In our study lorlatinib confirmed its efficacy in crizotinib resistant *ROS1+* NSCLC. Molecular profile of refractory patients suggests reduced efficacy in individuals developing secondary *ROS1* mutations after crizotinib failure.

Keywords: ROS1, lorlatinib, Acquired resistance

P1.14-04 FINAL RESULTS OF THE PROSPECTIVE GENOMICS OF YOUNG LUNG CANCER (GYLC), AN ADDARIO LUNG CANCER MEDICAL INSTITUTE STUDY

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Background: We hypothesized that young age at lung cancer diagnosis is a clinical characteristic associated with a higher likelihood for having a driver mutation. Our goals were to identify a genomically enriched subtype of lung cancer, facilitate delivery of targeted therapy and lay groundwork for studies of heritable and environmental lung cancer risk factors. **Method:** Eligible subjects had a diagnosis of bronchogenic lung cancer < 40 years old. We included a website to allow for virtual consenting and remote participation from anywhere in the world. An integrated data and biorepository allowed for completion of study activities and routing of specimens. We defined seven genes of interest based on the Lung Cancer Mutational Consortium (LCMC): EGFR, KRAS, HER2, BRAF, ALK, ROS1, RET. We hypothesized that the prevalence of targetable alterations in these genes would be greater in our population compared to the LCMC and powered our study to detect an increase from 35% to 50%. Subjects with advanced adenocarcinoma who were not tested for all seven genes or who were wild type for all seven underwent additional genomic profiling using Foundation Medicine testing. **Result:** We accrued 133 participants from July 2014 to June 2017. Notably, 44% entered the trial via the website. The mean age at diagnosis was 34 (range 16 to 39) and 57% were female; 77% were stage 4 at diagnosis and the majority had adenocarcinoma (86%). Of the 115 patients with adenocarcinoma, 83.5% were stage 4 and the focus of the comparison to the LCMC cohort. A targetable mutation was identified in 85.4%, with 76% harboring a combined ALK (38.5%), EGFR (31.3%), or ROS1 (6.3%) mutation. Of 14 patients who underwent on-protocol testing, a targetable driver was identified in eight (57%), including two with a RET rearrangement, two with ERBB2 mutations, two with MET amplification, one with an ALK rearrangement with a prior negative FISH and one with a novel EGFR-RAD fusion previously tested negative for EGFR. **Conclusion:** We have described a genomically distinct subset of NSCLC in patients < age 40. Those with stage 4 adenocarcinoma must undergo comprehensive genomic testing to identify a targetable driver. The extremely high rate of driver mutations particularly in ALK supports the need for an Epidemiology of YLC study. Additionally, use of remote consenting and the Addario Lung Cancer Foundation's advocacy enabled rapid accrual of this rare cohort (<1%) and has laid the foundation for innovative research partnerships with other rare oncogene-driven patient groups.

Keywords: targeted, young, NSCLC

P1.14-05 TP53 EXON 8 MUTATION AND PROGNOSIS IN EGFR-MUTATED NSCLC PATIENTS TREATED WITH FIRST-AND-SECOND-GENERATION TKIS

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Background: *TP53* mutation seems to be associated with a worse prognosis in *epidermal growth factor receptor (EGFR)* mutated non-small cell lung cancer (NSCLC) treated with first generation tyrosine kinase inhibitors (TKIs). We previously showed that this was mainly significant for exon 8 *TP53* mutations (Canale M et al, Clin Cancer Res 2017). However, its role on survival, as well as in relation to response to second generation TKIs is not clearly established. **Method:** A retrospective cohort of 270 *EGFR*-mutated NSCLC treated with first- (gefitinib and erlotinib) and second- (afatinib) generation TKIs, in the first line setting, were considered. *TP53* status was evaluated by Sanger Sequencing or Next generation Sequencing. The different mutations were evaluated in relation to disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Result:** One hundred and forty-four patients (53.3%) received a treatment with gefitinib, 84 (31.1%) with erlotinib and 42 (15.7%) with afatinib. In the overall cohort, ORR and DCR were 61.5% and 86.4%, respectively, with about 50% of patients responsive for more than 10 months. Median PFS and OS were of 11.08 (95% CI 9.3-12.6) and 22.9 (95% CI 20.4-27.5) months, respectively. Overall, 79 (30.7%) patients showed a *TP53* mutation. The presence of *TP53* exon 8 mutation was associated with a worse outcome with respect to patients wt or with other *TP53* mutations. In particular, a lower ORR and DCR were observed for patients with *TP53* exon 8 mutation (ORR 94.16% vs 5.84%, p=0.05, and DCR 94.04% vs 5.96%, p<0.001, respectively), together with a worse PFS (HR 1.88 [95% CI 1.20-2.96], p=0.006). These results was even more significant in the subgroup of patients with *EGFR* exon 19 deletion, where *TP53* exon 8 mutation was associated with both worse PFS (HR 4,72 [95% CI 2.31-9.65], p<0,001) and OS (HR 2.60 [95% CI 1.11-6.04], p=0.027). At the multivariable analysis, *EGFR* exon 19 deletion and *TP53* exon

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8 mutation remained independently associated with PFS (HR 0.56 [95% CI 0.35-0.89], p=0.014 and HR 1.81 [95% CI 1.13-2.88], p=0.013, respectively). Moreover, *EGFR* exon 19 deletion and age resulted independently associated with OS (HR 0.52 [95% CI 0.26-1.03], p=0.059, and HR 1.02 [95% CI 1.01-1.04], p=0.009, respectively). No other patient and clinical covariate showed an association with PFS and OS in the multivariable models. **Conclusion:** Our results confirm that *TP53* exon 8 mutation confers a worse outcome in patients treated with first and second generation TKIs and that this is particularly evident in patients with *EGFR* exon 19 deletion.

Keywords: resistance, TP53, TKIs

P1.14-06 TISSUE-BASED MOLECULAR AND HISTOLOGIC LANDSCAPE OF ACQUIRED RESISTANCE TO OSIMERTINIB IN PATIENTS WITH EGFR-MUTANT LUNG CANCERS

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Background: Even though osimertinib (osi) is now the initial treatment for patients with *EGFR*-mutant lung cancers, our knowledge about mechanisms of resistance (MOR) is largely derived from patients who received osi after acquiring EGFR *T790M* on treatment with another EGFR inhibitor. Other studies of osi resistance have mainly reported genotyping of plasma which suboptimally detects lineage plasticity, copy number changes, and chromosomal rearrangements. **Method:** To identify MOR to osi and characterize clinical, molecular and histologic factors associated with duration of response, we identified patients with *EGFR*-mutant lung cancers who had targeted next-generation sequencing (MSK-IMPACT) performed on tumor tissue obtained before treatment and after developing resistance to osi received as either first-line or later line EGFR-TKI. **Result:** From January 2016 to March 2019, we collected paired pre-treatment and resistance specimens from 53 patients (1st line osi: 21. Osi after prior TKI: 32). MOR are summarized in the table. Histologic transformation was identified in 18% of 1st line cases and 17% of all cases. When osi was given as initial treatment, with median follow up of 18 months, early emerging MOR rarely included on-target resistance mechanisms (acquired *EGFR* G724S in 1/21). Other acquired alterations representing potential resistance mechanisms not listed in the table included *CCNE1* and *MYC* amplifications, and mutations in *MTOR A1098S* and *MET H1094Y.*

	First line (n = 21)	Osi after prior TKI (n = 32)	All (n = 53)
Squamous transformation	3	3	6
Neuroendocrine transformation	1	2	3
On target mutation (*EGFR C797X* or other)	1	9	10
Loss of *EGFR T790M* only	-	8	8
Fusions (*ALK, RET, BRAF*)	0	3	3
Amplifications (*HER2, MET, EGFR*)	2	3	4
Off target mutations (*KRAS, BRAF, HER2*)	1	2	3

Conclusion: In this analysis of MOR identified on NGS from tumor tissue, we found a spectrum of resistance mechanisms to osi. By evaluating tissue rather than plasma we provide data on histologic transformation (including squamous cell transformation). Subsequent studies are needed to assess patients with a longer time on initial osi as early progressors may have different MOR, with off-target MOR emerging earlier and on-target resistance mutations later.

Keywords: EGFR, Osimertinib, resistance

P1.14-07 GENOMIC PROFILING OF LIQUID BIOPSIES DURING 2ND/3RD GENERATION ALK INHIBITOR THERAPY TO IDENTIFY NOVEL MECHANISMS OF RESISTANCE

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Background: Second- and third-generation ALK inhibitors each have diverse mechanisms of resistance. Only a fraction of resistance is due to secondary mutations of the ALK gene. Altered bypass tracts are likely the case in some other instances. Genomic alterations of other genes and pathways may be a third mechanism of resistance. Repeat liquid biopsies during the course of patients' treatments can provide a minimally invasive method for sampling cancer-specific genomic information that leads to improved treatment selection. **Method:** In the Lung Cancer Clinic of the Princess Margaret Cancer Centre, serial plasma samples were collected from six lung cancer patients with *ALK* rearrangement at multiple serial clinic visits pre- and post- progression on next-generation ALK inhibitors. We focused on next generation agents, as there has been previous focus on crizotinib resistance mechanisms already. Cell-free DNA (cfDNA) was extracted (median: 50 ng; range: 20-2760 ng) and profiled using a next-generation sequencing (NGS) platform with Geneseeq Prime 425-gene panel at a mean coverage depth of 4747X (and a deduplicated mean coverage depth of 2160X). **Result:** Somatic alterations from plasma cfDNA were detected in all six patients at various time points with three patients having detectable ALK alterations. Systemic progression (2/2 patients) correlated well with the ability of liquid biopsies to detect somatic mutations, while central nervous system (CNS)-predominant progression did not (4/4 patients). One patient, after disease progression on ceritinib, alectinib and brigatinib, exhibited variable allele fractions (AFs) of ALK G1202R mutation in cfDNA. The levels of G1202R decreased and ultimately became undetectable, corresponding to the patient's clinical response to lorlatinib. In a patient who exhibited significant systemic progression, a massive increase in mutation AFs and many newly acquired mutations were detected in the cfDNA, including *NOTCH1, DICER1, BRCA2, TP53, CDKN2A, ERBB3*, and *FAT1*mutations. However, the increase in the number of co-mutations was not related to increases in the amount of extracted cfDNA. **Conclusion:** Broad panel-based NGS of plasma cfDNA enabled noninvasive detection of systemic (but not CNS-predominant) progression during second and subsequent generation ALK inhibitor treatment, and can identify known and putative mechanisms of resistance for treatment decision-making.

P1.14-08 ACTIVITY OF POZIOTINIB AND OTHER 2ND-GEN QUINAZOLINE EGFR TKIS IN ATYPICAL EXON18 AND ACQUIRED OSIMERTINIB RESISTANCE MUTANTS

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Background: In EGFR, exon 18 encodes for the P-loop (L718-V726), and mutations in this region (G719S/A, L718Q/V, G724S) are known to reduce sensitivity to osimertinib and first-generation EGFR TKIs. Osimertinib resistance is associated with a number of acquired mutations in exons 19 and 20 (S784F, L747S, C797S and L792H). We investigated the frequency and drug sensitivity of these and other osimertinib-resistant EGFR mutations **Method:** We generated ~50 different Ba/F3 cell line models expressing classical and/or atypical EGFR mutations (exons 18-21) and evaluated the transforming ability and sensitivity to 14 EGFR TKIs including non-covalent (first-generation), afatinib, dacomitinib, and poziotinib (quinazoline and covalent, second-generation), and covalent T790M-specific (third-generation) inhibitors. Impact of atypical mutations was analyzed by *in silico* modeling. **Result:** We found 3.6% (N=32/895) of EGFR-mutant patients had atypical, exon 18, P-loop mutations in the MD Anderson GEMINI database. Modeling of classical EGFR mutations revealed osimertinib has distinct interactions between the solvent front of osimertinib and residues within the P-loop of EGFR, whereas second-generation quinazoline TKIs, such as poziotinib, extend into the pocket, near T790, lacking these interactions. Mutations in the P-loop were predicted to shift osimertinib out of alignment with V726 and F723, causing resistance to osimertinib but not quinazoline-based TKIs. Atypical exon 18 mutations (G719S/A, L718Q/V, G724S)

had IC_{50} values of 113.6nM, 1.6nM, and 137.5nM for first-, second-, and third-generation TKIs, respectively. Second-generation TKIs inhibited G719S/A-T790M mutations at concentrations 2-fold lower than third-generation TKIs (IC_{50} = 23.4nM and 46nM). Osimertinib-resistance mutations (L747S, S784F, C797S, L792H) co-occurring with classical sensitizing mutations (L858R or ex19del) had IC_{50} values of 56.8nM, 1.4nM, and 996nM to first, second and third-generation inhibitors. Of the second-generation TKIs tested, poziotinib was the most potent for atypical exon 18 P-loop mutations; G719S/A-T790M mutations; and classical mutants with acquired osimertinib-resistance mutations ($IC_{50=}$ 0.4nM, 3.2nM, 0.8nM). **Conclusion:** Exon 18 atypical P-loop mutations and osimertinib-resistance mutations demonstrated high sensitivity to second-generation quinazoline TKIs, compared to first- and third-generation inhibitors. Mutations in the P-loop of EGFR confer resistance to third-generation TKIs by destabilizing solvent front interactions of the molecule, and osimertinib-resistance mutations interfere with covalent binding at C797. Second-generation TKIs, especially poziotinib, are potent inhibitors of these mutations because they have increased hydrophobic interactions at the back of the drug binding cleft that are retained without covalent binding. Together, these data indicate that poziotinib and other second-generation TKIs may be useful for the treatment of NSCLC patients with atypical P-loop and selected osimertinib-resistant EGFR mutations.

Keywords: Atypical EGFR mutations, Osimertinib resistance mutations, Drug screening

P1.14-09 UNVEILING HIDDEN MET-MEDIATED PRIMARY ALECTINIB RESISTANCE IN ALK-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Alectinib is an ALK inhibitor that is currently used for the treatment of ALK-positive NSCLC. This next generation ALK inhibitor was initially used as second-line therapy following resistance to crizotinib. More recently, alectinib has superseded crizotinib, an ALK/ROS1/MET inhibitor, as a first-line therapy due to its superiority in phase III trials. Although patients enjoy durable responses to alectinib, they eventually develop resistance. Here we describe four cases of primary resistance to alectinib in which the patients show little to no response to alectinib when administered as first or second-line therapy. **Method:** In order to investigate primary resistance to alectinib, tissue was obtained during re-biopsy and subjected to routine clinical genetic analyses including gene fusion detection and genetic mutation analysis using the Archer FusionPlex and VariantPlex assays, respectively. Concurrently, at the time of biopsy, additional fresh tissue was procured for cell line derivation. The primary cell line was then used to assess ALK and other inhibitors' potency by cell viability assays. Targeted analysis of signaling pathways was performed in the cell lines via western blot analysis and proximity ligation assays to determine resistance mechanisms. **Result:** We present 4 cases of ALK patients with primary resistance to alectinib when used as either first (n=3) or second-line therapy (n=1). In 3 of the 4 cases, routine clinical resistance testing revealed no additional ALK or non-ALK related genetic abnormalities (e.g.; *ALK* kinase domain mutations, other oncogenic gain-of-function mutations, or gene amplification). However, examination of targeted gene expression data indicated elevated RNA transcripts of *MET* alone or combined *MET* and *AXL*. Analysis of the cell lines derived from these 4 patients further implicates MET in alectinib resistance alone or together with AXL or ERBB3. Signaling analysis shows that MET provides a prosurvival effect, signaling through the PI3K/AKT pathway. In the case where MET was the sole identified bypass mechanism of alectinib resistance, the patient also rapidly progressed through brigatinib, but a regimen of crizotinib plus brigatinib resulted in rapid tumor shrinkage. **Conclusion:** Here, we document cases of primary resistance to alectinib therapy using human-derived cell lines to expose novel resistance mechanisms not identified by routine clinical testing. We show that MET is a critical component and serves as a bypass mechanism of alectinib resistance either alone or in combination with AXL or ERBB3. We also demonstrate that crizotinib could overcome MET-mediated ALK resistance in a patient.

Keywords: alectinib, ALK, MET

P1.14-10 THE LANDSCAPE OF RET GENOMIC ALTERATIONS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: *RET* is known as a driver gene which accounts for 1-2% in NSCLC. Recently, RET inhibitors such as LOXO-292 and BLU-667 demonstrated promising efficacy in NSCLC and medullary thyroid cancer. The landscape of *RET* alterations of the Chinese NSCLC population will be explored in this study. **Method:** FFPE tumor and matched blood samples of 3433 Chinese NSCLC patients were collected for performing next-generation sequencing (NGS) based targeted panel sequencing. The genomic variants including single nucleotide variations, indels, copy number alterations and gene rearrangements were analyzed. Tumor mutational burden (TMB) and microsatellite instability (MSI) status were calculated and assessed by NGS algorithms. **Result:** The patients with *RET* alterations, including 61 males and 57 females with a median age of 59.5 years, were identified in approximately 3.4% (118/3433) of the Chinese NSCLC cohort. In this study, 58 out of 118 (1.7%) patients, including 21 males and 37 females with a median age of 58 years, harbored *RET* rearrangements, which is slightly higher than the published data of MSKCC (1.2%). The partner genes of *RET* rearrangements were identified by NGS, including *KIF5B* (38/58), *CCDC6* (6/58), and other genes (14/58). *TP53* was the most common compound gene with *RET* rearrangements. Two co-existing *EGFR* mutations, L858R and L861Q, were identified in 2 *RET* rearrangement patients without previous treatments. Harbored alterations in the cell cycle pathway and in the PI3K/mTOR pathway were found in 15.5% (9/58) and 12.1% (7/58) of patients, respectively. In addition, 8 patients with *RET* rearrangements had no other co-occurring common cancer gene mutations. Meanwhile, 56 (1.6%) patients carried *RET* mutations and 5 (0.2%) patients presented *RET* amplifications. The median TMB of patients with *RET* alteration was 4.6 muts/Mb, which was exactly the same as all the 3433 patients (4.6 muts/Mb). Interestingly, patients with *RET* rearrangements had lower TMB (2.3 muts/Mb, 0-16.2 muts/Mb). All patients with *RET* alternations were microsatellite stable (MSS). **Conclusion:** This is the first study to reveal *RET* genomic profiling in a large Chinese NSCLC cohort. *RET* rearrangements were found in 1.7% of Chinese NSCLC. Besides the most common partner genes, 14 *RET* rearrangements (24%) with uncommon or novel partner genes were identified by NGS. TMB of the patients with *RET* rearrangements was relatively lower.

Keywords: NSCLC, TMB, RET

P1.14-11 A PROSPECTIVE MULTICENTER STUDY OF TARGET-CAPTURE DEEP SEQUENCING IN PAIRED TISSUE AND CTDNA TO GUIDE EGFR-MUTATED LUNG CANCER TREATMENT

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Background: TKIs have significantly improved the survival of NSCLC pts carrying sensitive mutations. However, heterozygous responses were observed. We conducted a prospective multicenter clinical trial to explore factors associated with the efficacy of EGFR-TKI,

and assess the mutation and TMB concordance between plasma and tissue NGS. **Method:** Paired tumor and plasma samples were obtained from treatment naïve advanced NSCLC pts whenever applicable. DNA was sequenced by target-capture deep sequencing of 1021 tumor-related genes (pan-cancer panel). PFS was estimated using Kaplan-Meier method and compared using log-rank test. Tissue TMB (tTMB) and plasma TMB (bTMB) analysis interrogated SNVs/Indels with VAF ≥3 % and ≥0.5 %, respectively. TMB-H pts were identified with ≥9 muts/Mb. **Result:** From Feb. 2017 to Jan. 2019, 262 advanced NSCLC pts were enrolled from 12 centers. In 224 pts with paired tumor and plasma samples, 144 had *EGFR* sensitive mutations in tumor samples (L858R, 46%; Ex19Indel, 42%), of whom, 106 (74%) had the identical mutations detected in plasma. The detection rate of tissue *EGFR* mutations in paired plasma was significantly higher in pts with extrathoracic metastasis (81% vs. 61%, p = 0.03). In 38 pts lacking paired samples, 20 pts had *EGFR* sensitive mutations detected. Thus, 164 pts were identified as EGFR positive by either plasma or tissue NGS. One hundred of them were treated EGFR TKIs (ORR: 70%, mPFS: 20 mo). The ORR was affected by *EGFR* subtypes (Ex19Indel vs. L858R: 72% vs. 45%, p = 0.02), concomitant CNV/fusion (with vs. without: 11% vs. 68%, p = 0.002) and *CDKN2A* mutations (with vs. without: 0% vs. 66%, p = 0.007). Mutations in p53 pathway (p = 0.02), CDK12/13 (p = 0.0002), concomitant CNV/fusion (p = 0.003), and high number of alterations (≥ 5) (p = 0.003) significantly shortened mPFS. tTMB was correlated with bTMB ($r_{Pearson}$ = 0.9, p < 0.0001), with a concordance rate of 90% for TMB-H and TMB-L classification. Interestingly, 9.8% of the EGFR positive pts were bTMB-H, and mPFS was shorter in bTMB-H pts (6 mo, 95% CI: 5 - NR) than in bTMB-L pts (NR, 95%: 13 - NR) (p = 0.2). **Conclusion:** Deep sequencing with the pan-cancer panel effectively detected mutations and evaluated TMB in both tissue and plasma with a high consistence. Moreover, the presence of structure variation, high tumor heterogeneity and concomitant mutations in genes such as *CDKN2A* were associated with worse prognosis. Further studies of predictive factors are ongoing (NCT03059641).

Keywords: ctDNA, EGFR-TKI, TMB

P1.14-12 A NOVEL ACTIVATING MAP2K1 IN-FRAME DELETION MEDIATES ACQUIRED RESISTANCE TO ROS1 TKIS IN A PATIENT WITH ROS1 FUSION-POSITIVE NSCLC

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Background: *ROS1 tyrosine kinase inhibitors (TKIs) such as crizotinib, entrectinib and lorlatinib* provide significant benefit in non-small cell lung cancer (NSCLC) patients with *ROS1* fusions. As observed with all targeted therapies however, resistance arises. With the widespread adoption of large panel next generation sequencing (NGS) at the time of acquired resistance (AR), our appreciation of novel off-target mechanisms continues to grow. Detecting additional mechanisms of acquired resistance (AR) is crucial to find novel therapies and improve patient outcomes. **Method:** We reviewed targeted large-panel sequencing data (using the MSK-IMPACT assay) of paired pre-treatment and post-progression samples from patients treated with ROS1 TKIs. Genetic alterations hypothesized to confer AR were modeled in a patient-derived cell line (LUAD-0003, expressing *EZR/ROS1*) as well as isogenic human (HBEC) and murine (NIH-3T3) cell lines. *ROS1* fusions were expressed in these cells either by cDNA overexpression (*CD74/ROS1*, *SLC34A2/ROS1*) or CRISPR-Cas9-mediated genomic engineering (*EZR/ROS1*). Using these cell line models, alterations in drug sensitivity and downstream signal pathways were examined. We also explored possible therapeutic strategies to overcome the drug resistance caused by the novel AR mechanisms examined in this study. **Result:** *We identified a patient with NSCLC harboring a MAP2K1 (MEK1) variant encoding an in-frame deletion of amino acids E41-L54 (MEK1del) in a sample taken at the time of resistance to lorlatinib (after 9 months' treatment).* This mutation was not detected in the pre-TKI sample. Induction of ROS1 fusions in HBEC and NIH-3T3 cells increased the sensitivity of these cells to ROS1 TKIs and stimulated activation of MEK/ERK signaling in comparison with AKT signaling, suggesting the importance of the RAS-MAPK pathway in driving ROS1 fusion-positive cancers. Underscoring the importance of the RAS-MAPK pathway in ROS1-mediated tumorigenesis, we identified three patients (pancreatic, salivary, and breast cancer) with a *ROS1* fusion and *NF1* loss-of-function mutation concurrently, in TKI-naïve samples. Expression of MEK1del in HBEC and NIH-3T3 cells harboring ROS1 fusions, and knockdown of *NF1* in LUAD-0003, activated ERK signaling and conferred resistance to ROS1 TKIs. Combined targeting of ROS1 (crizotinib, lorlatinib) and MEK (selumetinib, trametinib) inhibited growth of cells expressing both ROS1 fusion and MEK1del. **Conclusion:** Our results suggest that the activation of the RAS-MAPK pathway plays a critical role in tumorigenesis mediated by *ROS1* fusions, and that activating mutations in this pathway can drive AR to ROS1 TKIs. Combined inhibition of ROS1 and MEK is a potential therapeutic strategy that should be explored clinically.

Keywords: Non-Small Cell Lung Cancer, Acquired resistance, ROS1 fusion

P1.14-13 EGFR AMPLIFICATION MEDIATES RESISTANCE TO THIRD-GENERATION EGFR TKIS AND IN VITRO VALIDATION OF COMBINATION STRATEGIES TO OVERCOME RESISTANCE

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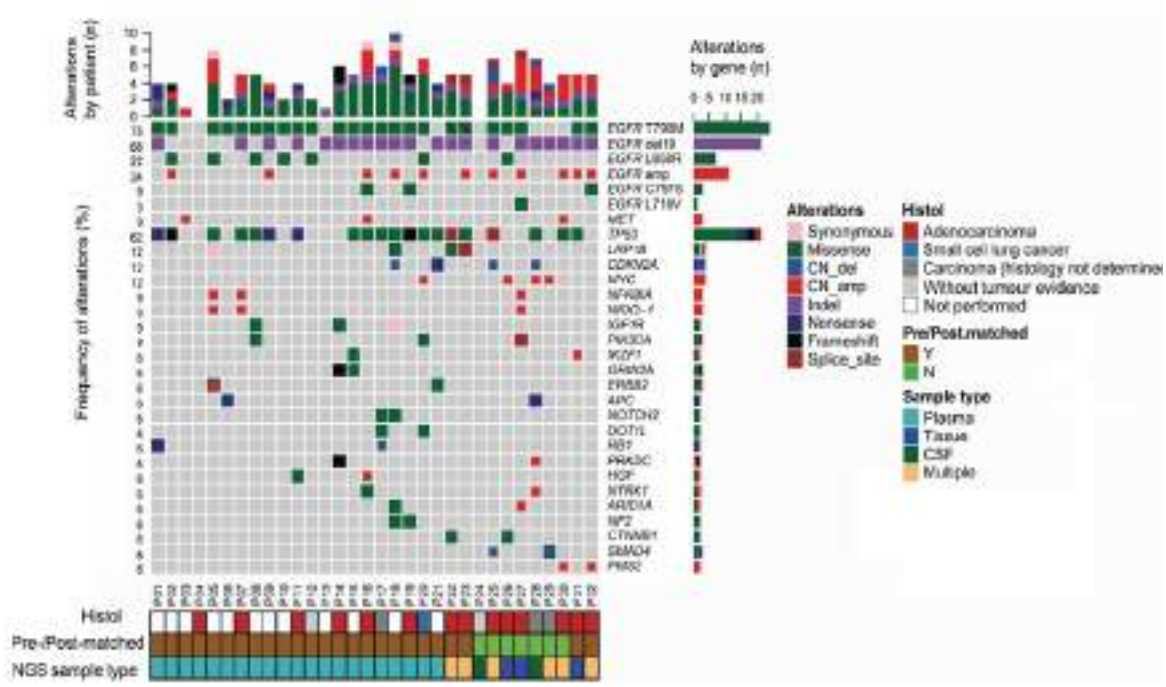
Background: As a concurrent genomic alteration in *EGFR*-mutant NSCLC, whether all detected *EGFR* amplification serve as a driver of resistance to third-generation EGFR-TKIs remains controversial. Furthermore, which subtype of *EGFR* amplification-mediated resistance is actionable has been poorly elucidated. Our study aims to investigate the driver role of *EGFR* amplification in mediating resistance to third-generation EGFR TKIs and potential strategy to overcome resistance mediated by *EGFR* amplification. **Method:** 44 resistance samples from 32 patients who experienced disease progression from to a third-generation EGFR TKI abivertinib in Guangdong Lung Cancer Institute underwent NGS-based genomic profiling (data cutoff: october 30, 2018). FISH analysis of tissue samples from patients with *EGFR* amplification detected by NGS was performed. Different alleles of EGFR over-expressed PC9GR cell line models was established. Cell proliferation assay and western blot were performed to determine the sensitivity of these cell lines to third-generation EGFR TKI abivertinib and osimertinib, and to screen for potential strategies to overcome resistance mediated by *EGFR* amplification. **Result:** Upon abivertinib progression, 27 patients provided plasma samples (six patients also provided paired samples from the progression sites) and five patients only provided samples from the progression sites for NGS. A heterogeneous landscape of resistance to abivertinib was observed with *EGFR* amplification being the most frequent, observed in 11 (34%) patients (Figure 1), and considered a putative resistance mechanism in seven (22%) patients. FISH analysis of 3 patients who had available tissue samples further confirmed the presence of *EGFR* amplification detected by NGS. We established 3 different EGFR-overexpressed PC9GR cell lines by lentivirus transfection of Del 19 *EGFR*, Del19/T790M *EGFR* and wild-type *EGFR*. Among them, introduction of wild-type *EGFR* resulted in significantly loss of cellular sensitivity to abivertinib and osimertinib under EGF stimulation, but retains sensitivity to combination treatment of abivertinib and afatinib. In addition, abivertinib plus nimotuzumab also demonstrated preliminary inhibitory effect on phosphorylation of EGFR downstream pathway in wild-type EGFR overexpressed PC9GR. Finally, abivertinib plus nimotuzumab or afatinib in is effective and tolerable in treating 2 patients who developed *EGFR* amplification-mediated resistance to abivertinib. One of them experienced a long-term benefit from the combination treatments with an overall progression-free survival of 23 months.



Conclusion: Wild-type *EGFR* amplification mediates resistance to third-generation *EGFR* TKIs and could be overcome by combination treatments. Future studies need to more precisely determine the presence of wild-type *EGFR* amplification in third-generation EGFR TKIs resistant setting.

Keywords: EGFR amplification, third-generation EGFR-TKIs, combination treatment

P1.14-14 MONITORING OF EGFR MUTATIONS DURING OSIMERTINIB TREATMENT IN ADVANCE EGFR-MUTANT T790M POSITIVE NSCLC

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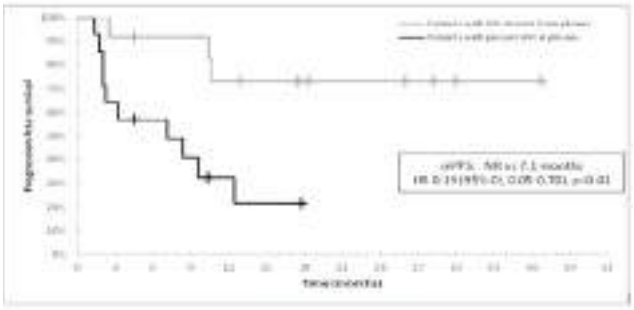
Background: Genotyping cell free circulating DNA (cfDNA) is a non-invasive method of detecting EGFR mutations (EGFRmu). The aim of our study was to investigate whether changes in the levels of plasma EGFRmu are associated with clinical outcomes of advanced T790M positive EGFRmu patients treated with osimertinib. **Method:** Single centre prospective observational study was performed with plasma being collected from patients with advanced EGFRmu T790M positive NSCLC routinely treated with second line osimertinib. Dynamical monitoring of cfDNA was performed at every scheduled visit (8 weeks) until disease progression. Cobas EGFR Mutation Test v1 and v2 (Roche, USA) was used to detect 42 mutations at EGFR gene in exons 18 to 21, including T790M mutation. Radiological assessment was performed in accordance with RECIST 1.1 criteria. **Result:** Twenty-seven patients were treated with osimertinib from October 2015 until December 2018. At the beginning of osimertinib treatment only 17/27 (63%) patients had detectable T790M mutation in plasma, but almost all patients 26/27 (96%) had detectable plasma EGFR activating mutations (AM). During osimertinib treatment T790M mutation was cleared from plasma in all 17 patients regardless of response to treatment. On the contrary, only 12/26 (45%) patients had AM plasma clearance. Only 3 of them had had progress at median follow up of 17.5 months, what demonstrates significantly longer progression-free survival (PFS) of patients with AM plasma clearance compared to patients without AM clearance (HR 0.19; 95% CI 0.05 – 0.70, p = 0.01) (*Figure 1*). Of the 14 patients that progressed during the observation period all had AM reapperance in cfDNA at the time on progression, while T790M only recurred in one.



Conclusion: Clearance of EGFR AM in plasma during osimertinib treatment is associated with longer PFS, while clearance of T790M has no impact on survival in our small group of patients. Dynamic changes in EGFR AM might be a useful marker of outcome in patients treated with osimertinib, but further studies are needed.

Keyword: EGFR mutations, osimertinib, NSCLC

POSTERS

P1.14-15 LORLATINIB IN ALK- OR ROS1-POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS: EXPERIENCE FROM AN EARLY ACCESS PROGRAM IN TURKEY

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Background: Lorlatinib, a third generation ALK and ROS1 inhibitor, is indicated for the treatment of patients with *ALK+* metastatic NSCLC whose disease has progressed on crizotinib and at least one second-generation ALK inhibitor. The aim of this study is to evaluate the efficacy and safety of lorlatinib in an Expanded Access Program (EAP) in Turkey. **Method:** The EAP was open-label, multicenter, and single-arm. Patients were eligible to receive lorlatinib (100 mg p.o/day) if they had advanced stage *ALK*- or *ROS1*-positive NSCLC and had progressed on crizotinib and/or second generation ALK inhibitors such as ceritinib or alectinib. The primary endpoint was PFS with lorlatinib. Secondary endpoints were objective response rate, overall survival, and safety. **Result:** Between February 2017 and December 2018, a total of 91 patients were admitted to the EAP at 27 oncology centers in Turkey. Eleven patients died before receiving the drug. Four patients were excluded from the EAP because of lost of the follow-up. Of the 76 patients who received drug, 13 were excluded from the analysis due to inability to access patient information. Six of these 13 patients were on lorlatinib treatment at the time of data collection. The median age of patients was 53.5 (17-84) years. Of 63 evaluable patients, 55 (87.3%) had *ALK+* NSCLC and 8 (12.7%) had *ROS1+* NSCLC. All patients had adenocarcinoma histology, and 54% (n=34) had brain metastasis before lorlatinib treatment. Twenty-one patients received lorlatinib as third-line treatment (mostly after chemotherapy and crizotinib). Median follow-up was 9.1 months. Five patients died before the first evaluation of response. In patients who received at least 1 dose of lorlatinib, median PFS was 12.6 months, and 1-year PFS rate was 53%. In *ALK+* patients, median PFS was 14.7 months and 1-year PFS rate was 55%. In *ROS1+* patients, median PFS was 9.1 months and 1-year PFS rate was 47%. In patients who received only crizotinib prior to lorlatinib, median PFS was 14.8 months and 1-year PFS rate was 59%. In patients who received ≥2 ALK inhibitors prior to lorlatinib, median PFS was 5.1 months and 1-year PFS rate was 27%. One-year OS rate was 65%. In response-evaluable patients (n=55), the ORR and DCR were 68.6% and 87.0% all patients. However, ORR and DCR were 69.6% and 87.0% for *ALK+* and 62.5% and 87.5% for *ROS1+* patients. Of response-evaluable 55 patients, the frequency of brain metastasis before lorlatinib was 54.5% (n=30). In only 7 patients (12.7%), brain metastasis developed under lorlatinib treatment. CNS control rate with lorlatinib was 87.3%. Dose reduction occurred in 9 patients (14.3%). Reasons for discontinuation of treatment were disease progression (n=17, 26.8%), adverse events (n=2, 3.2%), death (n=13, 20.6%), and unknown reasons (n=13, 20.6%). **Conclusion:** In this EAP, lorlatinib showed systemic activity in patients with advanced *ALK+* or *ROS1+* NSCLC, regardless of CNS metastases and previous TKI treatment.

Keyword: ALK positive; ROS1 positive; Lorlatinib; Advanced stage lung cancer

P1.14-16 RESOLVING RESISTANCE TO OSIMERTINIB BY COMBINING APATINIB AND OSIMERTINIB IN EGFR-MUTANT NSCLC PATIENTS

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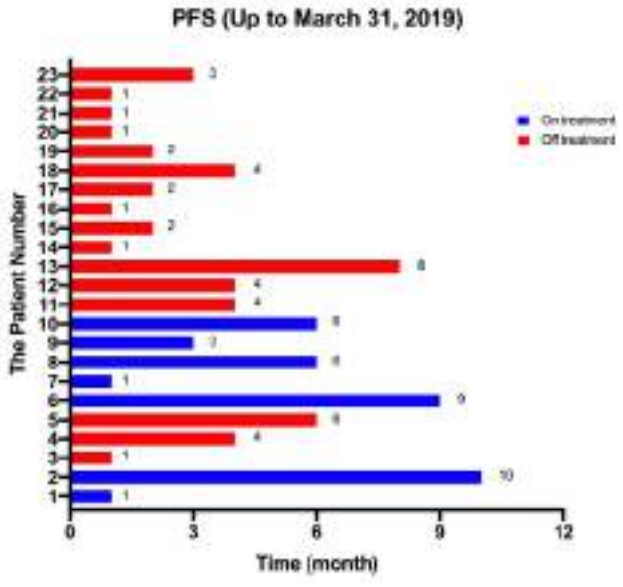
Background: There are currently limited treatment options after osimertinib resistance.Resistance to epidermal growth factor receptor(EGFR) inhibitors is frequently associated with enhanced vascular endothelial growth factor(VEGF) levels.Dual inhibition of the VEGF receptor(VEGFR) and EGFR signaling pathways has the potential to overcome osimertinib resistance. Apatinib is an oral tyrosine kinase inhibitor(TKI) against VEGFR-2. This study was conducted to evaluate the efficacy of Apatinib plus osimertinib after osimertinib resistance in EGFR-mutant NSCLC patients. **Method:** The study was expected to enroll 30 EGFR-mutant NSCLC patients resistant to osimertinib. Patients received oral apatinib 250mg QD plus osimertinib 80mg qd. Efficacy evaluation was conducted after first month, then every two months once again. The primary endpoint was progression free survival (PFS). **Result:** From March 01, 2018 to February 28, 2019, 23 patients were enrolled. The overall response rate(ORR) and disease control rate(DCR)of apatinib plus osimertinib after osimertinib resistance was 8.7%(2/23) and 73.9%(17/23),respectively.Until the last follow-up(March 31,2019), 17 patients (73.9%,17/23)showed disease progression,the other 6 patients (26.1%,6/23) still received combination therapy,as shown in figure 1.The median PFS was 4.0 months (95% CI 2.4-5.5).Six patients had received at least six-month combination therapy,four of whom were still on treatment.The most common adverse event was hypertension, diarrhea,rash and hand-foot syndrome.What calls for special attention is that one patient achieved partial response, however, stopped the combination therapy due to seriously decreased left ventricular ejection fraction.



Conclusion: Apatinib plus osimertinib might be a choice after osimertinib resistance.For further investigation, large sample and additional clinical trials are warranted.

Keywords: combination therapy, osimertinib resistance, apatinib

POSTERS

P1.14-17 GENOMIC EVOLUTION DURING TKI TREATMENT IN NON-SMALL CELL LUNG CANCER PATIENTS WITH OR WITHOUT ACQUIRED T790M MUTATION

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Background: *EGFR*-mutant non-small-cell lung cancer (NSCLC) patients inevitably develop drug resistance when treated with EGFR tyrosine kinase inhibitors (TKIs). Clonal and clinical analyses of genetic alterations at baseline and progressive disease (PD), as well as differences between acquired T790M and T790M-negative patients in drug-resistant mechanisms, have not been systematically studied. **Method:** We performed targeted sequencing of pre-treatment and PD tumor samples from 54 *EGFR*-mutant NSCLC patients. Ten additional patients were sequenced using whole exome sequencing to infer the clonal evolution patterns. **Result:** We observed new co-occurring alterations and pathways limiting *EGFR*-inhibitor response, including 9p34.3/19p13.3 (*NOTCH1/STK11)* co-deletion and TGF-beta pathway alterations. Besides acquired T790M mutation, chromosomal instability (CIN) related genes including *AURKA* and *TP53* alterations were the most frequently acquired events. CIN significantly increased with TKI treatment in T790M-negative patients. Transcriptional regulators including *HNF1A*, *ATRX* and *NKX2-1* acquired alterations were enriched in T790M-positive patients, and diverse oncogenic pathway alterations were more common in T790M-negative patients. T790M-positive patients had improved PFS compared to T790M-negative patients. We further identified subgroups within T790M-positive or T790M-negative patients with distinct PFS. Clonal evolution analysis indicated progression of T790M-positive patients depends on competition between T790M and non-T790M resistant subclones. **Conclusion:** Our study is the first attempt to identify co-occurring copy number events to stratify patients resistant to TKI treatment. Besides acquired T790M mutation, chromosomal instability (CIN) related genes were identified as the most frequently acquired events. Clonal evolution analysis indicated indicate that higher competitive advantage of T790M was associated with improved PFS.

Keywords: EGFR mutant NSCLC, resistant mechanism, Clonal evolution

P1.14-18 ALK INHIBITOR SEQUENCING AND OUTCOMES AMONG ALK-POSITIVE (ALK+) NSCLC PATIENTS IN THE US COMMUNITY ONCOLOGY SETTING

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Background: Several ALK inhibitors, including 2nd and 3rd generation agents are available for patients with ALK+ NSCLC. Treatment patterns and outcomes with use of multiple sequential ALK inhibitors is limited. **Method:** A retrospective observational cohort study of patients with ALK+ NSCLC treated with 1st generation (crizotinib) and 2nd generation (alectinib, brigatinib, ceritinib) ALK inhibitors from 1 September 2011 to 31 December 2017. Structured data were obtained via programmatic extraction from the iKnowMed EHR database of the US Oncology Network. Patient demographics and treatment sequences were characterized. Index was the start date of the first ALK. Duration of therapy (DOT) from index to end of the last ALK, and overall survival (OS) were assessed using the Kaplan-Meier method. **Result:** A total of 410 ALK+ NSCLC patients were included. Median age at index was 62 years, 54% were female, 78% Caucasian, 87% adenocarcinoma histology, and 54% never smokers. 233 (57%), 144 (35%), and 33 (8%) patients received 1, 2, or 3-4 different ALK inhibitors, respectively. Crizotinib monotherapy (50%) was most common. Among patients that received 2 or more ALK inhibitors (n=177), most were crizotinib-led sequences. In 59% of patients, chemotherapy was given prior to the first ALK (median time from start of chemo to index 6.64 mo), and 53% of patients ended their ALK sequence and received subsequent chemo. Median cumulative ALK DOT in the full study population, regardless of line of therapy or sequence was 16 mo (95% CI 6-19). Median OS from index for the full study population was 28 mo (95% CI 24, 36). Median OS among patients who received 1, 2, or 3-4 ALK inhibitors was 15 mo (95% CI 10, 22), 42 mo (95% CI 38, 60) and 56 mo (95% CI 31, 72). **Conclusion:** Patients received a range of 1 to 4 ALK inhibitors. Crizotinib-led sequences were most common, likely reflecting the approval history of ALK inhibitors during the study period. Longer DOT and OS were observed in patients receiving multiple ALK inhibitors. This study provides an initial view of treatment patterns following the emergence of new ALK inhibitors and suggests feasibility of sequential ALK therapies. Follow-up studies will help improve understanding of outcomes of patients treated with 2nd generation-led sequences.

Keywords: ALK-inhibitor, treatment-sequence, NSCLC

P1.14-19 EXOME ANALYSIS OF PATIENTS TREATED WITH AFATINIB REVEALS GENETIC VARIATIONS DISCRIMINATING EXTREME RESPONDERS

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Background: Non-small cell lung cancer is a dramatic disease. For several years, molecular analyses highlighted several genetic alterations (mutations, gene fusions) enabling use of targeted therapies. Among targetable mutations, the most frequent (11% of lung adenocarcinomas) are *EGFR* mutations spanning from exon 18 to exon 21, except insertion in exon 20 and T790M mutation. In clinical practice, progression free survival under EGFR Tyrosine Kinase Inhibitor is between 12 and 14 months, but some patients rapidly progress in less than 6 months, whereas other patients are treated with EGFR TKI during more than 16 months, and even more in some cases. **Method:** ALCAPONE clinical trial (NCT02281214) included 165 patients with a non-small cell lung cancer divided in 2 different groups: EGFR mutated (n=63) and EGFR wild-type tumors (n=102). All tumors at baseline had an exome analysis performed with SureSelect Human all exon v5 or v6 kit. After adapter trimming and quality check, GATK tools were applied to process the data. After variant calling (Haplotype Caller) and annotation, genetic variations were separated in 3 categories: intron variants, synonymous variants and transcripted variants. Only variants with a general population frequency <1% were conserved for statistical analyses. For the first analysis of the trial, we focused on a training set of 33 EGFR mutated patients homogenously treated by afatinib. We selected 18 extreme responders (10 short responders with PFS<180 days and 8 long responders with PFS>500 days) to select genetic markers predictive of extreme responses and used them to evaluate survival including 15 patients with PFS between 180 and 500 days. **Result:** Thanks to 2 different predictive models, it appeared that 5 genes were able to discriminate short responders from long responders: *AKR1B1, WNK1, IHH*, PLA2G16*, and SMYD3**, whose those with an asterisk selected by the 2 different predictive models. For these genes, the presence of a non-synonymous variant in transcripted (UTR and coding) sequences of the genes was associated with a worse response to afatinib. By studying PFS probability with the 33 EGFR mutated patients of the training set, it appeared that 2 genes discriminated responders from non-responders. Indeed, patients with a variation in *IHH* or in *WNK1* gene had a significant worse PFS than patients with no variation (p=0.0003, median PFS=9 vs 16 months for *IHH* and p=0.0052, median PFS=9 vs 17 months for *WNK1*). Interestingly, in the literature, IHH (Indian HedgeHog) decreased expression are correlated with increased sensitivity to treatment, and WNK1 (With No lysine Kinase 1) activation are linked to cellular migration and epithelial mesenchymal transition in non-small cell lung cancer. **Conclusion:** This first analysis from the ALCAPONE clinical trial identified 2 genes that could discriminate responders from non-responders. As the analysis was performed from 33 EGFR mutated patients, it will be confirmed thanks to a validation set of 30 new EGFR mutated patients treated with afatinib. If these results are confirmed, the analysis of genetic variations on both genes could be

new biomarkers bringing new information to clinicians for the choice of EGFR TKI treatment sequence. ALCAPONE study was supported by Boehringer Ingelheim

Keywords: EGFR TKI, extreme responders, biomarkers

P1.14-20 TARLOXOTINIB AS A NOVEL THERAPEUTIC STRATEGY FOR ONCOGENIC ALTERATIONS ACROSS THE ERBB FAMILY OF RECEPTORS

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Background: The ErbB family of receptors tyrosine kinases (EGFR, HER2, HER3, and HER4) have been implicated in multiple different tumor types. The implementation of comprehensive next generation sequencing has allowed the identification of diverse gene alterations that function as oncogene drivers in these receptors. Some of the non-common gene alterations identified are resistant to marketed EGFR/HER2 inhibitors. Tarloxotinib is a prodrug that generates a potent and irreversible pan-HER inhibitor (tarloxotinib-E) under hypoxic conditions associated with tumors. In this study we evaluated the effect of tarloxotinib on several types of oncogenic mutations and fusions that involve the ErbB family of receptors. **Method:** cDNAs encoding *EGFR* kinase domain duplications (*EGFR-EGFR*), *EGFR-RAD51* gene fusion, *EGFR-ERBB4*, *ERBB2-GRB7* and *EZR-ERBB4* gene fusion were expressed in Ba/F3 cells. Using spheroid assays we evaluated the proliferation of A172 glioblastoma cell line treated with tarloxotinib, tarloxotinib-E or 1st, 2ndor 3rdgeneration EGFR/HER2 TKIs. We analyze the on target and signaling effects elicited by tarloxotinib-E via immunoblots. Using a nude mice xenograft model of the human derived cell line CUTO17 wi the EGFR exon 20 insertion p.N771_H773dupNPH, we evaluated tumor, tissue and blood drug levels by mass spectrometry and the effect of tarloxotinib on tumor growth. **Result:** Our results demonstrate that tarloxotinib-E inhibits phosphorylation of EGFR with a kinase duplication and inhibits proliferation in a spheroid invasion assay in A172 cells. In the CUTO17 EGFR exon 20 model, treatment with tarloxotinib inhibited tumor growth. Intratumor levels of tarloxotinib-E were ~20 times higher than skin and ~50 times higher than plasma demonstrating selective tumor conversion of tarloxotinib. Cell growth inhibition (EC_{50}) of novel HER family fusions (EGFR-EGFR, EGFR-RAD51, EGFR-ERBB4, ERRB2-GRB7 and EZR-ERBB4) will be presented. **Conclusion:** Tarloxotinib is a potent irreversible inhibitor *in vitro* for cells that harbor oncogenic alterations across the *ERBB* gene family, including EGFR kinase domain duplications, ErbB fusions and exon-20 insertions. Tarloxotinib is selectively activated in hypoxic tumor regions demonstrating a novel mechanism to generate a therapeutic window and avoid on-target EGFR-related toxicities.

Keywords: ERBB family, TKI, Hypoxia

P1.14-21 PROPENSITY-MATCHED GENOMIC PROFILING COMPARISON OF LUNG ADENOCARCINOMAS AMONG 3 RACES, A MULTICENTER STUDY OF 4655 PATIENTS

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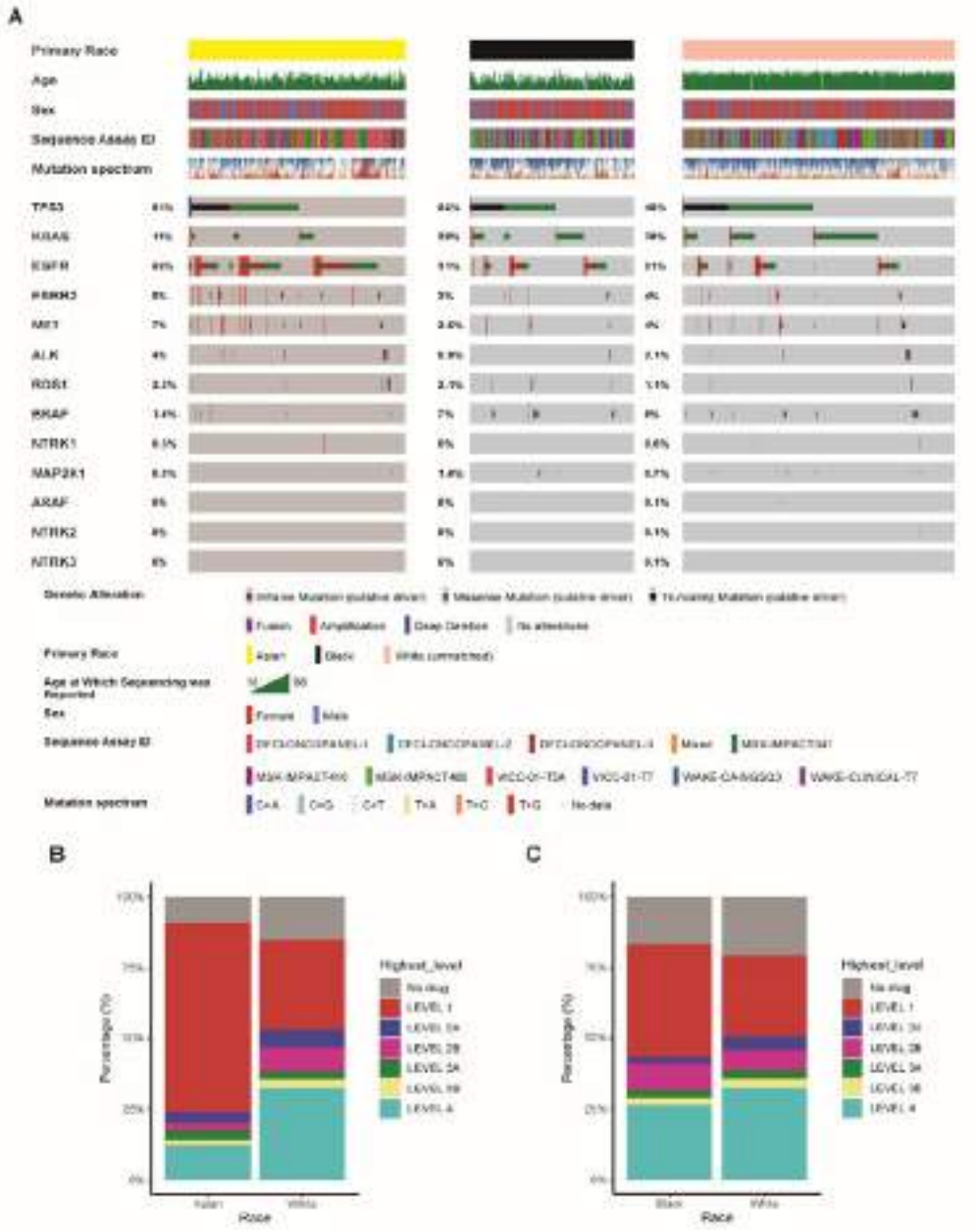
Background: The mutation rates of multiple genes are reported to differ among lung adenocarcinoma samples from different races. However, the baseline heterogeneity among different race cohorts may confound the interpretations of the results. This study is the first propensity-matched study designed to determine the genomic and therapeutic actionable disparities among the samples of Asian vs White and Black vs White races. **Method:** Sequencing data from 4 centers with primary races documented as "Asian", "Black", or "White" was accessed from GENIE database. Propensity score analysis (nearest neighbor matching method) was applied to Asian vs White and Black vs White cohorts using age, sex, sample type (primary/metastasis) and enrolling center. Mutation rates, pathway alterations, and therapeutic actionability were compared among the cohorts. Therapeutic actionability was annotated using OncoKB annotator. Fisher's exact test and FDR adjust method were used for comparison. **Result:**



A total of 4655 patients were included before matching (Figure A). 2 pairs of cohorts, 350 Asian vs 1400 White patients and 208 Black vs 832 White patients were identified for study after propensity matching. 11 genes, including *EGFR, KRAS, STK11, KEAP, BRAF, SMARCA4, PIK3CA* et.al. were significantly differentially mutated among Asian and White patients (adjusted P value<0.05), while only *EGFR* mutation rate was significantly different between Black and White cohorts (adjusted P value=0.04). In the analysis of 10 oncogenic pathways, RTK/RAS, cell cycle, hippo, notch, nrf2, wnt pathway alteration rates are different among Asian and White samples (adjusted P value<0.05). The comparison between matched Black and White samples observed no significant difference in pathway alterations. In the therapeutic actionability analysis, 4663 mutations, 974 copy number alterations, 196 fusions were annotated with at least one actionable drug in the whole cohort. 67% of samples from Asian patients embraced at least one genomic alteration corresponding to level 1 drugs, compared to 30% in matched White samples (P<0.001) (Figure B). In the Black vs White group, the rate of coresponding level 1 drugs per sample is 39% vs 29% (P=0.003) (Figure C). **Conclusion:** In this propensity-matched study, samples from Asian LUAD patients displayed significantly different genomic mutation rate, pathway alteration rate, and therapeutic actionability characteristics compared to White patients. Samples from Black patients have a higher rate of EGFR mutations and level 1 therapeutic actionability than white patients. But the difference is more prominent in the Asian vs White group compared to Black vs White group.

Keywords: Propensity matched study, Next generation sequencing, racial differences

POSTERS

P1.14-22 SASH1, A NOVEL PROGNOSTIC AND PREDICTIVE FACTOR FOR PARP INHIBITORS IN LUNG CANCER

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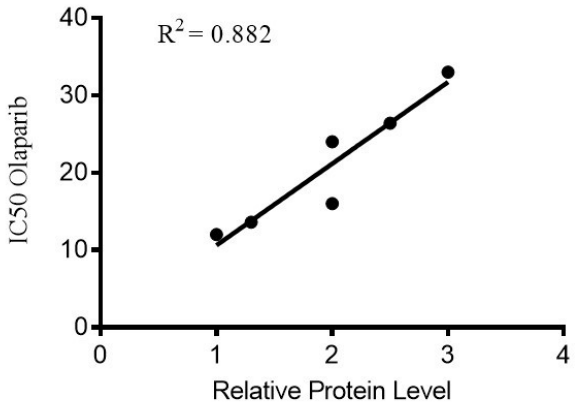
Background: Genomic instability is a universal hallmark of all cancers. Many of the most commonly used chemotherapeutic agents target this genomic instability by directly damaging the DNA, which results in tumour cell death. Our previous work has revealed that loss of SASH1 is associated with impaired apoptosis and increased cellular proliferation. A new generation of drugs have been developed that target the DNA repair enzyme PARP to induce DNA damage and cell death. SASH1 (SAM and SH3 domain containing protein 1) has been described as a tumour suppressor and in support of this SASH1 mRNA levels are decreased in lung, breast, thyroid and colorectal cancers. Our data demonstrates that SASH1 functions in the repair of DNA damage and loss of SASH1 protein expression could be used as a companion diagnostic for PARP inhibitors. **Method:** SASH1 IHC staining of lung cancer was correlated with patient survival. DNA damage repair was assessed following the depleted of SASH1 (siRNA). SASH1 protein levels in cell lines were correlated to PARP inhibitor sensitivity. **Result:** A lung cancer tissue microarray (TMA) of 225 patients was assessed for SASH1 protein level. Low SASH1 levels were associated with an improved patient prognosis in adenocarcinoma on univariate analysis (p = 0.03). Analysis of DNA repair pathways demonstrated that SASH1 plays a role in homologous recombination (HR). Based on this observation, the impact of SASH1 expression on sensitivity to PARP inhibitors was explored. An inverse correlation between SASH1 levels and sensitivity to Olaparib was identified in lung cancer cell lines Figure 1 (R^2 = 0.882). We subsequently analysed Olaparib sensitivity in a panel of SASH1 depleted lung cancer cells that demonstrated increased Olaparib sensitivity.

Figure 1



Conclusion: Our results indicate that SASH1 protein expression is a prognostic factor in lung cancer, high levels being associated with a worse prognosis in adenocarcinoma. Low SASH1 expression is associated with loss of HR and has the potential to be a predictive biomarker for sensitivity to PARP inhibitors in this disease.

Keywords: Biomarker, PARP Inhibitor, NSCLC

P1.14-23 RESISTANCE MECHANISMS TO OSIMERTINIB TREATMENT IN EGFR-MUTATED LUNG CANCER IN A REAL LIFE COHORT

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Background: Targeted therapies in Epidermal Growth Factor Receptor (EGFR)-mutated advanced lung cancer are developing rapidly, with registration for third generation EGFR-tyrosine kinase inhibitor (TKI) osimertinib for first line treatment recently. The resistance mechanisms that develop during first line treatment with osimertinib seem to differ from resistance developing during treatment for p.T790M mutation after first- or second generation EGFR-TKI based on current limited knowledge. We investigated the resistance mechanisms at progression on osimertinib treatment in a real life cohort. **Method:** In the START-TKI study, patients with EGFR-mutated lung cancer were pospectively sampled for plasma analysis during TKI treatment. We analysed the included osimertinib cohort until March 1, 2019, which included both first line and second line (based on p.T790M positivity) treated patients. Exclusion criteria were lack of subsequent samples until progression, double gene/TKI treatment or switch to other treatment because of toxicity. Next-generation sequencing (NGS) analysis was performed at progression on plasma and tissue specimens (when available). **Result:** A total of 42 patients was included, which consisted of N=27 in the p.T790M positive (second line treatment) and N=15 in the p.T790M negative (first line treatment) subgroup. We excluded 4 patients in the first, and 5 patients in the second line treatment group. Evaluable progression was reached by N=11 and N=3 patients respectively. In the second line (p.T790M positive) subgroup, resistance mechanisms were identified in 7 patients, and comprised MET amplification (N=2), small-cell transformation (N=2), EGFR p.C797S mutation (N=2) and BRAF mutation (N=1). In the p.T790M negative (first line) subgroup, resistance mechanisms were not identified. **Conclusion:** Tissue specimen can provide important additional information on resistance mechanisms to EGFR-TKI treatment next to plasma analysis due to morphological information and in situ analyses (immunohistochemistry and in situ hybridization). Resistance mechanisms to osimertinib in EGFR-mutated lung cancer are still under investigation, and may differ in a p.T790M positive and p.T790M negative setting. This study was partly funded by a grant from AstraZeneca.

P1.14-24 CHARACTERIZATION OF ACQUIRED RECEPTOR TYROSINE KINASE FUSIONS AS MECHANISMS OF RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS

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Background: Responses to *EGFR* targeted therapy are generally temporary due to evitable drug resistance. The prevalence and characteristics of receptor tyrosine kinase (RTK) fusions as acquired resistance to EGFR-TKIs are rarely investigated. **Method:** We retrospectively reviewed genomic profiling data of 3873 *EGFR* (exon 18-21)-mutant lung cancer patients with more than once NGS detection. A total of 16 patients who acquired RTK fusions during EGFR-TKI treatment with paired pre- and post- EGFR-TKI samples were identified. Their treatment history was collected. **Result:** The newly acquired RTK fusions during EGFR-TKI treatment included *RET* (n = 6, 37.5%), *ALK* (n = 5, 31.3%), *NTRK1* (n = 4, 25.0%), *ROS1* (n = 1, 6.3%) and *FGFR3* (n = 1, 6.3%). All the *RET* and *EML4-ALK* fusions were uncommon variants non-*KIF5B-RET* and E2:A20 (V5), respectively. Interestingly, *RET* fusion occurred only after osimertinib treatment, and contributed to drug resistance in 50.0% (6/12) of patients treated with osimertinib, indicating that fusions had different prevalence when functioned as resistance mechanisms to EGFR-TKI. Moreover, we found that in all patients developing drug resistance to EGFR-TKIs due to fusion emergence (n=16), those had treatment history of third-generation EGFR-TKI accounted for 75.0% (n=12). **Conclusion:** We extended the current knowledge of resistance mechanisms to EGFR-TKIs in non-small cell lung cancer. Detection of RTK fusions should be included in genomic profiling panels to uncover potential resistance mechanism of EGFR-TKI which might inform therapeutic strategies such as combination therapy approaches to circumvent tumorigenesis.

Keywords: EGFR-TKI, acquired drug resistance, fusion

P1.14-25 TARGETING NRG1-FUSIONS IN LUNG ADENOCARCINOMA: AFATINIB AS A NOVEL POTENTIAL TREATMENT STRATEGY

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Background: Neuregulin 1 (*NRG1*) gene fusions result in activation of ErbB2-/ErbB3-mediated signaling pathways, and may function as oncogenic drivers. *NRG1* fusions have emerged as a potential therapeutic target across multiple tumor types, including non-small-cell lung cancer (NSCLC). Afatinib, a pan-ErbB-family blocker, may be a treatment option for patients with *NRG1+* NSCLC, as supported by preclinical evidence and seven published case reports (Table). **Method:** Here, we report clinico-pathological and molecular characteristics of four new cases of *NRG1* fusion-positive lung adenocarcinoma treated with afatinib. Afatinib activity is reported. **Result:** Case 1 is a 70-year-old, female, never-smoker, diagnosed with pan-wildtype, non-mucinous, adenocarcinoma. She received afatinib in the fifteenth-line setting and experienced a partial response (PR) for 24 months. Following further progression on chemotherapy, *NRG1*-fusion was identified using NanoString analysis (re-biopsy was performed to find an explanation for afatinib efficacy). The patient was re-challenged with afatinib (best response: PR [3 months]), before switching to atezolizumab (best response: progressive disease). Case 2 is a 66-year-old female, never-smoker, diagnosed with metastatic, non-mucinous adenocarcinoma. A *CD74-NRG1* fusion was identified by Oncomine™ Comprehensive Assay, and fifth-line afatinib treatment was initiated. She experienced a PR, ongoing after 14 months of treatment. Case 3 is a 68-year-old male diagnosed with lung adenocarcinoma. A *SDC4-NRG1* fusion was subsequently identified using Next Generation Sequencing and the patient initiated second-line afatinib treatment. He achieved stable disease as best response, lasting for four months. Case 4 is a 43-year-old, female, non-smoker, diagnosed with advanced invasive mucinous adenocarcinoma. A *CD74-NRG1* fusion was subsequently identified by RNA sequencing and the patient initiated third-line afatinib treatment; PR is ongoing. **Conclusion:** These findings add to a growing body of evidence suggesting afatinib activity in *NRG1*-fusion positive NSCLC. Prospective study of a larger cohort of patients with *NRG1*-fusion positive NSCLC treated with afatinib is warranted to better evaluate this potential activity.

Patient	Tumor type	NRG1 fusion partner	Best response	Duration of response (months)	Reference
i	Non-mucinous lung adenocarcinoma	*SLC3A2*	PR	12	Gay, et al. *J Thoracic Oncol* 2017
ii	IMA	*CD74*	PR	10	Gay, et al. *J Thoracic Oncol* 2017
iii	Non-mucinous lung adenocarcinoma	*SDC4*	PR	12	Jones, et al. *Ann Oncol* 2017
iv	IMA	*CD74*	PR	6.5	Cheema, et al. *J Thoracic Oncol* 2017
v	IMA	*CD74*	SD	3	Drilon, et al. *Cancer Discov* 2018
vi	IMA	*SDC4*	PD	-	Drilon, et al. *Cancer Discov* 2018
vii	IMA	*CD74*	PD	-	Drilon, et al. *Cancer Discov* 2018

IMA, invasive mucinous lung adenocarcinoma; PD, progressive disease; SD, stable disease

P1.14-26 ALK FUSION VARIANT DETECTION BY TARGETED RNA-SEQ IN TKIS TREATED ALK-POSITIVE LUNG ADENOCARCINOMA

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Background: Clinical outcomes of ALK positive (ALK+) Non-Small-Cell Lung Cancer (NSCLC) and the identification of the most effective anaplastic lymphoma kinase inhibitor (ALKi) according to the specific ALK fusion variants are not well assessed. We retrospectively characterized fusion variant distribution in a cohort of ALK+ lung adenocarcinomas (ADC) with paired clinical data about treatments and outcomes. **Method:** Diagnostic tumor tissue from advanced ALK+ (by FISH and/or IHC) ADC diagnosed from 2010 to 2018 and treated with single or multiple ALKis were collected (expanded cohort from Gobbini et al. Lung Cancer, 2017). The Oncomine™ Solid Tumor Fusion Transcript Kit on an Ion PGM™ system and the Ion Reporter™ software were used to identify

targeted ALK fusion gene products (ThermoFisher). **Result:** Specific fusion variant transcripts were found in 34/55 (62%) of collected samples. As expected, EML4-ALK fusion transcripts were the most common (31/34 samples, 91%), but HIP-ALK transcripts were also detected (3/34 - 9%). Among EML4-ALK fusions the following variants were detected: V1 (n=11); V2 (n=2); V3a/b (n=12) V5a/b (n=5) and E6A19 (n=1). Patient median age was 60 year [range 36-85], 22 were male and 12 female. Three patients were current, 11 former and 20 never smokers. Crizotinib, alectinib, ceritinib, brigatinib and lorlatinib were the ALKis used. Independently of the therapy line, 12 patients received crizotinib only, while 22 patients received crizotinib followed by one or two other ALKis. Regardless of the type of transcript, those patients who received more than one ALKi had a better median overall survival compared to those receiving crizotinib only, as expected (74 vs 21 months, HR: 5.31; 95%CI: 1.464-19.26, log rank p=0.0006). Furthermore, a significant difference in the mean duration of the different ALKi treatment was found according to the ALK variants (Chi-square p<0.0001), suggesting a private ALKi efficacy profile for specific fusion variants. Finally, the 3 HIP-ALK cases showed a better outcome with respect the EML4-ALK variants (not reached vs 51 months). **Conclusion:** Our analysis suggests that different ALK fusion variant might affect ALKi treatment duration in ALK+ lung ADC.

Keywords: ALK, ALK inhibitor, Fusion variant

P1.14-27 DURATION OF TARGETED THERAPY IN ADVANCED NSCLC (ANSCLC) WITH DRIVERS IDENTIFIED BY CIRCULATING TUMOR DNA (CTDNA) ANALYSIS

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Background: Identifying targetable genomic drivers is critical for optimal first-line treatment planning in aNSCLC. ctDNA testing can aid treatment selection when tissue specimens are inadequate for complete genotyping or when a rapid turnaround time is advantageous. Targeted therapy (TT) outcomes for ctDNA-detected drivers have not been widely reported in the first-line setting given the relatively recent adoption of this technology into clinical practice. **Method:** We conducted a multicenter retrospective review of patients with aNSCLC who received matched TT following identification of a driver on a validated commercial ctDNA assay (Guardant360). Eligible patients were tested per regular clinical care between March 2014-October 2018 and must not have received a TT prior to ctDNA testing (prior chemotherapy or immunotherapy was permitted). Kaplan-Meier analysis was used to estimate median duration of TT (DTT) for both the first and all subsequent sequential targeted therapies where applicable (e.g. osimertinib following erlotinib). Patients still on TT were censored at last follow-up. **Result:** 76 patients met inclusion criteria. Median age of diagnosis of aNSCLC was 64.5 years (range 31-87y), 67% were female, 74% were never smokers, and 97% had adenocarcinoma histology. 21/76 (28%) patients received chemotherapy (n=17), immunotherapy (5), and/or a biologic (4) prior to receiving TT. 41/76 (54%) patients remain on TT at the time of data analysis, 32 of whom are still on their first TT. 38/41 patients still on TT have at least 6 months follow-up. Treatment outcomes are summarized in Table 1.

Table 1. Duration of Targeted Therapy

Driver	Therapy	n, total patients/ discontinued therapy	Median (95% CI) DTT in weeks[1]
EGFR	Erlotinib Osimertinib Afatinib Gefitinib Any EGFR TKI[2]	21 / 19 23 / 6 3 / 2 1 / 1 48 / 20	33 (23-54) NR 3, 13, 93* 63 86 (48-197)
ALK fusion	Alectinib Crizotinib Any ALK TKI[3]	7 / 2 2 / 2 9 / 2	NR 20, 44 NR
BRAF V600E	Dabrafenib + Trametinib	10 / 7	51 (13-88)
MET exon 14 skipping	Crizotinib Investigational	3 / 2 1 / 1	4, 77, 63* 14
ROS1 fusion	Investigational	2 / 1	50, 79*
ERBB2 exon 20 insertion	Ado-trastuzumab emtansine	2 / 1	46, 14*
RET fusion	Investigational	1 / 1	47

1 – individual data rather than median provided for counts <5 2 – includes 15 patients receiving sequential EGFR TKIs 3 – includes 3 patients receiving sequential ALK TKIs * indicates therapy is ongoing for individual data points Abbreviations: NR – not reached; TKI – tyrosine kinase inhibitor

Conclusion: This study provides interim data on targeted therapy outcomes for aNSCLC patients with Guardant360-detected drivers treated in everyday clinical practice. Outcomes are in line with what is expected for tissue-detected drivers in the TT naïve setting and this cohort will continue to be followed. Identification of NSCLC driver mutation using well-validated ctDNA assays can be used for clinical decision-making.

Keywords: ctDNA, Targeted therapy, advanced NCLC

P1.14-28 CORRELATION BETWEEN THE QUALIFICATION FOR THE BEVACIZUMAB USE AND THE SURVIVAL OF NSCLC PATIENTS WITH EGFR MUTATIONS

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Background: Previously, the combination of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and bevacizumab (BEV) has been investigated. A subgroup analysis of a phase III trial investigating the combination of atezolizumab, carboplatin, paclitaxel, and bevacizumab (ABCP) demonstrated the benefit of ABCP in patients harboring *EGFR* mutations. This study aims to assess the prognostic significance of the qualification for the BEV use on the survival and proportion of patients who potentially benefit from BEV before and after first-line EGFR-TKIs. **Method:** We retrospectively analyzed the data of 283 patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) harboring *EGFR* mutations who had received EGFR-TKIs. We performed statistical analyzes using the Kaplan–Meier method and Cox regression adjusted for risk factors. **Result:** Of 283 patients, 196 (69%) were eligible to administer BEV ("BEV fit") at the time of EGFR-TKIs initiation. Among "BEV unfit" patients at the baseline (n = 67), 14 (21%) became "BEV fit" at the time of EGFR-TKIs failure. The median overall survival (OS) time of "BEV fit" and "BEV unfit" patients were 25.0 [95% confidence interval (CI): 23.0–29.4] and 18.8 (95% CI: 14.4–22.0) months, respectively (P = 0.0001). The multivariate analysis revealed a marked correlation between survival and the qualification for the BEV use. **Conclusion:** The qualification for the BEV use at the baseline is independently related to the OS. Some patients harboring *EGFR* mutations, including "BEV unfit" at the baseline, could be eligible for the ABCP regimen after the first-line EGFR-TKIs failure.

Keywords: Bevacizumab, epidermal growth factor, tyrosine kinase inhibitor

P1.14-29 DISRUPTING THE PARADIGM: PARTNERING WITH ONCOGENE-FOCUSED PATIENT GROUPS TO PROPEL RESEARCH

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Background: Genomic alterations drive more than 60% of adenocarcinoma cases of non-small cell lung cancer (NSCLC). About 20% of cases will have an oncogenic driver (EGFR, ALK, ROS1, BRAF, NTRK, etc.) that can be treated with approved targeted therapy drugs, and more (RET, Exon 20 insertions, etc.) have clinical trial options. Patients and caregivers dealing with these cancers have organized globally into oncogene-focused groups ("Groups"—see Table 1) and are building partnerships that seek to provide support, increase awareness and education, accelerate and fund research, and improve access to effective diagnosis and treatment.

Method: We partnered in a variety of ways to accelerate research. While each Group sets its own research priorities, we've found successful collaborative research has the following seven characteristics. It includes patients from the start, in all aspects of the project. It addresses questions meaningful to patients. It develops patient-centered measurements. It accommodates patients' clinical realities. It leverages social media and patient groups. It shares progress with participants frequently. It makes results rapidly and freely available. **Result:** These methods have enabled the Groups to collaborate successfully with clinicians, researchers, advocacy organizations, and industry to generate ideas for next steps in research for their disease, forge new studies and clinical trials for a specific oncogenic driver, create new patient-derived models of oncogene-driven cancers to study acquired resistance, develop registry-based studies to collect real-world data, and guide patients to clinical trials. **Conclusion:** Oncogene-focused patient-caregiver groups are creating new paradigms across the research continuum. They have demonstrated that their partnerships with advocacy organizations, clinicians, researchers, and industry, can increase available patient-derived models, patient data, and specimens among geographically distributed, oncogene-driven cancer populations.

GROUP	FOCUS	CONTACT EMAIL	WEBSITE
ROS1ders	ROS1+ cancer	ros1cancer.patient@gmail.com	ros1cancer.com
ALK Positive	ALK+ NSCLC	info@alkpositive.org	www.alkpositive.org
Exon 20 Group	EGFR & HER2 Exon 20 insertions	exon20@exon20group.org	exon20group.org
EGFR Resisters	EGFR+ NSCLC plus cancers resistant to EGFR TKIs	egfrresisters@gmail.com	www.egfrcancer.org
RET Renegades	RET+ NSCLC	retrenegades@gmail.com	N/A
ALK Fusion	ALK+ NSCLC	mail@alkfusion.org	www.alkfusion.org

Table 1. Oncogene-focused patient and caregiver groups.

Keywords: oncogene-focused patient groups, targeted therapies research, patient-partnered research

P1.14-30 PHASE I STUDY OF AFATINIB PLUS BEVACIZUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER HARBORING EGFR MUTATIONS

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Background: Afatinib, a second-generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI), is one of the standard therapies for patients with advanced non-small cell lung cancer (NSCLC) harboring *EGFR* mutations. The first-generation EGFR-TKIs in combination with bevacizumab have been reported to improve progression-free survival (PFS). However, data on afatinib plus bevacizumab are limited. **Method:** In this phase I study, we examined the safety and the efficacy of afatinib plus bevacizumab in patients with advanced non-squamous NSCLC harboring *EGFR* mutations. This study comprised two cohorts. In the dose-finding cohort, eligible patients received afatinib 20, 30, or 40 mg/day (days 1–21) plus bevacizumab 15 mg/kg (day 1) in 21-day cycles. This cohort was designed and conducted in a 3 + 3 manner. In the expansion cohort, the patients were treated with the recommended dose (RD) based on the findings in the dose-finding cohort, and we evaluated the preliminary efficacy of this combination therapy. The serum trough concentration of afatinib was assessed at the steady state. **Result:** Sixteen patients were enrolled in this study (5 patients in the dose-finding cohort and 11 patients in the expansion cohort). No dose-limiting toxicities (DLTs) occurred with afatinib 30 mg/day. With afatinib 40 mg/day, 2 out of 2 patients had DLTs (grade 3 diarrhea) in cycle 1. From these results, afatinib 30 mg/day plus bevacizumab 15 mg/kg was decided as the RD. Additionally, 11 patients in the expansion cohort were treated with RD. Common treatment-emergent adverse events (AEs) with the RD were diarrhea (79%), rash (71%), perionychia (64%), and stomatitis (50%). Grade 3 AEs with the RD were diarrhea (7%), perionychia (7%), and hypertension (7%). There were no grade 4/5 AEs and interstitial lung disease. The response rates and median PFS were 56% and 16.8 months in EGFR-TKI naïve patients, and 0% and 4.9 months in patients pretreated with EGFR-TKIs. The median serum concentration at the steady state was 13.7 ng/mL (range: 8.1–38.1 ng/mL) in the patients treated with the RD. Rebiopsy was conducted in eight patients after disease progression with afatinib plus bevacizumab, and three patients acquired an exon 20 T790M mutation. **Conclusion:** Afatinib 30 mg/day plus bevacizumab 15 mg/kg was well tolerated. Large-scale studies are warranted to evaluate the efficacy of this combination therapy.

Keywords: Bevacizumab, Non-Small Cell Lung Cancer, Afatinib

POSTERS

P1.14-31 LACK OF ASSOCIATION BETWEEN BIM DELETION POLYMORPHISM AND CLINICAL EFFICACY OF EGFR-TKIS IN NSCLC BASED ON NGS

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Background: BIM deletion polymorphisms are most common in Asian population, with an incidence of 12-16% in lung cancer patients with EGFR mutations. Previous studies showed BIM deletion polymorphisms could predict poor treatment response to EGFR-TKIs, owing to loss function in mediating apoptosis of tumor cells. Recently, available data on BIM is inconsistent on its predictive role and we don't know if NGS could bring us something new. **Method:** Data were pooled from clinical trial CTONG0901 and local database in our hospital (GLCI). 194 and 117 EGFR mutant patients with IIIB-IV NSCLC are enrolled for survival analysis in the two cohorts, respectively. BIM status of all these patients were confirmed by NGS. 28 patients have baseline NGS results with 168 genes panel. **Result:** The incidence of BIM deletion polymorphism in patients with EGFR mutation was 11.3% (22/194) and 17.6% (26/148) in CTONG0901 and GLCI, respectively. In CTONG0901, median PFS of patients treated with erlotinib or gefitinib between BIM deletion polymorphism and BIM wild type is 10.47m versus 11.17m (P=0.59). Median OS is 20.5m versus 20.47m (P=0.82). In GLCI, median PFS between BIM deletion polymorphism and BIM wild type is 10.13m versus 12.87m (P=0.33). Median OS is 58.5m versus 54.97m (P=0.82). No survival differences on PFS and OS present in the two cohorts. 28 patients with baseline NGS were analyzed from two cohorts. Three patients with MET amplification, ALK rearrangement and PD-L1 expression (20%+++) are lower than median PFS (8.63m). Two patients with MET amplification are around median PFS.

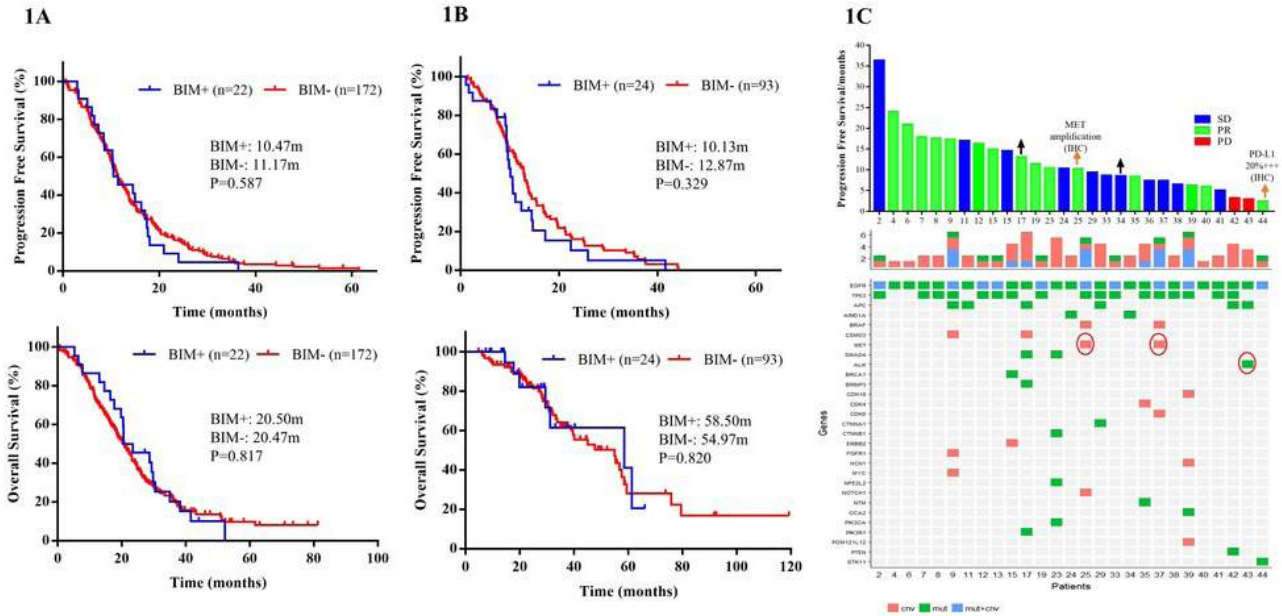

Figure 1A: Survival analysis in CTONG0901 with comparation of PFS and OS between advanced NSCLC patients with BIM deletion polymorphisms and wild type. **Figure 1B:** Survival analysis in local database (GLCI) with comparation of PFS and OS between advanced NSCLC patients with BIM deletion polymorphisms and wild type. **Figure 1C:** Waterfall plot and heatmap of 28 patients with BIM deletion polymorphisms based on the NGS results at baseline. The black up arrows indicates that the PFS has not been reached; the orange up arrows indicates one patient with MET amplification (IHC) and one with PD-L1 20%+++ (IHC); the red circles indicates two patients with MET amplification (NGS) and one with ALK rearrangement (NGS).

Conclusion: In our study, BIM deletion polymorphism has no relationship with the efficacy of EGFR-TKIs in CTONG0901. The result is confirmed in our local database. Outcomes of NGS showed that combined molecular variations, such as MET amplification, ALK rearrangement and PD-L1 expression seems more important to the prediction of EGFR-TKIs on NSCLC patients.

Keyword: BIM deletion polymorphism; EGFR-TKIs; NGS

POSTERS

P1.14-32 RASH AND EFFICACY IN ANAPLASTIC LYMPHOMA KINASE POSITIVE (ALK+) NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH ENSARTINIB

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Background: Ensartinib is a potent ALK small molecule tyrosine kinase inhibitor (TKI). In a phase 1/2 study, ensartinib was generally well tolerated and demonstrated good clinical activity in pts with ALK+ non-small cell lung cancer (NSCLC). This post hoc analysis sought to determine the relationship between ensartinib-related rash and clinical benefit. **Method:** Adverse events (AEs) were coded using MedDRA v15.0; severity was assessed by investigators using NCI CTCAE v4.03. Objective response rate (ORR) and median progression-free survival (mPFS) were explored in the efficacy-evaluable population, which included ALK+ pts receiving ensartinib 225 mg QD who had a postbaseline response assessment. **Result:** As of Feb 07, 2019, 80 pts were dosed at the phase 3 dose of 225 mg QD and were efficacy evaluable (13 were ALK TKI naive, 37 had received prior crizotinib only, and 30 had received a prior second-generation ALK TKI). Rash was the most common AE observed in 69% of pts, mostly grade 1/2. The rashes started most frequently (33%) at day 7 or 8. The most common types of rash were general rash, rash maculopapular, and rash erythematous. Rash was primarily managed with topical corticosteroids, with some dose reductions, or no intervention at all and rarely led to discontinuation (2% [n=2]). The median duration of rash was 22 days. The ORR and mPFS were better in pts with rash vs those without (ORR, 53% vs 40%; mPFS, 8.6 vs 5.7 mo; P=.0044) (Table). A multivariate Cox proportional hazards model controlling for baseline factor (eg, age, sex, ECOG PS, and prior ALK TKI) revealed a correlation between rash and PFS (HR=0.556; P=.0755). Pts are still being accrued in this study.

Table. Efficacy in *ALK*+ Pts at 225 mg QD with a Postbaseline Response Assessment

	Evaluable Pts (n=80)[a]	
	Rash (n=55)	**No rash (n=25)**
ORR, n (%)	29 (52.7)	10 (40.0)
mPFS, mo 95% CI	8.6 5.8-11.3	5.7 2.9-7.3
Log-rank *P* value	.0044	

[a]13 *ALK* TKI naive, 37 received prior crizotinib only, and 30 received a prior second-generation ALK TKI.

Conclusion: Ensartinib was associated with mild to moderate rash that was easily managed. Preliminary findings suggest that rash is potentially associated with better clinical benefit with ensartinib.

Keywords: ALK, rash, clinical benefit

P1.14-33 CANAGLIFLOZIN INHIBITS LUNG CANCER SURVIVAL AND ENHANCES ITS RESPONSE TO RADIOTHERAPY; EFFECTIVE BLOCKADE OF MTOR PATHWAY, HIF1A, AND MITOSIS

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Background: Non-small cell lung cancer (NSCLC) presents frequently at an advanced stage where standard treatment with radiotherapy (RT) and chemotherapy (CT) provides limited benefit. Driver mutations and alterations of NSCLC cell metabolism contribute to rapid growth, resistance to cytotoxic therapy and survival. In normal cells, these events are controlled by the metabolic stress sensor AMP-activated protein kinase (AMPK), a key regulator of cell metabolism that also responds to cytotoxic therapy. AMPK induces a p53-mediated cycle checkpoint and inhibits the mammalian Target of Rapamycin (mTOR) pathway. Canagliflozin (CANA), a new diabetes agent, was developed to target the renal Na^+-glucose co-transporter 2 and control glycemia through blockade of glucose re-absorption. Earlier, we found that clinically achievable doses of CANA suppress cell survival, mainly through an off-target action, to block complex I of the mitochondria oxidative phosphorylation chain, leading to activation of AMPK. In the present study, we examined the CANA's anti-tumor efficacy in combination with RT. **Method:** Adenocarcinoma (A549, H1299, H1975) and squamous cell carcinoma (SK-MES-1) NSCLC cells were subjected to proliferation, clonogenic survival and metabolic assays after combined CANA (0–30mM) and RT (0–16Gy) treatments. Immunodeficient nude mice were grafted with H1299 cells and treated with Canagliflozin (100 mg/kg/day by oral gavage) and/or RT (10 Gy). Cell and tumor lysates are analyzed with immunoblotting and immunohistochemistry. **Result:** At low micromolar doses achieved routinely in the circulation of diabetic patients, CANA inhibited proliferation and clonogenic survival of NSCLC cells and enhance NSCLC response to RT. In control and irradiated cells, CANA inhibited de novo lipogenesis and abolished histone H3 phosphorylation, an established marker of mitosis. This was associated with the induction of cyclin-dependent kinase inhibitor p27kip1. CANA activated AMPK and mediated effective suppression of the mammalian target of rapamycin (mTOR) pathway, with inhibitory Raptor phosphorylation and blockage of p70S6k and S6 phosphorylation. Importantly, CANA also blocked early signaling events of the Epidermal Growth Factor Receptor (EGFR) pathway such Shc, Gab and PLCg1 phosphorylation and suppressed HIF1a expression. CANA suppressed H1299 tumor growth. On-going experiments analyze tumors proliferation, angiogenesis, cell death, and microenvironment markers. **Conclusion:** Canagliflozin (CANA), an approved and well-tolerated diabetes drug suppresses proliferation, radio-resistance and survival pathways and improves NSCLC response to RT, at doses well within its therapeutic window. This suggests a strong potential for clinical development of CANA in combination with RT for the treatment of NSCLC. Acknowledgments: This work was supported by an RFA grant from Hamilton Health Science and funds from Canadian Institutes for Health Research (CIHR).

P1.14-34 THE LANDSCAPE OF MET ALTERATIONS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Mesenchymal-to-epithelial transition (*MET*) is a therapeutic target in non-small cell lung cancer (NSCLC), which has a variety of genomic variants. *MET* amplification and *MET* exon 14 skipping (*MET* ex14) have been notable for meaningful clinical response to *MET* inhibitor therapy. However, comprehensive molecular characteristics of *MET* variants of Chinese NSCLC patients are not well understood. **Method:** FFPE tumor and matched blood samples from 3433 Chinese NSCLC patients were collected for targeted next generation sequencing (NGS). Genomic variants including single nucleotide variations (SNV), short/long insertion/deletions (Indel), copy number alterations and gene rearrangements were analyzed. *MET* amplification, *MET* ex14 skipping and gene fusion were defined as *MET* druggable variations. Tumor mutational burden (TMB) was analyzed in all patients. **Result:** In total, *MET* variations were identified in 3.3% (115/3433) of Chinese NSCLC patients. Mutation rates varied in different histological types: 3.3% (N=95) in adenocarcinoma, 1.7% (N=7) in squamous cell carcinoma, 10.1% (N=7) in adenosquamous carcinoma and 15.0% (N=3) in sarcomatoid carcinoma. *MET* druggable variations had been found enriched at an advanced clinical stage accounted for 3.8% of stage IV cases while only 1.2% of cases at earlier stages. Consistent to the previous studies, *MET* amplification and *MET* ex14 skipping were identified in 1.5% and 0.8% of NSCLC patients respectively. *MET* rearrangement was identified in seven patients in this cohort with partner genes as *CD47*, *ST7*, *TMEM168*, *MYTKL* and *FOXP2*. Moreover, 39.5% of *MET* point mutations resulting in pathway activation (D1010, D1228 and H1094) in this cohort could then be potential targets for *MET* inhibitors. Twenty six percent of all *MET* variations co-mutated with *EGFR* sensitive mutations, which may be a resistance mechanism for EGFR-TKI therapy. The median TMB of patients with *MET* variations was 6.1 muts/Mb. Cases with *MET* SNV/Indel alterations had higher median TMB than wild type *MET* (8.1 vs. 4.6 muts/Mb, respectively, $P = 0.03$). In particular, a newly acquired *MET* fusion was detected in a 60-year old female NSCLC patient when disease progressed on TKI against the original *EGFR* L858R-mutant. She achieved a partial response to crizotinib plus osimertinib treatment. **Conclusion:** Our study revealed that *MET* variations occurred in 3.3% of Chinese NSCLC patients. Besides *MET* amplification and *MET* ex14 skipping, *MET* rearrangements and targetable point mutations we identified might be potential therapeutic targets for these patients.

Keywords: Non-Small Cell Lung Cancer, MET, Targeted therapy

P1.14-35 EPITHELIAL-TO-MESENCHYMAL TRANSITION IS A MECHANISM OF ALK INHIBITOR RESISTANCE IN LUNG CANCER INDEPENDENT OF ALK MUTATION STATUS

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Background: *ALK* rearrangement, most commonly *EML4-ALK*, is detected in approximately 3%–5% of NSCLC. ALK tyrosine kinase inhibitor (TKI), shows dramatic clinical efficacy, however, almost all patients acquire resistance over time. The most defined mechanism of crizotinib resistance is secondary *ALK* mutations. A recent study reported that epithelial-to-mesenchymal transition(EMT) and *ALK* resistance mutation were simultaneously detected in a single tumor lesion in patients with *ALK*-rearranged lung cancer who were resistant to ALK-TKIs. However, it is still unknown whether ALK-TKI resistant tumor cells combine mesenchymal phenotype with *ALK* resistance mutation, or each of the mesenchymal type tumor cells and *ALK* resistance mutation–positive cells coexist in a single lesion. In any of these cases, no therapy for EMT-associated targeted drug resistance has yet been established. **Method:** Specimens from a patient with *ALK*-rearranged lung adenocarcinoma who acquired resistance to crizotinib were stained with IHC, and the epithelial regions (ALK$^+$, vimentin$^+$, and E-cadherin$^-$) and the mesenchymal regions (ALK$^+$, vimentin$^-$, and E-cadherin$^+$) were collected by microdissection. The DNA from the each regions were isolated and the *ALK* L1196M mutation was detected by degital PCR analysis. Crizotinib-resistant cell line was developed by continuous treatment with crizotinib in the pleural carcinomatosis mouse model inoculated with the crizotinib-sensitive human lung cancer cell line, A925LPE3, which harbors the *EML4-ALK* gene fusion. The clones were estabilish by limiting dilution and the mechanism of crizotinib resistance was examined by microarray analysis, miRNA array analysis, western blot, and MTT assay. Compounds that overcame crizotinib resistance were screened from a library of 200 kinase inhibitors. **Result:** Digital PCR analyses combined with microdissection after IHC staining for EMT markers revealed that *ALK* L1196M was predominantly detected in epithelial-type tumor cells, indicating that mesenchymal phenotype and *ALK* mutation can coexist as independent mechanisms underlying ALK inhibitor–resistant cancers. Preclinical experiments with crizotinib-resistant lung cancer cells showed that EMT associated with decreased expression of miR-200c and increased expression of ZEB1 caused cross-resistance to new-generation ALK inhibitors alectinib, ceritinib, and lorlatinib. Moreover, pretreatment with the histone deacetylase (HDAC) inhibitor quisinostat overcame this resistance by reverting EMT *in vitro* and *in vivo*. **Conclusion:** These findings indicate that HDAC inhibitor pretreatment followed by a new ALK inhibitor may be useful to circumvent resistance constituted by coexistence of resistance mutations and EMT in the heterogeneous tumor.

Keywords: Epithelial-mesenchymal-transition (EMT), resistance, Anaplastic lymphoma kinase(ALK)

P1.14-36 PHASE II TRIAL OF AFATINIB IN ELDERLY PATIENTS AGED OVER 75 YEARS WITH EGFR MUTATION POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Although reports on the use of gefitinib or erlotinib in elderly patients were occasionally found, those on afatinib were rare. According to the analysis of 54 Japanese patients in the LUX-Lung3 study, the dose reduction of afatinib from 40 mg/day was necessary for 76.0% of patients. However, the prolonged administration was possible after a dose reduction to 30 or 20 mg/day, and antitumor effects were maintained with the reduced dose. **Method:** The efficacy and safety of afatinib at 30 mg/day in PS 0-1 patients who were aged 75 years with *EGFR* mutation positive chemotherapy-naïve non-small cell lung cancer were studied. The primary endpoint was the response rate (RR), and the planned number of registered cases was set at 35, with a threshold RR of 50%, an expected RR of 75%, α of 0.05, and β of 0.1. The secondary endpoints were progression-free survival (PFS), overall survival (OS), the incidence rate of adverse events (AEs), QOL survey (FACT-L), and trough plasma concentration of afatinib at steady state (PK, collected between the 8th to 15th day after the start of oral administration). **Result:** The data of 35 patients were collected from May 2015 to August 2017. Patient background was, median age of 79 years (75-92), male/female: 8/27, PS 0/1: 8/27, adenocarcinoma/NSCLC: 30/5, IIIA/IIIB/IV/postoperative recurrence (TNM 7th edition): 2/2/22/9, and exon19del/exon21L858R/exon19del+exon21L858R: 15/19/1. The best overall efficacy was PR/SD/PD/NE: 28/4/1/2, and the RR was 80.0% (95% CI, 63.1-91.6). The median PFS and OS were 16.3 months (95% CI, 11.8-27.0) and not reached, respectively. The main AEs were rash 69%, diarrhea 60%, and paronychia 51%. While the initial afatinib dose was 30 mg, nine (26%) patients continued with

30 mg, 23 (66%) were reduced to 20 mg, and 3 (8%) discontinued due to AEs (2 ILD and 1 stomatitis). Treatment-related death was not observed. There were no significant change of QOL at baseline, after 4, 8, and 12 weeks. PK analyses showed steady state plasma concentration as 22.8 ng/mL which was comparable to reported plasma concentration of 40 mg afatinib in LUX-LUNG3 and 6 (24.3 ng/mL). No obvious PK differences were found according to dose reduction, adverse event, and response. **Conclusion:** Afatinib at 30 mg/day could be an effective treatment option for elderly patients, over 75 years of age, with good PS. (UMIN 0000177050)

Keywords: Afatinib, Elderly patients, Adverse events

P1.14-37 LUNG CANCER IN NEVER-SMOKERS: A NATIONWIDE POPULATION BASED MAPPING OF TARGETABLE ALTERATIONS

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Background: Lung cancer among never-smokers is common and increasing [1]. A smoking-independent subgroup of lung adenocarcinoma with certain molecular and clinical features exists [2-3]. In an ongoing project within the Swedish Molecular Initiative against Lung cancer (SMIL) we currently characterize lung cancer in never-smokers for etiological, diagnostic and therapeutic purposes. **Method:** Through the Swedish National Lung Cancer Registry [1], we identified all individuals who underwent surgery for lung cancer in Sweden 2005-2014 and who were registered as never-smokers (n=540). At each study site, clinical data were reviewed by a thoracic oncologist or pulmonologist through patients' medical charts and archived tumor tissues were retrieved and reviewed by a thoracic pathologist. For subsequent studies, we extracted DNA and RNA (using the Qiagen AllPrep kit for FFPE tissue) and constructed tissue microarrays. As first preplanned analyses, we performed fusion gene mapping using an RNA based NanoString nCounter Elements assay and mutational profiling by Next Generation Sequencing (NGS) using a 26-gene exon-focused panel, as previously described [4]. **Result:** Of the 540 never-smokers with surgically resected lung cancer, 69% were females and the majority of cases were adenocarcinomas. The median age at diagnosis was 69 years. In the first 310 analyzed tumor samples, we so far detected 24 fusions involving *ALK* (8%), 10 involving *RET* (3%) and 2 involving *NRG1* (<1%). In addition, *MET* exon 14 skipping was found in 33 samples (11%). Furthermore, among the so far 147 cases where we have completed both the DNA and the RNA analyses, 59 tumors (40%) harbored *EGFR* mutations. In total, targetable alterations were revealed either by NanoString or NGS in 63% of tumors from never-smokers in our study. **Conclusion:** SMIL is an ongoing nation-wide molecular research collaboration on lung cancer where we currently characterize one of the largest never-smoking lung tumor cohorts worldwide. From the first pre-planned analyses, we conclude that, in a population-based cohort of early stage lung cancer from never-smokers, targetable oncogenic fusions and mutations are frequent. References 1. http://www.cancercentrum.se/vast/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister 2. Staaf J, Jönsson G, Jönsson M, Karlsson A, Isaksson S, Salomonsson A,Pettersson HM, Soller M, Ewers SB, Johansson L, Jönsson P, Planck M. Relation between smoking history and gene expression profiles in lung adenocarcinomas. *BMC Med Genomics*. 2012 Jun 7;5:22. 3. Karlsson A, Ringnér M, Lauss M, Botling J, Micke P, Planck M, Staaf J. Genomic and transcriptional alterations in lung adenocarcinoma in relation to smoking history. *Clin Cancer Res*. 2014 Sep 15;20(18):4912-24. 4. Lindquist KE, Karlsson A, Levéen P, Brunnström H, Reuterswärd C, Holm K, Jönsson M, Annersten K, Rosengren F, Jirström K, Kosieradzki J, Ek L, Borg Å, Planck M, Jönsson G, Staaf J. Clinical framework for next generation sequencing based analysis of treatment predictive mutations and multiplexed gene fusion detection in non-small cell lung cancer. *Oncotarget*. 2017 May 23;8(21):34796-34810.

Keywords: mutations, fusion genes, Never-smokers

P1.14-38 IDENTIFICATION OF FGFR1-3 FUSIONS IN LUNG CANCERS USING COMPREHENSIVE NEXT-GENERATION SEQUENCING

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Background: Fusions have been described in the fibroblast growth factor receptors (*FGFR*) 1-3 genes with multiple partners in a variety of tumors. Here we focused on the prevalence of *FGFR* fusions in lung cancers for whom might benefit from FGFR inhibitors in clinical development. **Method:** We reviewed *FGFR* alterations in 10833 lung cancer patients (pts) who underwent genetic testing at our institute from 2016 to 2019. Mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which covers all exons of *FGFR1-3* and specific intron regions containing the break points of fusions. All patients were also analyzed for mutations in *EGFR, KRAS, HER2, BRAF, ALK, RET, MET, ROS1*, as well as other oncogenes. **Result:** *FGFR* fusions were identified in 25 lung cancer pts, including 9 adenocarcinoma pts, 4 squamous-cell carcinoma pts, 1 patient with large cell neuroendocrine carcinoma and 11 pts with non-specific pathology. *FGFR3-TACC3* fusion was detected in 72% (18/25) of pts and the remaining were previously unreported fusions (table). Concurrent *EGFR* mutations were identified in 44% (11/25) of pts with *FGFR* fusions (32%, treated with EGFR tyrosine kinase inhibitors (EGFR-TKIs); 12%, not treated with EGFR-TKIs). PI3K-AKT-MTOR signaling pathway was also activated in 28% (7/25) of pts, and cell-cycle gene alterations were also detected in 16% (4/25) of pts.

Table. Frequency of FGFR fusions

Fusions	Fusion region	N (%)
FGFR3-TACC3	EX17:EX11	6 (24%)
	EX18E:EX11	4 (16%)
	EX18E:EX13	2 (8%)
	EX17:EX10	2 (8%)
	others	4 (16%)
FGFR1-chr8:21672159	EX1:chr8:21672159	1 (4%)
FGFR1-MTUS1	EX19E:EX8	1 (4%)
EFHA2-FGFR1	EX2:EX3	1 (4%)
TNRC18-FGFR1	PMT:EX10	1 (4%)
ZMAT4-FGFR1	EX2:EX2	1 (4%)
ZNF696-FGFR1	EX2:EX18E	1 (4%)
OPALIN-FGFR2	EX6E:EX2	1 (4%)
Total		25 (100%)

Conclusion: *FGFR1-3* fusions define a unique molecular subtype of lung cancer. Depending on the concurrent genetic alterations, combined targeted therapy might be an optimal strategy to control tumor growth for these pts.

Keywords: Targeted therapy, Lung cancer, FGFR1-3

P1.14-39 ACQUIRED ALK REARRANGEMENT IN EGFR-MUTANT LUNG ADENOCARCINOMA TREATED WITH EGFR TKIS

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Background: Few studies have been reported on acquired anaplastic lymphoma kinase (*ALK*) rearrangement in epidermal growth factor receptor (*EGFR)*-mutant lung adenocarcinoma patients with EGFR tyrosine kinase inhibitors (TKIs). **Method:** *EGFR*-mutant lung adenocarcinoma patients were screened after resistance to EGFR TKIs from September 2017 to December 2018 at the Guangdong Lung Cancer Institute. Both *EGFR* mutation and *ALK* rearrangement were tested by next-generation sequencing (NGS). Acquired *ALK* rearrangement was defined as positive *ALK* rearrangement after resistance to EGFR TKIs, but negative result detected by NGS at the baseline of EGFR TKI treatments. **Result:** Totally 320 patients were tested by NGS after resistance to EGFR TKIs (175, 42 and 103 with first-, second- and third-generation EGFR-TKIs respectively). Frequency of acquired *ALK* rearrangement was 1.14% (2/175), 2.38% (1/42) and 1.94% (2/103) in patients treated with first-, second- and third-generation EGFR TKIs respectively. The fusion partners of *ALK* were *EML4* in 2 patients, *CLIP4* (1), *NPM1* (1) and *PIBF1* (1). Non-*EML4-ALK* fusion accounted for 60%. One with acquired *EML4-ALK* achieved minor response with osimertinib plus crizotinib. One with acquired *NPM1-ALK* achieved partial response with erlotinib plus crizotinib. Unfortunately, one with acquired *CLIP4-ALK* fusion and *BRAF V600E* mutation did not respond to ensartinib single agent. One with acquired *PIBF1-ALK* had no clinical benefit with osimertinib plus alectinib. Finally, one with acquired *EML4-ALK* died shortly without any treatment due to poor performance status. **Conclusion:** The frequency of acquired *ALK* rearrangement is similar in *EGFR*-mutant lung adenocarcinomas after resistance to the first-, second-, or third-generation EGFR TKIs. The majority of acquired *ALK*-fusion partners are non-*EML4*. Combination of EGFR TKIs and ALK inhibitors might be a strategy to overcome such resistance.

Keywords: ALK rearrangement, EGFR mutation, lung adenocarcinoma

P1.14-40 EGFR-TKIS MAY SENSITIZE RADIATION LUNG DAMAGE IN STEREOTACTIC BODY RADIOTHERAPY BASED ON INTENSITY ANALYZING

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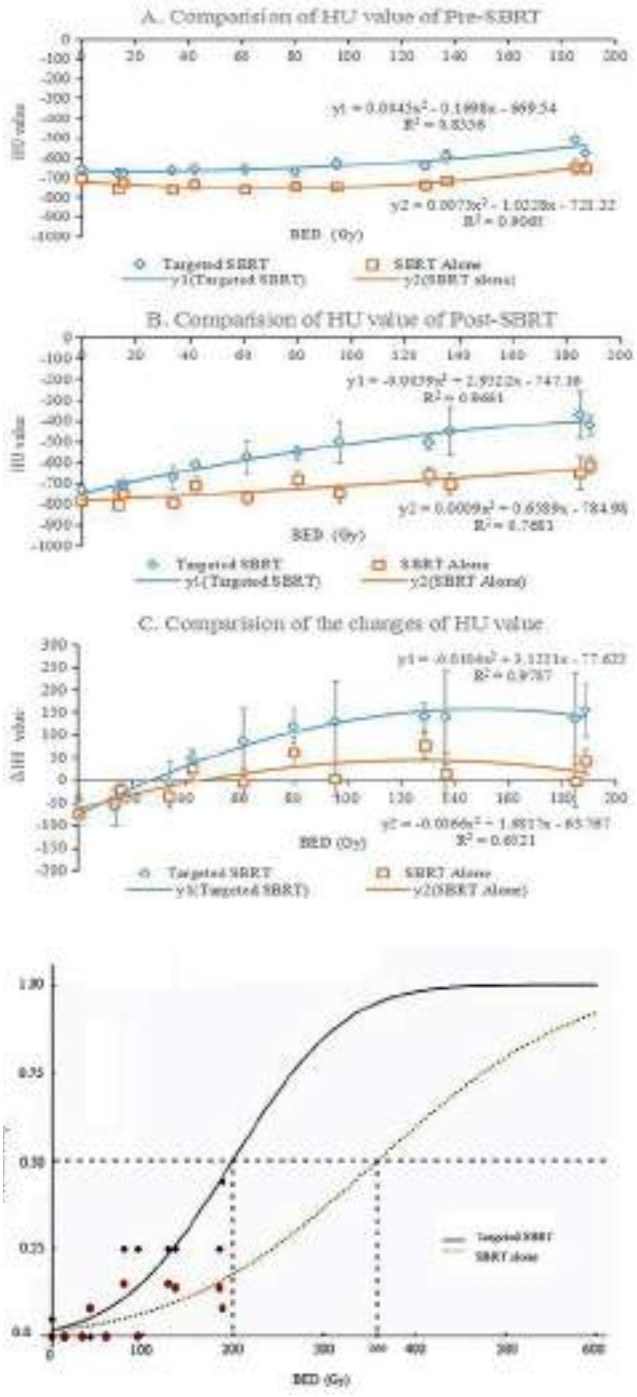
Background: To measure early radiographic changes of acute radiation pneumonitis after stereotactic body radiotherapy (SBRT) and compare the differences between patients treated with and without the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). **Method:** Patients with SBRT with 3-month follow-up CT scans were eligible. 20 patients treated with EGFR-TKIs a month before stereotactic body radiotherapy (Target-SBRT group) were formed the primary study population. Another 20 patients received SBRT alone were selected from our SBRT data bank to serve as control, by matching dose prescription, tumor size and location. Pre- and post-SBRT CT scans from these 40 patients were registered to each other and the mean value of CT intensity (Hounsfield unit, HU) were extracted for regions of the lungs receiving the same dose at 10 Gy intervals to generate dose-response curves (DRC). The frequency of density changes>200 HU was modeled depending on the fractionation using a Probit model for different treatments. **Result:** There were significant differences in the DRC of pre-SBRT, post-SBRT and the differences of HU value (△HU) in lung between the SBRT alone and Target SBRT groups (all P<0.050)(Figure 1). The respective dose for a 50% complication risk (TD50) for changes>200HU was 72Gy (95% confidence interval (CI 58-107) in SBRT alone group versus 52Gy (CI 46-59) in targeted SBRT group (Figure 2).



Conclusion: Compared to SBRT alone, targeted SBRT group has a lower TD50 and m value, both suggesting an increased complication probability of normal lung tissue.

Keywords: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), Stereotactic body radiotherapy (SBRT), Lung damage

P1.14-41 THE COMBINATION OF THE PARP INHIBITOR OLAPARIB AND THE ATR INHIBITOR VE-821 SELECTIVELY TARGETS ATM-DEFICIENT LUNG CANCER CELLS

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Background: The driving principle behind precision medicine is to specifically target genetic variations that arise in tumorigenesis while leaving normal cells unaffected. Mutations in Ataxia Telangiectasia Mutated (ATM) may offer such a therapeutic target. ATM is mutated in approximately 12% of lung cancers and up to 40% of lung

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adenocarcinoma have been reported to lack ATM protein expression. ATM is an apex signaling kinase that responds to DNA-double strand breaks, playing a direct role in DNA repair as well as the initiation of signaling cascades that can lead to cell cycle arrest and apoptosis. We asked whether ATM-deficient human lung cancer cells are sensitive to the poly-ADP ribose polymerase (PARP) inhibitor olaparib, and investigated the mechanism of action of olaparib in these cells. **Method:** We analyzed drug sensitivity for 61 lung adenocarcinoma cell lines from the Genomics of Drug Sensitivity in Cancer (GDSC) project and deleted ATM from lung adenocarcinoma A549 cells using CRISPR/Cas9. We determined the effects on cell viability using trypan blue exclusion and clonogenic survival assays. To investigate the mechanism of sensitivity of ATM-deficient cells to PARP and ATR inhibitors we used flow cytometry and cell viability assays as above. **Result:** We observed a positive correlation between olaparib IC50 values and ATM mRNA expression. ATM mutant cell lines were more sensitive to olaparib compared to ATM wild-type cell lines or cell lines with amplified ATM. Additionally, ATM-deficient lung cancer cells were sensitive to olaparib, as are lung cancer cells (A549) with CRISPR/Cas9 deletion of ATM. Mechanistically, olaparib caused the temporary and reversible accumulation of G2 phase cells in ATM-deficient cells which manifested as a decrease in proliferation in both the trypan blue exclusion assay and clonogenic survival assay. Olaparib did not induce cell death in ATM-deficient cells, however cell death was induced when olaparib was used in combination with the ATR inhibitor VE-821. **Conclusion:** We show that olaparib acts as a cytostatic agent in ATM-deficient lung cancer cells, inducing a reversible and temporary growth arrest in G2 phase. Only when combined with the ATR inhibitor VE-821 was cell death observed and only in ATM-deficient cells. Our data suggest that patients with ATM-deficient lung cancer could benefit from combinatorial treatment with PARP and ATR inhibitors.

Keyword: Olaparib, VE-821, ATM

P1.14-42 APATINIB COMBINED WITH EGFR - TKI IN TREATING ADVANCED NON-SMALL CELL LUNG CANCER WITH EGFR - TKI RESISTANCE (DATA UPDATED)

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Background: EGFR-TKI has been widely used in patients with EGFR mutations in non-small cell lung cancer (NSCLC) and gained significant benefits.But resistance to EGFR-TKI is inevitable.Previous studies have shown that apatinib (a TKI against VEGFR-2) combined with EGFR-TKI might prevent progression of the disease. We conducted this trial to investigate the efficacy and safety of apatinib combined with EGFR-TKIs(including erlotinib, gefitinib,icotinib,afatinib and osimertinib) compared with traditional chemotherapy for EGFR-TKI resistant NSCLC pts. **Method:** This study enrolled 39 advanced NSCLC pts who acquired resistance to the EGFR-TKI therapy from Mar 2017 to Jan 2019. 25 pts received apatinib combined with EGFR-TKI (apatinib in start dose of 250 mg+prior EGFR-TKI dose),14 pts received chemotherapy (pemetrexed or vinorelbine with platinum). Efficacy was evaluated every 6 weeks based on RECIST 1.1. This study was registered on Chinese Clinical Trail Registry, and the registration number was ChiCTR-OIN-17012051. **Result:** In the apatinib group, 88%(22/25) pts were available evaluated. The objective response rate was 13.6%(3/22) and the disease control rate was 95.5% (21/22). The most common adverse events in the apatinib group were diarrhea (60%,15/25), hypertension (56%,14/25), hand-foot syndrome (40%,10/25), fatigue (30.4%,7/23). Main grade 3 or 4 toxicities were proteinuria (12%, 3/25). Two pts with brain metastases in the apatinib group got metastases lesions decreased. The lesions of two pts who have been taken the dose of 250mg apatinib and progressed had decreased when they change the dose to 500mg. In the chemotherapy group,78.6%(11/14) pts were available evaluated. The objective response rate was 27.3%(3/11) and the disease control rate was 90.9% (10/11).None new adverse event occured. The objective response rate and disease control rate were similar in two group, there were differences in length of treatment. The median length of treatment of apatinib group was 8.7 month,and chemotherapy group was 4.3 month.The longest treatment period in the apatinib group was 24 months. **Conclusion:** Apatinib combined with EGFR-TKI shown a good clinical efficacy in pts with acquired EGFR-TKI(1st 2nd or 3rd generation) resisitance.Patient's quality of life and the compliance of therapy had been increased by oral drugs.Besides,We found that in the patients who were treated with erlotinib, or patients with EGFR 21 mutation, or male, their PFS tended to be prolonged compared to other patients.

Keywords: apatinib, EGFR-TKI, resistance

P1.14-43 A NOVEL PATIENT DERIVED SYNCHRONOUS CELL PAIR WITH DIFFERENT MUTATIONS IN AN ALK-REARRANGED LUNG ADENOCARCINOMA UNDERLINES TUMOR HETEROGENEITY

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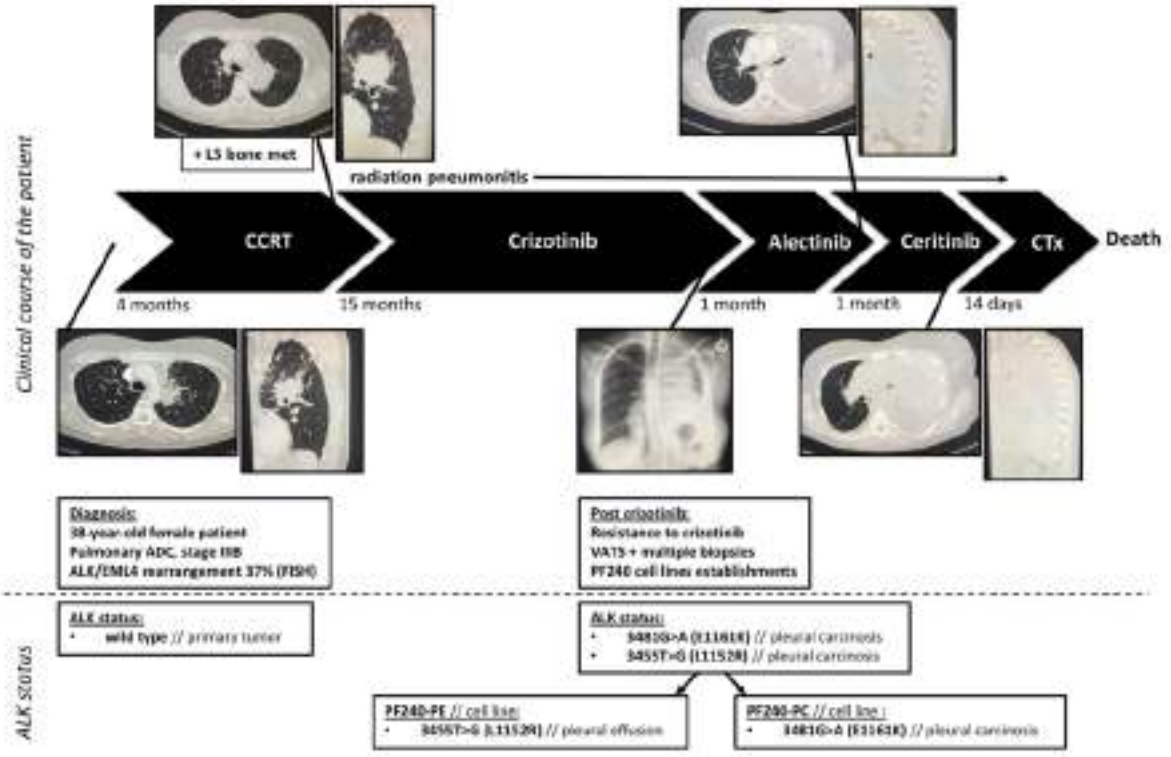
Background: ALK targeted therapy can provide prolonged clinical response rates in ALK-rearranged lung adenocarcinoma (ADC) patients. However, most tumors relapse within a few years of treatment pressure due to a variety of resistance mechanisms, including intratumoral heterogeneity. Understanding these mechanisms is of utmost importance to more precisely tailor future targeted therapies. **Method:** We established a novel synchronous ALK-translocated lung ADC cell pair from the malignant pleural effusion (PF240-PE) and the pleural carcinosis (PF240-PC) of a 38-year-old female patient following sequential ALK targeted therapy. Immunohistochemistry and mutational analyses were executed in pleural carcinosis tissue specimens and in the tumor cell lines. SRB assays were performed for viability testings following different generations ALK inhibitor treatment alone and combined with SAHA, a pan-HDAC inhibitor. As positive control for all treatment lines we used PF521, another newly established ALK-rearranged but treatment naïve lung ADC cell line. In vivo tumorigenicity was evaluated by performing subcutaneous xenografts. **Result:** We identified two distinct resistance mutations in both tissue specimens: a so far non-characterized E1161K and the already described L1152R. Strikingly, PF240-PC harbored E1161K and PF240-PE carried L1152R. Immunohistochemistry showed changes from epithelial/carcinomatous to mesenchymal/sarcomatous differentiation following resistance acquisition. *In vitro* testing revealed that both cell lines were significantly different in morphology and sensitivity to different generation ALK inhibitors including crizotinib, alectinib and lorlatinib. However, the novel tyrosine kinase inhibitor entrectinib was effective in both E1161K and L1152R mutant cells. Importantly, combination treatment of crizotinib or alectinib plus pan-HDAC inhibitor SAHA yielded strong synergism. Of note, both novel cell lines were highly tumorigenic in vivo. In vivo treatment response profiles are currently under evaluation.



Conclusion: This is the first evidence of the synchronous establishment of two highly distinct patient-derived ALK translocated lung ADC cell lines carrying different resistant mutations. This concept supports the paramount significance of spatiotemporal intratumoral heterogeneity under targeted therapy. Furthermore, our findings showed that HDAC inhibition could enhance sensitivity of resistant tumor cells to ALK targeted therapy *in vitro*. Altogether, our findings provide strong evidence for the synchronous emergence of multiple resistance mechanisms and emphasize the importance of multiple site re-biopsies to better identify acquired resistance mechanisms under targeted therapy.

Keywords: targeted therapy resistance, Anaplastic lymphoma kinase, tumor heterogeneity

P1.14-44 POSITIVE PD-L1 EXPRESSION IS ASSOCIATED WITH UNFAVORABLE CLINICAL OUTCOME IN EGFR-MUTATED LUNG ADENOCARCINOMAS TREATED WITH EGFR-TKIS

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Background: Clinical implication of programmed death ligand 1 (PD-L1) expression in oncogene-addicted non-small cell lung cancer treated with tyrosine kinase inhibitors (TKIs) is largely unknown. The objective of this study was to determine the frequency of PD-L1 expression and the clinical outcome according to PD-L1 expression in lung adenocarcinomas harboring EGFR mutation and treated with EGFR-TKIs. **Method:** We retrospectively evaluated PD-L1 expression using 22C3 pharmDx assay in lung adenocarcinoma patients with EGFR mutations at two referral hospitals between January 2017 and June 2018. Samples were obtained from surgically resected tumors, small biopsy, or cytologic cell blocks. **Result:** Of all 71 patients analyzed, 44 (58.7%) had PD-L1 tumor proportion score (TPS) of < 1%, 23 (30.7%) had PD-L1 TPS of 1%-49%, and 8 (10.7%) had PD-L1 TPS of ≥ 50%. Of the 37 patients treated with first-line EGFR-TKIs, PD-L1 TPS ≥ 1% was associated with a significantly decreased response rate, compared with PD-L1 TPS < 1% (45.7% vs. 67.3%, p=0.005). Furthermore, PD-L1 TPS ≥ 1% was associated with a significantly shorter median progression free survival, compared with PD-L1 TPS < 1% (9.3 months vs. 14.2 months, p = 0.024). Multivariate analysis showed that PD-L1 TPS ≥1% is independently associated with shorter PFS (hazard ratio 1.32, p=0.012). **Conclusion:** PD-L1 was positive in approximately 40% of patients with EGFR-mutated lung adenocarcinoma. Postive PD-L1 expression may be associated with unfavorable clinical outcome to EGFR-TKIs among those patients group.

Keywords: EGFR-TKIs, programmed death ligand, Clinical outcome

P1.14-45 SURGICAL OUTCOME OF NON-SMALL CELL LUNG CANCER WITH CLINICAL SINGLE ZONE N2 IN AORTOPULMONARY ZONE (LN#5 AND LN#6)

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Background: Current staging work-up methodology could not exactly reflect clinical nodal status of aortopulmonary zone (AP zone) without invasive diagnostic tools. The aim of the study is to evaluate the surgical outcome of single zone clinical N2 in AP zone (LN #5 or #6). **Method:** Between 2009 and 2018, a retrospective data of 7488 patients was reviewed. Patients were included when only lymph nodes in AP zone was suspected to be metastasized based on the results of computed tomography (CT), positron

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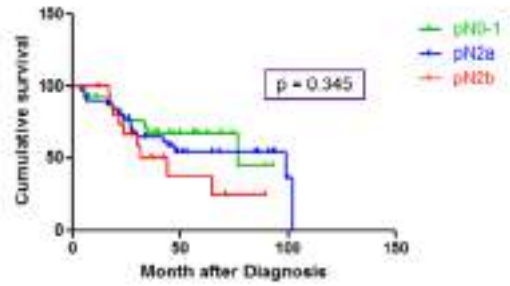
emission tomography (PET-CT) and endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA). Patients were excluded when metastasis was detected by EBUS-TBNA in other mediastinal lymph node zones. Clinicopathologic variables such as pathologic subtype, differentiation and nodal status were evaluated to identify prognostic factors for survival rate and disease-free survival rate (DFS). **Result:** Ninety-five patients were included, and median duration of follow-up was 35 months (IQR; 20 – 50). Eighty-four patients underwent upfront surgery, and their pathologic nodal staging was pN0 in 20 patients (23.8%), pN1 in 7 (8.3%), pN2a in 40 (47.6%) and pN2b in 17 (20.2%). Overall 5-year survival and 5-year DFS rate was 55.9% 54.5%, respectively. There was no survival difference between patients with pN0-1, pN2a and pN2b (p = 0.345, figure). Neither pathologic N2 nor N2b was not a risk factor for overall survival rate (p = 0.418, 0.159, respectively) and DFS (p = 0.606, 0.650, respectively). In univariate analysis, there was no other significant clinicopathologic factors for survival and DFS. Eleven patients with neoadjuvant treatment showed a similar 5-year survival rate (43.6%) compared with patients with upfront surgery.

Kaplan-Meier survival curves for each nodal stage



Conclusion: Current work-up without invasive tools for cN2a in AP zone showed relatively high false-positive rate (32.1%). However, surgical outcome of cN2a in aortopulmonary zone was comparable. Upfront surgery should be considered in highly selected patients.

Keywords: Lung cancer, Mediastinal Lymph nodes, Survival outcome

P1.14-46 GENOMIC PROFILING OF LARGE CELL NEUROENDOCRINE CARCINOMAS OF LUNG: A PATH TOWARDS INDIVIDUALIZED TREATMENT OPTIONS

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Background: Large cell neuroendocrine carcinomas of lung (LCNEC) are aggressive tumors which straddle the non-small cell / small cell lung carcinoma dichotomy. We performed comprehensive genomic profiling (CGP) to compare genomic alterations (GA) in LCNEC with those in small cell lung carcinoma (SCLC) and lung adenocarcinoma (LUAD). **Method:** FFPE tissue from 657 LCNEC, 2232 SCLC, and 28,052 LUAD underwent hybrid-capture based CGP to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was calculated using 114 loci. **Result:** Genomically, LCNEC's tended to segregate towards either SCLC or LUAD (Table 1). *RB1* and *PTEN* inactivation, hallmarks of SCLC, often co-occurred and were detected in 38% and 10% of LCNEC, respectively. These cases were also enriched for other "SCLC" alterations, including *CCNE1, NOTCH1, SOX2, FGFR1. KRAS, STK11*, and *CDKN2A/B* alterations, hallmarks of LUAD, often co-occurred and were each detected in 15% of LCNEC. These cases were enriched for other "LUAD" alterations, including *SMARCA4, ATM, NKX2-1, KEAP1*. Only 20 of 657 (3%) LCNEC had co-occurring *RB1* and *KRAS* alterations. 20 of 657 (3%) LCNEC carried *EGFR* activating alterations. GA involved other receptor tyrosine kinases (*ALK, ERBB2/3, FGFR1/2/3, KIT, MET, NTRK1/2/3, PDGFRA/B, RET, ROS1*), and *PI3K, MAPK*, and *CCND1* pathway genes. 17% and 49% of LCNEC had TMB of ≥20 and ≥10 mut/Mb, respectively. 0.2% of LCNEC were MSI-High, and 19.4% were PD-L1 positive.

COMPARISON OF GENOMIC PROFILES						
Tumor Type	SCLC		LUAD		LCNEC	
Number of Cases	2232		28,052		657	
TMB ≥ 10 mut/Mb	41.6%		31.5%		48.7%	
TMB ≥ 20 mut/Mb	7.9%		11.5%		17.2%	
Mean TMB	10.1		9.4		12.3	
Median TMB	8.7		6.1		9.6	
MSI-High	0.4%		0.2%		0.2%	
PD-L1 Low Positive (TPS: 1-49%)	7.2%		26.1%		13.3%	
PD-L1 High Positive (TPS ≥ 50%)	1.5%		27.2%		6.1%	
Top 25 Altered Genes	Gene	Freq	Gene	Freq	Gene	Freq
	TP53	91.0%	*TP53*	57.6%	*TP53*	77.5%
	RB1	71.5%	*KRAS*	36.2%	*RB1*	38.4%
	LRP1B	9.8%	*CDKN2A*	24.5%	*CDKN2A*	15.4%
	PTEN	9.3%	*EGFR*	20.6%	*KRAS*	15.1%
	MYC	6.2%	*STK11*	17.5%	*STK11*	14.9%
	CREBBP	5.9%	*CDKN2B*	16.2%	*LRP1B*	14.3%
	RICTOR	5.7%	*NKX2-1*	9.6%	*MYC*	12.5%
	NOTCH1	5.6%	*LRP1B*	8.3%	*PTEN*	9.9%
	PIK3CA	5.2%	*RBM10*	8.2%	*CDKN2B*	9.1%
	SPTA1	5.0%	*MYC*	8.0%	*ARID1A*	7.9%
	FAT1	4.7%	*NFKBIA*	7.6%	*APC*	7.6%
	FGF10	4.5%	*KEAP1*	6.7%	*SMARCA4*	7.6%
	CCNE1	4.4%	*SMARCA4*	6.5%	*KEAP1*	7.5%
	FGFR1	4.1%	*NF1*	6.4%	*FGFR1*	6.7%
	CDKN2A	4.1%	*ARID1A*	6.1%	*SPTA1*	6.6%
	SOX2	4.0%	*BRAF*	6.0%	*PIK3CA*	6.4%
	ARID1A	4.0%	*RB1*	6.0%	*RICTOR*	6.2%
	KMT2C	3.4%	*PIK3CA*	5.7%	*NF1*	6.1%
	EGFR	3.4%	*MDM2*	5.5%	*ZNF703*	5.8%
	KRAS	3.4%	*MET*	5.3%	*NOTCH1*	5.5%
	KIT	3.2%	*ERBB2*	5.2%	*NKX2-1*	5.2%
	NKX2-1	3.0%	*ATM*	5.1%	*FAT1*	5.2%
	APC	2.9%	*RICTOR*	4.8%	*CCNE1*	5.0%
	FBXW7	2.9%	*SPTA1*	4.7%	*NFKBIA*	4.9%
	NF1	2.9%	*DNMT3A*	4.6%	*MCL1*	4.3%

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Conclusion: Treatment for LCNEC is not standardized and often requires choosing between "SCLC" or "NSCLC" chemotherapy regimens based on clinical impression and anecdotal evidence. CGP can help inform these crucial decisions. Identification of actionable GA will enable use of targeted agents as alternatives or adjuncts to chemotherapy (Table 2). Immunotherapy is an important option, as a significant proportion of LCNEC patients have high TMB or PD-L1 positive tumors.

LCNEC: POTENTIAL TARGETED THERAPIES								
PI3K-AKT PATHWAY			**RECEPTOR TYROSINE KINASES**			**CCND1 PATHWAY**		
AKT1	1.2%	mTOR inhibitors	*ALK*	0.5%	ALK/MET TKI's	*CCND1*	3.80%	CDK4/6 inhibitors
FBXW7	2.3%	mTOR inhibitors	*EGFR*	2.9%	EGFR TKI's	*CDK4*	1.4%	CDK4/6 inhibitors
MTOR	0.8%	mTOR inhibitors	*ERBB2*	1.1%	ERBB TKI's	*SMARCA4*	7.6%	CDK4/6, EZH2, BRM inhibitors
NF2	0.8%	mTOR inhibitors	*ERBB3*	0.8%	ERBB TKI's	**HOMOLOGOUS RECOMBINATION PATHWAY**		
PIK3CA	6.4%	PI3K, mTOR inhibitors	*FGFR1*	6.7%	Multikinase inhibitors	*ATM*	3.8%	PARP inhibitors
PTEN	9.9%	mTOR inhibitors	*FGFR2*	0.9%	Multikinase inhibitors	*BRCA1*	1.4%	
STK11	14.9%	mTOR, SRC inhibitors	*FGFR3*	0.6%	Multikinase inhibitors	*BRCA2*	1.5%	
TSC1	1.1%	mTOR inhibitors	*KDR*	2.0%	Multikinase inhibitors	*BRIP1*	0.6%	
TSC2	0.8%	mTOR inhibitors	*KIT*	2.6%	Multikinase inhibitors	*PALB2*	0.9%	
RAS-RAF-MAPK PATHWAY			*MET*	1.7%	ALK/MET TKI's	*RAD51C*	0.3%	
ARAF	0.5%	RAF inhibitor	*NTRK1*	1.1%	NTRK inhibitors	**PD-L1/2**		
BRAF	2.7%	RAF, MEK inhibitors	*NTRK2*	0.2%	NTRK inhibitors	*CD274 (PD-L1*	1.2%	Immune checkpoint inhibitors
GNAQ	0.2%	MEK inhibitors	*NTRK3*	0.5%	NTRK inhibitors	*PDCD1LG2 (P*	1.0%	Immune checkpoint inhibitors
HRAS	1.4%	MEK inhibitors	*PDGFRA*	1.8%	Multikinase inhibitors			
KRAS G12C	4.4%	KRAS G12C inhibitors	*PDGFRB*	0.2%	Multikinase inhibitors			
MAP2K1	0.9%	MEK inhibitors	*RET*	2.1%	Multikinase inhibitors			
MAP2K2	0.3%	MEK inhibitors	*ROS1*	0.5%	ALK/MET TKI's			
NF1	6.1%	MEK ihhibitors						
NRAS	0.9%	MEK inhibitors						
RAF1	0.3%	RAF, MEK inhibitors						

Keywords: Large cell neuroendocrine carcinoma, Targeted therapy, genomic profiling

P1.14-47 CTDNA NGS FOR GUIDING CRIZOTINIB TREATMENT IN ALK-REARRANGED ADVANCED NSCLC PATIENTS (PTS)

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Background: FISH and IHC are commonly used and the golden standard for testing *ALK* rearrangement. However, they provide no information on fusion types or mutation status of other genes, which could be important prognostic factors. In addition, a tissue biopsy is not always applicable/preferred by pts. **Method:** 43 *ALK*-rearranged treatment naïve advanced NSCLC pts were included. *ALK*-rearrangement was confirmed by ctDNA NGS with a panel of 59 tumor-related genes in 25 pts (ctDNA arm) and by IHC/FISH/tissue NGS in 18 pts (control arm). All pts received crizotinib as first-line therapy. PFS was estimated using Kaplan-Meier method and compared using log-rank test. **Result:** On average, Pts in ctDNA arm were significantly older at diagnosis than pts in the control arm (56 vs. 45, p = 0.02), indicating the preferability of ctDNA NGS in elderly pts. Though older, pts in ctDNA arm had a similar mPFS with pts in the control arm (8 vs. 10 mo, p = 0.9). *ALK* fusion types in ctDNA arm and their associated statistics were listed in Table 1. Concomitant mutations were identified in 15 genes in 9 pathways. Frequently mutated pathways include p53 (in 8 pts) and DNA repair pathways (in 3 pts). Mutations in DNA repair pathway (5 vs. 10 mo, p = 0.06), high frequency of *EML4-ALK* (>= 1.5%) (6 mo vs. NR, p = 0.06), and bone metastasis (6 vs. NR, p = 0.05) were associated with shorter mPFS.

Table 1. ALK fusion types and associated statisticss

ALK fusion types	# of pts	(Median) age at diagnosis (year)	(m)PFS (mo)	Average # of mutations per pt
V1	11	52	10	1.5
V3	10	61	6	2.8
V2	1	60	-	1
V5'	1	65	-	1
V7	1	49	3	2
DCTN1-ALK	1	47	-	2

Conclusion: Information on ALK fusion types, concomitant mutations, and mutation frequencies provided by NGS could be valuable prognostic factors and deserves further investigation. ctDNA NGS could be used as an effective alternative to identify *ALK*$^+$ pts, especially for elderly pts, when tissue biopsy is inapplicable or not preferred.

Keywords: crizotinib, ctDNA, ALK

P1.14-48 WHOLE EXOME SEQUENCING (WES) IN NON-SMALL CELL LUNG CARCINOMA (NSCLC): IDENTIFICATION OF NOVEL BIOMARKERS

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Background: Significant advancement has been made in the treatment of patients with pulmonary adenocarcinoma (ADC) on the basis of the molecular profile. However, no such molecular target exists for squamous cell carcinoma (SCC) or small cell lung cancer (SCLC). WES has been in wide use for the discovery of new genetic markers, which may offer more information for the development of personalized medicine for all subtypes of lung cancer. The aim of the current study is to find out novel genetic markers for NSCLC which can be used as a universal biomarker for the treatment. **Method:** WES of 20 advanced NSCLC patients (10 ADC and 10 SCC) was done on the Illumina HiSeqX10 with paired end 151bp chemistry. The Male: female ratio was 5.6:1 and a median age 56 years. Only 3 patients were non-smoker and in one case smoking history was unknown. 75% of patients were present with co-morbidities, all patients were either in stage III or IV and performance status was either 1 or 2. **Result:**

Table 1: WES data statistics and the total number of variants identified:

S.No	WES data	Numbers
1	Average raw data	13.6 GB
2	Average processed data	12.1 GB
3	Average reads aligned	80.2%
4	Average total variations	34173
5	Average SNPs	26030
6	Average INDEL	81423
7	Average frameshift deletions	2185
8	Average frameshift insertions	3571
9	Average non-frameshift deletions	368
10	Average non-frameshift insertions	1292
11	Average non-synonymous	13418
12	Average stop gain	10337
13	Average stop loss	38
14	Average synonymous SNPs	11607
15	Average variations reported in databases	20269
16	Unknown mutations	659

WES data statistics has been depicted in table 1 including number of variants identified. After excluding common variants (MAF > 0.05), a total of 23 rare variants (0 < MAF < 0.01), *possibly linked to lung carcinoma was identified in the exome. Further stringent filtering showed allele frequencies of mutations in GPRIN2 (G protein-regulated inducer of neurite outgrowth 2), KCNJ18 (potassium voltage-gated channel subfamily J member 18) and TEKT4 (Tektin 4) genes which were present in all the cases.* The variations of amino acid substitutions were i) *TEKT4*: p.A223T and p.A405T (rs75603622); ii) *GPRIN2*: p.V241M (rs9422022), p.V47M (rs3127819); iii) *KCNJ18*: p.L211F (rs1435776313), p.I262S (rs1450551937) **Conclusion:** Although the mechanism of *GPRIN2*, *KCNJ12* and *TEKT4* in tumorigenesis is unclear; our results suggest that these may play a major role in NSCLC and it is worth to be investigated in future. Validation of these genes is under process.

Keywords: NSCLC, Biomarkers, WES, Whole exome sequencing, Biomarkers, NSCLC

P1.14-49 THE ROLE OF CTDNA DETECTION (LIQUID BIOPSY) IN PATIENTS WITH NSCLC

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Background: The analysis of the circulating tumor DNA has attracted interest in the last 6-7 years and is being actively introduced into everyday practice. "Liquid biopsy" will eliminate the shortcomings of routine biopsy, accelerate the time of clinical decision-making, to conduct a more comprehensive study of the tumor in terms of personification of treatment and development of resistance. Results of liquid biopsy provide real-time information on the molecular pathologies and morphological features, identify early resistance to treatment and can modify the therapy regimen. **Method:** From 2016 to 2018 year we studied patients with NSCLC. The ctDNA was detected in the baseline plasma samples and then every 2 months after treatment started by RT-PCR. The aim of the study was to assess the relationship between the presence of EGFR positive ctDNA in tumor tissue and blood plasma **Result:** The study was 1050 patients, 462 cases are represented by adenocarcinoma of NSCLC. EGFR mutations was detected in 145/462 cases (31.38%). Among 145 person 109 were women (72.5%) and 36 were men (24.8%). The mean age was 65.18 (35 - 85). The mutational profile was heterogeneous: ex19del – 94/145 (63.8%), L858R – 47/145 (32.4%), others – 4/145 (2.8%). The results of the study demonstrated that analyzing ctDNA from plasma is feasible for the identification of EGFR mutations with mutation status concordance in 79 matched samples of 53.2% (EGFR mutation positive was detected in 42/79 samples). The T790m resistance mutation was detected in the baseline plasma sample in 8/79 cases (10.1%). EGFR-activating mutations were identified in 13/56 (23.3%) plasma samples after 2 months of Gefitinib. Among the 42 patients in whom the CtDNC was detected in the baseline, after 2 months of therapy was determined only in 6/42 (14.2%). Thus, the disappearance of the mutation was observed in 85.71% (36/42). Mediana of PSF for patients who retained ctDNA after 2 months was 16.25 months (CI 95% 11.24 – 19.94), and for patients in whom the mutation disappeared after 2 months was 21.10 (CI 19.21 - 22.98). Currently the study of molecular genetic markers in blood plasma are continuing. The relationship between effectiveness of treatment and ctDNA detection in blood samples will be analyzed. **Conclusion:** This new, minimally invasive method has the potential to change the prognostic and predictive landscape for lung cancer genotyping and patient management, which will improve treatment outcomes

Keyword: liquid biopsy, NSLC, ctDNC, EGFR mutations

P1.14-50 A PHASE 2 TRIAL OF CABOZANTINIB IN ROS1-REARRANGED LUNG ADENOCARCINOMA

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Background: To date, no ROS1 inhibitor is approved for the treatment of *ROS1*-rearranged lung cancers after progression on crizotinib. Progression on crizotinib can be mediated by the acquisition of *ROS1* kinase domain mutations (e.g. $ROS1^{G2032R}$ or $ROS1^{D2033N}$). Cabozantinib is a highly potent ROS1 tyrosine kinase inhibitor that has superior activity over lorlatinib against these mutations. We evaluated the activity of cabozantinib in patients with *ROS1*-rearranged lung cancers on a phase 2 trial. **Method:** In this single-center, open-label, Simon two-stage, phase 2 study, eligible patients had *ROS1*-rearranged unresectable/metastatic non-small cell lung cancer, a Karnofsky performance status >70%, and measurable disease. *ROS1* fusion was identified by local testing in a CLIA-compliant environment. Cabozantinib was dosed at 60 mg once daily. The primary endpoint was objective response (RECIST v1.1). In the first stage of this trial, 1 response was required to move to the second stage. Secondary endpoints included safety. **Result:** Six patients received cabozantinib in the ongoing first stage of this study. All patients had ≥1 prior ROS1 inhibitor. The median age was

59 years; all were never smokers. The best response to therapy was: 1 partial response (-92%, confirmed), 1 unconfirmed partial response (-31%), and 4 stable disease. All patients had disease regression (-7 % to -92%); no patients had primary progressive disease. The only patient with a confirmed partial response was a patient whose cancer acquired a $ROS1^{D2033N}$ solvent front mutation after crizotinib. None of the other five ROS1 inhibitor pre-treated patients (who did not have a confirmed response) had a known on-target acquired resistance mutation in their cancer. After progression on cabozantinib (9.1 months after therapy initiation), the patient whose cancer harbored the $ROS1^{D2033N}$ mutation acquired a MET^{D1228N} kinase domain mutation on paired sequencing of pre-cabozantinib and post-progression tumor. The most common grade 3 treatment-related adverse events were hypertension (50%), and mucositis, palmar-plantar erythrodysesthesia, and hypophosphatemia (each in 17%). Most patients (83%) required a dose reduction. **Conclusion:** Cabozantinib can re-establish disease control in *ROS1*-rearranged lung cancers after progression on a prior ROS1 inhibitor. The first stage of this ongoing trial met its prespecified endpoint for efficacy to move into the second stage. Response was only observed in the setting of a known *ROS1* kinase domain resistance mutation.

Keywords: lung adenocarcinoma, cabozantinib, ROS1

P1.14-51 LOC440416 LNCRNA-MEDIATED CELL CYCLE ARREST REGULATED CRIZOTINIB-INDUCED HEPATOTOXICITY

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Background: To evaluate crizotinib-induced hepatotoxicity in mice and investigate the role of cell cycle arrest mediated by LOC440416lncRNA during liver injury, furthermore, to provide experiment evidence for screening available hepar protector and expending the clinical application of crizotinib. **Method:** The levels of blood serum ALT, AST, LDH were detected using ICR mouse model. Liver samples of mouse fixed were stained with hematoxylin and eosin for histopathological analysis. The cell inhibition rate of primary hepatocytes was detected by MTT assay.Cell cyclin distribution was detected by flow cytometry(FCM) and the expressions of cell cycle protein cyclinB1 and CDK1 were detected with Westblot after mouse primary hepatocytes were treated with 2.5 μM, 5μM, 10 μM crizotinib for 48h. Apoptosis was evaluated by DAPI staining and PI staining for flow cytometry and the expressions of cell apoptosis protein c-PARP and c-caspase-3 were detected with Westblot. LncRNAs regulating hepar cell cycle arrest were screened using Microarray Chip technique after primary hepatocytes were treated with 5μM crizotinib for 24h. The expressions of cell cyclin protein cyclin B1 and CDK1 were tested with Westblot, after siRNA gene silencing technology was used to knock down LOC440416lncRNA. **Result:** The levels of blood serum ALT, AST, LDH elevated significantly in mice after crizotinib treatment.Slices of liver by HE staining for analysis showed cellular swelling of hepatocytes, nucleolus staining deepened and karyokinesis phenomenon with inflammatory cell infiltrate. *In vitro*, MTT assay showed crizotinib-induced hepatotoxicity in mouse primary hepatocytes presented dose-dependented and IC50 value was 4.6μM. DAPI staining exhibited clear chromatin condensation, fragment and apoptotic bodies and FCM showed sub-G1 apoptosis peak was formed after 5μM and10 μM crizotinib treatment. Westblot demonstrated caspase-3 activation and PARP cleavage. All these data revealed that crizotinib-induced hepatotoxicity was through the process of apoptosis. FCM showed the population of G2/M phase elevated, these of G0/G1 phase decreased and G2/M arrested while the concentration of crizotinib was increased. Reduced protein levels of Cyclin B1 and increased protein level of CDK1 were also observed with Westblot. After crizotinib treatment, sixteen elevated or decreased lncRNAs were found more than ten times separately by terms of Microarray Chip technique. LOC440416lncRNA regulating cell cycle arrest was screened by Real-time PCR. The restoration of reduced Cyclin B1, increased CDK1 expressions, even if hepatocytes were treated with crizotinib, after siRNA gene silencing technology was used to knock down LOC440416lncRNA. **Conclusion:** Crizotinib-induced hepatotoxicity was demonstrated by experiment in vivo and *in vitro*. Cell cyclin G_2/M check point arrest accompanied with decreased expression of cyclin B1 protein and increased expression CDK1, mediated by LOC440416 lncRNA, could be the possible mechanism.

Keyword: LOC440416 lncRNA, cell cycle, crizotinib, hepatotoxicity

P1.14-52 CLINICAL RESPONSE TO OSIMERTINIB IN A PATIENT WITH METASTATIC NSCLC HARBORING EGFR A763_Y764INSFQEA EXON 20 INSERTION MUTATION: A CASE REPORT

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Background: Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations represent approximately 4-10% of EGFR-mutant non-small-cell lung cancer (NSCLC). The majority of *EGFR* exon 20 insertion mutations do not respond to approved EGFR tyrosine kinase inhibitors (EGFR-TKIs). Preclinical data suggest that EGFR A763_Y764insFQEA mutation is associated with sensitivity to EGFR-TKI therapy. A few case reports have shown that patients with this rare variant of *EGFR* exon 20 insertion mutation may respond to first- and second-generation EGFR-TKIs. However, efficacy of the third-generation EGFR-TKI osimertinib against the EGFR A763_Y764insFQEA mutation has not been described. Here, we present a patient with metastatic NSCLC harboring EGFR A763_Y764insFQEA alteration treated with osimertinib. **Method:** A 56-year-old never-smoker Asian female presented with complete atelectasis of the left upper lobe, a left circumferential pleural effusion, and diffuse osseous sclerotic lesions. Pathology confirmed the diagnosis of metastatic lung adenocarcinoma. Circulating tumor DNA (ctDNA) assay utilizing InVisionSeq™ Tagged-Amplicon next-generation sequencing (NGS) identified EGFR A763_Y764insFQEA, MET amplification, and TP53 G266*. The patient was started on osimertinib 80 mg once a day. Later, tumor NGS came back positive for EGFR A763_Y764insFQEA, TP53 G266*, and BRCA-2 A2351G. **Result:** The patient's symptoms of cough and shortness of breath started to improve shortly after initiation of osimertinib. A CT scan of the thorax and abdomen obtained 5 weeks after starting osimertinib showed improvement in aeration of the previously collapsed left upper lobe, visualization of a 1.9 x 1.4 cm spiculated left upper lobe lung mass, improved infiltrative soft-tissue in the left hilum, and improved partially loculated left pleural effusion, suggesting response to osimertinib. **Conclusion:** In this patient with the EGFR A763_Y764insFQEA mutation, osimertinib has shown effectiveness as monotherapy, suggesting it could serve a viable therapeutic treatment option in NSCLC with this rare variant of exon 20 insertion mutations. Future studies should validate this finding.

Keywords: exon 20 insertion mutation, A763_Y764insFQEA, Osimertinib

P1.14-53 CO-OCCURRING CDKN2A/2B ALTERATION IS ASSOCIATED WITH POORER SURVIVAL IN ALK-POSITIVE LUNG CANCER

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Background: Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have shown promising clinical outcomes for ALK-positive (ALK+) lung cancer patients. However, clinical outcomes are varied, distinct mechanisms have been suggested for different ALK fusion variants or co-occurring mutations in response to various TKIs. We analyzed whether variants or co-occurring mutations influence the outcome of AKL TKI treatment in ALK+ non-small-cell lung cancer (NSCLC). **Method:** Between March 2017 and October 2018, 489 NSCLC tumor specimens were examined with OncoPanel AMC version3 which is a NGS based assay for the detection of single-nucleotide variants, insertions, deletions, copy number alterations and structural variants across 382 genes. 43 patients were identified as having ALK rearrangement. And 37 patients received ALK TKI treatment. Progression free survival (PFS) and overall survival (OS) were analyzed respectively according to ALK variants and other co-occuring mutations. **Result:** Among 37 patients with ALK+ NSCLC, 32 (86.5%) of patients received crizotinib, and 5 (13.5%) with alectinib as first ALK TKI treatment. The most frequent ALK variant was variant 3a/b in 13 patients (35.1%), followed by variant 1 in 10 patients (27.0%), variant 5 in 4 patients (10.8%), variant 2 in 3 patients (8.1%), and others in 7 patients (18.9%). The similar median PFS was observed in patients ALK variant 3 and non-variant 3 regardless of first ALK TKI treatment strategy (crizotinib, 18.9 vs. 15.2 months, p=0.35; alectinib, both not reached). As a co-occurring mutation, TP53 mutation was detected in 17 (45.9%) patients. And

there was no statistical difference in PFS or OS between the wild type and TP53 mutation group [PFS 18.2 vs 15.3 months, p=0.92; OS 62.1 vs 62.2 months, p=0.44]. CDKN2A/2B alteration was the second most common mutation and observed in 9 (24.3%) patients. Median PFS and OS in ALK-CDKN2A/2B co-mutated patients were lower than wild type patients [PFS 15.3 months (95% CI: 8.1-22.5) versus 18.2 months (95% CI: 13.0–23.4), P=0.064, OS 26.7 months (95% CI: 14.2–39.3) versus not reached, P=0.022]. **Conclusion:** In ALK+ NSCLC, having co-occurring CDKN2A/2B alteration was associated with a poorer OS when treated with an anti-ALK agent.

Keywords: ALK, CDKN2A/2B, TKI

P1.14-54 PREVIOUS THERAPY STRATEGY IMPACT ON EFFICIENCY OF ANLOTINIB HYDROCHLORIDE AS 3RD LINE TREATMENT: A SUBGROUP ANALYSIS OF ALTER0303 TRIAL

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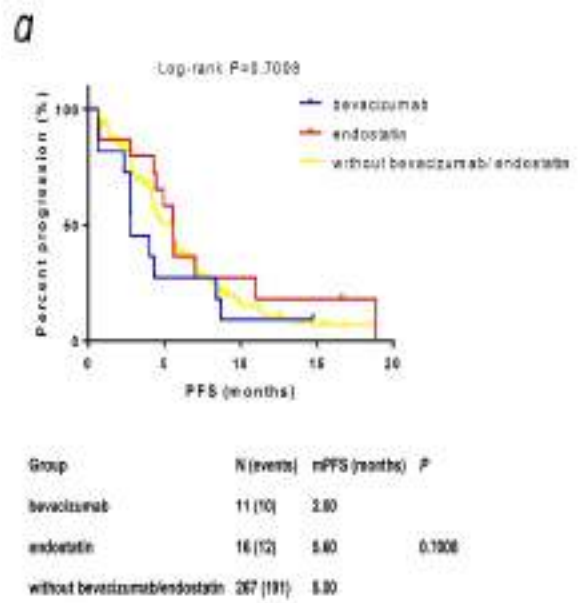
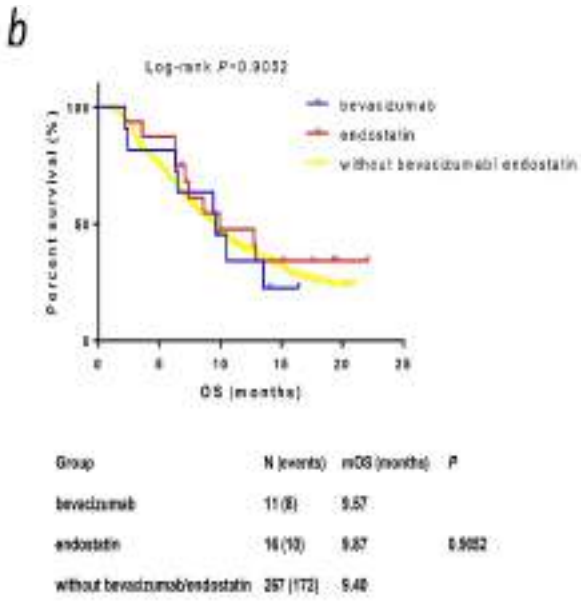
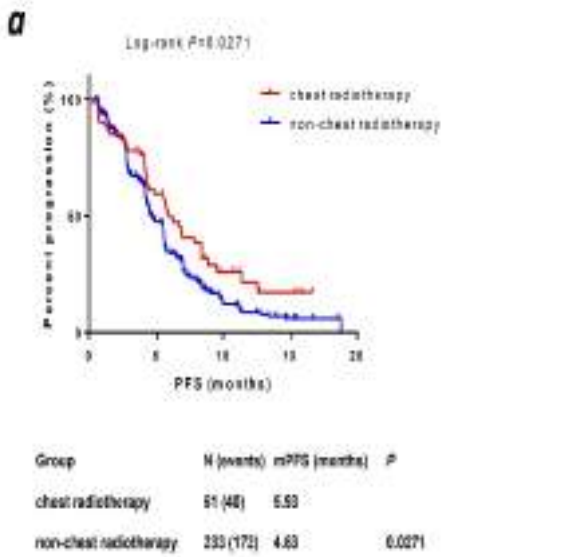
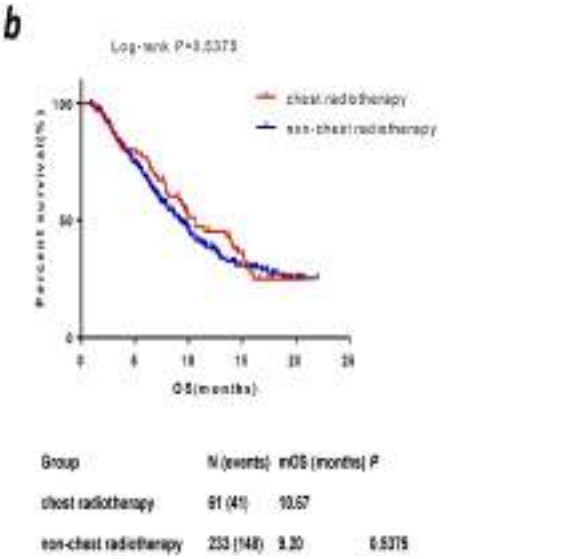
Background: Lung cancer remained one of the deadest cancers throughout worldwide. ALTER0303 trial revealed anlotinib might be used as a third-line or further treatment in non-small-cell lung cancer patients. While previous therapy strategy would have impact on efficiency of anlotinib still remained unknown. **Method:** The subgroup of patients in ALTER0303 were analyzed by using Kaplan-meier estimates, Pearson X^2 or Fisher exact test. **Result:** There is no statistical significance on progression-free survival (PFS) and overall survival (OS) among patients in different previous antiangiogenic treatments groups. Patients in the chest radiotherapy (CRT) group had longer median PFS than non-CRT group (5.93m vs. 4.63m, *P*=0.027). No matter what kind of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) and chemotherapy regimens used previously, all patients gained longer PFS from anlotinib. While only patients treated with vinorelbine/platinum in EGFR wild type group, pemetrexed/platinum, vinorelbine/platinum and gefitinibin in EGFR mutation group, EGFR TKI used as the first line group could benefit from anlotinib on OS. When the OS was calculated from the time of diagnosis to death, anlotinib may improve about 6 months median OS (33.8m vs.27.8m, *P*<0.001) compared to placebo with HR (95%CI): 0.77 (0.60, 1.00).

Figure 1. Kaplan-Meier estimate of overall and progression-free survival among different previous antiangiogenic therapy subgroup in patients treated with anlotinib.









Conclusion: This study indicated previous bevacizumab or endostatin treatments had no impact on the efficiency of anlotinib. Patients with CRT history benefited more from anlotinib on PFS. EGFR TKI and chemotherapy treatments history had more impact on OS than PFS in patients treated with anlotinib compare to placebo.

Keywords: non-small-cell lung cancer, Anlotinib, antiangiogenic therapy

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P1.14-55 COST-EFFECTIVENESS OF CERITINIB AND ALECTINIB VS CRIZOTINIB IN FIRST-LINE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NSCLC

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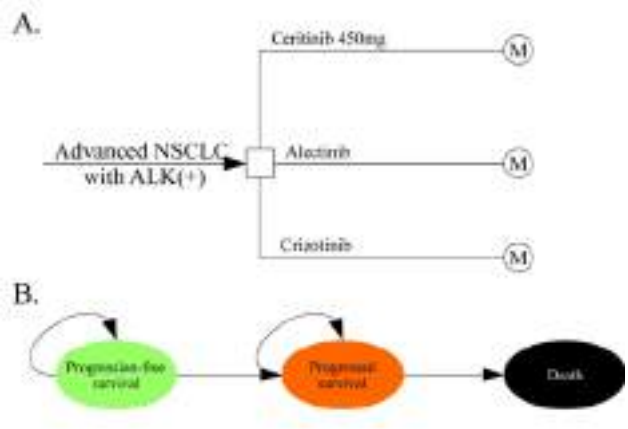
Background: The recently completed ASCEND and ALEX trials demonstrated that ceritinib and alectinib improved progression-free survival and overall survival in patients with anaplastic lymphoma kinase (ALK) arrangement non-small-cell lung cancer (NSCLC). However, the long-term economic outcomes of using ceritinib and alectinib versus crizotinib is still unclear. The aim of this analysis was to evaluate the cost-effectiveness of ceritinib and alectinib versus crizotinib in the Chinese setting. **Method:** A Markov model was developed to project the economic and health outcomes of treatment of advanced NSCLC with ceritinib, alectinib or crizotinib. The model used the partition survival methods and three health states: progression-free, post-progression, and death. Network meta-analysis was performed to calculate the hazard ratios of ceritinib and alectinib versus crizotinib by pooling published trials. Costs and utility values were obtained from literature. One-way and probabilistic sensitivity analyses were carried out to determine the robustness of the model outcomes. The primary outputs of the model included the total cost, life-years (LYs), quality-adjusted LYs (QALYs), and incremental cost-effectiveness ratio (ICER).



Result: Treatment with ceritinib and alectinib versus crizotinib yielded additional 1.01 and 1.00 QALYs, and incremental costs of US$ 14,217 and 62,168, resulting in an incremental cost-effectiveness ratio of US$14,017 and 62,168/QALY. Drug costs and probabilities of PFS and OS were the main drivers of the model in the one-way sensitivity analysis. From the probabilistic sensitivity analysis, ceritinib and alectinib had a 100% and 0% probability of being cost effective at a willingness-to-pay threshold of US$27,351/ QALY (3× the per capita gross domestic product of China in 2017).

Tab 1. Summary of cost ($) and outcome results in base-case analysis.

Strategy	Cost	Progression-free LYs	Overall LYs	QALYs	Incremental cost per QALY*
Crizotinib	55,204	1.30	4.56	1.99	NA
Alectinib	117,372	2.89	5.45	2.99	62,168
Ceritinib	69,420	3.19	4.94	3.01	14,017

Conclusion: Our results indicate that compared with crizotinib and alectinib, ceritinib is a cost-effective option for treatment-naïve patients with ALK-positive advanced NSCLC.

Keywords: cost-effectiveness, Ceritinib+Alectinib vs Crizotinib, advanced NSCLC

P1.14-56 THE DYNAMIC RANGE OF MUTANT ALLELE FRACTION DETECTED IN CTDNA FROM PATIENTS WITH NSCLC: CLINICAL EXPERIENCE DATA AND CLINICAL IMPLICATIONS

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Background: The detection of both activating and resistance mutations in the circulating tumor DNA (ctDNA) fraction of total cell free DNA (cfDNA) isolated from plasma in patients with NSCLC has gained widespread adoption and clinical practice guideline recommendations. However, the vast majority of cfDNA in blood samples is derived from non-cancerous tissue or white blood cells (WBCs). In patients with NSCLC, ctDNA must be distinguished from cfDNA. Studies have suggested that the contribution of non-tumor genetic material in circulation is greater than 90% whilst the DNA derived from tumor or circulating tumor cells (CTCs) is < 1%. Hence the ability to accurately identify mutations in patients with NSCLC, who would potentially benefit from targeted therapy as well as for monitoring for both emergence of resistance, recurrence and tumor burden, require assays to consistently and reliably detect low level mutations. Additionally, blood collection tubes should maximally stabilize cells to prevent excess breakdown of WBCs that would significantly increase the amount of cell free non-tumor DNA in the plasma fraction leading to potential false negative results for mutations analyzed in patients with NSCLC. **Method:** Patient samples were collected in CEE-Sure™ blood collection tubes to minimize the non-tumor cfDNA content. Plasma was removed from the blood samples and circulating nucleic acid was extracted. The plasma fraction was then used in the highly sensitive EGFR, BRAF, and KRAS Target-Selector™ assays. The Target-Selector™ assays utilize forward and reverse primers and a Target-Selector™ probe to specifically block wild-type amplification of cfDNA, and selectively enrich for mutant sequences (ctDNA). Sanger sequencing of the amplified Target-Selector™ product is used to confirm presence of the mutation. **Result:** A total of 1410 NSCLC patient samples were analyzed for EGFR, 877 for BRAF and 300 for KRAS. Overall mutations were detected in 28% of cases. The dynamic range of the mutant allele frequency (MAF) was 0.05% to 77%. For EGFR mutations, 23% of total mutations per sample were detected at <1% and for individual EGFR alterations (del19, L858R, T790M) within a sample, 74% were detected at <1% MAF. 37% of cases were positive for BRAF and 41% positive for KRAS at <1% MAF. 3% of EGFR mutant NSCLC, 10% of individual EGFR alterations and 11% of BRAF mutations were detected at <0.1% MAF. **Conclusion:** The consistent detection of mutations at a lower MAF of <1% corresponds to previously published biological thresholds of ctDNA in patients with cancer against an excess of non-tumor cfDNA. The ability of an assay to detect mutations consistently at <1% and <0.1% as demonstrated, is an important performance characteristic, as 26%, 47% and 41% of patients with NSCLC harbor mutations at <1% for EGFR, BRAF and KRAS respectively. This has potential clinical implications regarding patient qualification for targeted therapies and monitoring. The blocking of amplification of non-tumor cfDNA component allows for a more sensitive analysis of ctDNA.

Keyword: EGFR,Liquid biopsy, sensitive detection

P1.14-57 POST-ENSARTINIB OUTCOMES IN REFRACTORY ANAPLASTIC LYMPHOMA KINASE (ALK)-REARRANGED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The effectiveness of the next-generation ALK inhibitor, ensartinib, in refractory ALK-rearranged, advanced NSCLC patients represents a promising therapeutic option. With the advent of novel ALK inhibitors utilized in sequence, the survival of patients with ALK-rearranged tumors has improved dramatically. This case series serves to compare tumor response rates and long-term survival outcomes among four patients treated with ensartinib over the course of four years at our institution. **Method:** We conducted an open-label, first-in-human, IRB approved phase 2 clinical trial using

single-agent ensartinib at a dose of 225 mg once daily. Patients were selected from UC San Diego Moores Cancer Center with ALK-rearranged NSCLC who had previously progressed on crizotinib. Other prior therapies included platinum/pemetrexed chemotherapy (n=3) and pembrolizumab (n=1). Objective response was determined every eight weeks according to RECIST 1.1. Patients were treated until disease progression or unacceptable toxicity. Circulating tumor DNA (ctDNA) sequencing was obtained in 3 patients at baseline and 2 patients at the time of progression. **Result:** Four patients were enrolled (age range, 43-61 years) and all had brain metastases at baseline. All four patients achieved an objective partial response to ensartinib, including one patient with an acquired ALK F1174V crizotinib resistance mutation. Intracranial responses included one partial response, two stable disease, and resolution of a non-target lesion in another patient. The median progression free survival was 12.5 months (range, 8-15 months) and the median decrease in tumor size was 42% (range, 39-48%). Primary sites of disease progression included lung (n=1), brain (n=2), both lung and brain (n=1). No somatic alterations were identified in the two patients who received post-ensartinib ctDNA sequencing. At progression, all patients received brigatinib as subsequent therapy with clinical benefit; one received lorlatinib after brigatinib failure and response is ongoing. Median post-ensartinib survival was 27 months (range, 20-38 months). Two patients remain alive 27 and 95 months after first anti-cancer therapy. The most common adverse events with ensartinib were mild rash, diarrhea, and fatigue that did not require dose reduction. **Conclusion:** Ensartinib is well tolerated and has clinical activity in advanced ALK-rearranged NSCLC patients with brain metastases, despite previously progressing on crizotinib, with durable post-ensartinib survival on subsequent next-generation ALK inhibitors such as brigatinib and lorlatinib. (Trial funded by Xcovery Holdings, Inc.; ClinicalTrials.gov number: NCT01625234)

Keywords: ALK, ensartinib, NSCLC

P1.14-58 A PHASE II STUDY TO EVALUATE NEOADJUVANT OSIMERTINIB FOR SURGICALLY RESECTABLE, EGFR-MUTANT NON-SMALL CELL LUNG CANCER

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Background: The third-generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib is well-tolerated and effective for first-line treatment of metastatic EGFR-mutant non-small cell lung cancer (NSCLC). The efficacy of osimertinib in the treatment of early stage EGFR-mutant NSCLC, however, is unknown, and cytotoxic chemotherapy is considered the standard of care when systemic therapy is necessary for these patients. Neoadjuvant chemotherapy is an established therapeutic modality in locally-advanced NSCLC, in which a major pathologic response is associated with improved survival. Neoadjuvant use of targeted therapies in oncogene-driven NSCLC may offer the dual advantages of increased response rates and of more favorable toxicity profiles compared to cytotoxic chemotherapy, and also provides the opportunity to identify mechanisms underlying tumor cell persistence despite optimal oncogene-targeted therapy. **Method:** This ongoing phase II, multi-institution study aims to enroll 27 patients with surgically resectable stage I-IIIA EGFR-mutant NSCLC. Patients are treated with one to two months of osimertinib 80 mg orally daily followed by surgical resection. The primary endpoint is major pathologic response (mPR) rate, defined as less than 10% residual viable tumor at surgical resection. Secondary endpoints include safety assessment, unanticipated delays to surgery, surgical complication rate, pathological complete response rate (pCR), unconfirmed objective response rate (ORR), rate of lymph node downstaging, disease-free survival, and overall survival. Tumor biopsies are obtained prior to osimertinib treatment in order to permit comparative correlative studies between pre- and post-osimertinib treated tumors. This includes genomic and transcriptomic analyses, evaluation of tumor immune cell infiltrates, and development of patient-derived model systems for functional validation studies. **Result:** As of March 2019, five patients with EGFR-mutant NSCLC (2 stage IIIA, 1 stage IB, 2 Stage IA) have been enrolled and treated with osimertinib for an average of 56 days prior to surgical resection. Restaging imaging prior to surgical resection demonstrated an unconfirmed radiographic partial response in three patients (60% ORR) and stable disease in two patients (100% disease control rate). The mPR rate is 20% (1 of 5). No pCR's were observed. One patient demonstrated lymph node downstaging from N2 to N0. Treatment was well-tolerated without SAEs and all patients proceeded to surgical resection without unscheduled delay or surgical complications. Genomic and immunophenotyping analyses are underway and will be reported. **Conclusion:** Preliminary data from this phase II study indicates that neoadjuvant osimertinib treatment in surgically-resectable, EGFR-mutant NSCLC is well-tolerated and can induce pathological responses and downstaging of disease prior to surgery.

Keywords: Targeted therapy, EGFR, neoadjuvant

P1.14-59 CLINICAL IMPLICATIONS OF THE PHARMACOKINETICS OF DACOMITINIB CO-ADMINISTRATION WITH H2-RECEPTOR ANTAGONISTS IN CANCER PATIENTS

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Background: Dacomitinib (Vizimpro®) is a competitive, irreversible, small-molecule inhibitor of epidermal growth factor receptor (EGFR) and is currently approved for first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations. Similar to other EGFR inhibitors, the aqueous solubility of dacomitinib is pH dependent, with its highest solubility observed at acidic pH. Therefore, it is important to evaluate the potential impact of gastric pH-elevating agents on the pharmacokinetics (PK) of dacomitinib. Co-administration of a proton pump inhibitor (rabeprazole 40 mg once daily for 4 days) resulted in approximately a 40-50% decrease in dacomitinib exposure after a single 45-mg dose of dacomitinib. There was no effect on the extent of absorption of dacomitinib during treatment with a short-acting antacid (Maalox Maximum Strength). This report evaluated the effect of co-administration of histamine 2-receptor antagonists (H2RA) on dacomitinib PK based on a retrospective analysis of pooled PK data collected from clinical studies in patients treated with dacomitinib. **Method:** Data were drawn from 11 Phase 1, 2 and 3 clinical studies in advanced NSCLC or solid tumor patients. For each patient, steady-state trough concentrations ($C_{trough,\ ss}$) of dacomitinib after ≥14 days of consecutive dacomitinib dosing at a dose level of 15, 30, 45 or 60 mg once daily were measured at various times during the treatment period. Withinpatient comparison of a 45-mg dose of normalized dacomitinib$C_{trough,\ ss}$ between dacomitinib dosing alone and dacomitinib coadministered with an H2RA (cimetidine, famotidine, nizatidine and ranitidine) consecutively for ≥3 days was performed using a linear mixed effects model with time and treatment as fixed effects and patient within time as a random effect. **Result:** A total of 86 (5.9%) patients from the pooled patient studies received an H2RA. In this analysis, 16 patients had dacomitinib $C_{trough,ss}$ for both dacomitinib dosing alone and dacomitinib co-administered with an H2RA. The adjusted geometric mean ratio of a 45-mg dose of normalized dacomitinib $C_{trough,ss}$ following co-administration with an H2RA was 85.9% (90% confidence interval [CI]: 72.9%, 101.1%) relative to dacomitinib dosing alone. The 90% CI for the ratio includes 100%, suggesting no statistically significant difference between the reference and test groups (P>0.05). **Conclusion:** Co-administration of an H2RA is not expected to have a clinically relevant effect on dacomitinib exposure. In accordance with knowledge derived from other EGFR inhibitors, it is recommended that the time of dacomitinib dosing with an H2RA should be staggered to allow dacomitinib absorption at the time of lowest gastric pH and to minimize any potential impact from the concomitant use of an H2RA.

Keywords: NSCLC, histamine 2-receptor antagonist, dacomitinib

P1.14-60 STATINS OVERCOME RESISTANCE TO TYROSINE KINASE INHIBITORS IN PATIENT-DERIVED, ONCOGENE-DRIVEN NSCLC MODELS

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Background: Despite the improved efficacy of newer generation targeted TKIs, nearly all patients with EGFR- and ALK-driven NSCLC eventually acquire resistance and succumb to the refractory metastatic disease. Previous studies have shown that simvastatin has more potent antitumor effects compared to other statins. The objective of this study was to determine whether simvastatin could overcome TKI resistance using *in vitro* and *in vivo* NSCLC models. **Method:** Human NSCLC cell lines A549 (*KRAS* G12S), H3255 (*EGFR* L858R), and H1975 (*EGFR* L858R and T790M) were treated with simvastatin either alone or in combination with an TKI. Antitumor effect was measured by growth inhibition by MTS assay and expression of molecular targets by immunoblots. Malignant pleural effusion and biopsied tumors were collected under an IRB-approved protocol and used for primary cell culture and generation of patient-derived xenograft models in NSG mice. Mice implanted with H1975 xenografts were treated with vehicle, simvastatin, osimertinib, or both. Mice engrafted with an ALK-TKI resistant PDX were treated with vehicle simvastatin, brigatinib, or both. Tumor growth was measured every other day for 28 days or the tumor volume reached ~2 cm^3. Tumors were subjected to histomorphological assessment and immune blot analyses. All data are shown as mean ± standard deviation (SD). The two-sample t-test was used for continuous variables. All statistical tests were two-sided and a p-value less than 0.05 was considered statistically significant. **Result:** We found that simvastatin alone had a strong antitumor effect in tested NSCLC cell lines, regardless of tumor genotypes. Simvastatin and osimertinib combination showed synergistic cytotoxic effect in these NSCLC cell lines and several primary culture of patient's pleural effusion. Simvastatin alone reduced the tumor volume by 41% and 57% compared to controls in both the EGFR- and ALK-TKI resistant PDX models. In the H1975 xenograft model, simvastatin and osimertinib combination produced a greater reduction in tumor volume than osimertinib alone ($P < 0.01$). In an ALK TKI-resistant lung PDX model, simvastatin and brigatinib combination resulted in a greater reduction in tumor volume than brigatinib alone ($P < 0.01$) and showed a synergistic effect based on a simple multiplicative model of a fixed dose, two-drug combination. **Conclusion:** Simvastatin displays anti-tumor activity in multiple EGFR and ALK TKI resistant models, and preliminary analysis suggests potential synergism with the two tested TKIs (osimertinib and brigatinib). Further study is needed to characterize the molecular mechanisms responsible for the statin-mediated anti-tumor effect and its interactions with TKIs.

Keywords: statin, oncogene-driven non-small cell lung cancer, resistance

P1.14-61 EGFR INHIBITORS PLUS BEVACIZUMAB ARE SUPERIOR COMPARED TO EGFR INHIBITOR MONOTHERAPY IN ADVANCED EGFR+ NSCLC PATIENTS WITH BIM DELETIONS

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Background: BIM activation is essential for EGFR-TKIs triggered apoptosis in *EGFR*-mutant Non-small-cell lung cancer (NSCLC). A 2903-bp germline deletion in intron 2 of the BIM gene results in generation of alternatively spliced isoforms that lack the crucial BH3 domain, impairing the apoptotic response to TKIs and conferring NSCLC cells intrinsic resistance to these medications. Patients with both alterations have poor clinical evolution. The current study aimed to investigate the clinical efficacy and tolerability of EGFR-TKIs plus bevacizumab (Bev) versus EGFR-TKIs alone as first-line treatment in advanced NSCLC patients with *EGFR* mutations and BIM deletions (BIM*del*). **Method:** A retrospective analysis was conducted. BIM*del* was detected using polymerase chain reaction (PCR) analysis and direct sequencing of DNA from tumor and peripheral blood cells (PBCs). We also assessed BIM protein expression by immunohistochemistry and BIM mRNA levels by RT-PCR. Clinical characteristics, overall survival (OS), progression-free-survival (PFS), objective response rate (ORR) and treatment-related adverse events were compared in the EGFR-TKIs versus EGFR-TKIs plus Bev groups. **Result:** 32 patients were included; 16 of them received EGFR-TKIs and 18 received EGFR-TKIs plus Bev. The addition of Bev resulted in a significantly higher ORR compared with TKIs alone (94% vs. 44%, p=0.0014). Median PFS was longer with the use of the combination compared with TKIs alone (11.1 vs. 7.77 months; $p < 0.001$). Median OS tended to be longer in the EGFR-TKIs plus Bev group than in TKIs alone (30.9 vs. 25.4 months; $p = 0.06$). EGFR-TKIs plus Bev was associated with more grade >3 hematological and thrombotic adverse events. The expression of BIM by immunohistochemistry did not influence PFS and OS, however when stratifying BIM mRNA levels by the median (≥2.2 vs. <2.1) allowed to find a prognostic trend in favor of those with higher BIM mRNA levels (32.2 vs. 25.2 months respectively; $p = 0.058$). **Conclusion:** EGFR-TKIs plus Bev conferred a significantly higher ORR and PFS in advanced NSCLC patients with *EGFR* mutation and BIM*del*. Further prospective studies are needed to validate these findings.

Keywords: EGFR inhibitors, Non small cell lung cancer, BIM deletions

P1.14-62 AFATINIB IN EGFR TKI-NAÏVE PATIENTS WITH EGFR MUTATION-POSITIVE NSCLC: COMBINED ANALYSIS OF TWO SINGLE-ARM PHASE IIIB STUDIES

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Background: First-line afatinib significantly improved progression-free survival (PFS) compared with platinum-doublet chemotherapy in patients with *EGFR* mutation-positive *(EGFR*m+; including uncommon mutations) NSCLC in two Phase III studies (LUX-Lung 3: median 11.1 vs 6.9 months, hazard ratio [HR]=0.58; p=0.001; LUX-Lung 6: 11.0 vs 5.6 months, HR=0.28; p<0.0001). First-line afatinib also significantly improved PFS compared with gefitinib in the Phase IIb LUX-Lung 7 study (11.0 vs 10.9 months, HR=0.73; p=0.017). However, some patients still receive chemotherapy as a first-line treatment choice in clinical practice. Here, we report a combined analysis of outcomes from two large Phase IIIb studies of afatinib in EGFR TKI-naïve patients treated in a setting similar to real-world practice. **Method:** In both studies, EGFR TKI-naïve, including chemotherapy-pretreated, patients with locally advanced or metastatic *EGFR*m+ NSCLC received 40 mg/day afatinib until progressive disease or lack of tolerability (dose reduction was permitted [minimum: 20 mg/day]). Study 1 enrolled patients across eight European countries, and Russia, Israel and Australia; Study 2 enrolled patients from centres in China, Hong Kong, India, Singapore, and Taiwan. Interim (Study 1; data cut-off: 30 April 2018) and final (Study 2; data cut-off: 06 July 2018) data were used for this combined analysis of time to symptomatic progression (TTSP), PFS, objective response, and safety. **Result:** A total of 1020 patients were treated with afatinib (female: 59%; Asian/White/other: 54%/46%/<1%; median age

[range]: 61 years [25–89]; ECOG PS 0/1/2: 26%/69%/5%; common/uncommon *EGFR* mutations: 82%/18%; treatment line 1st/2nd/≥3rd: 69%/23%/8%; presence of brain metastases: 18%). Overall, median TTSP was 14.6 months (95% confidence interval [CI]: 13.8–15.8 months); median PFS was 12.9 months (95% CI: 11.6–13.7 months). Objective response rate was 52.7%. Adverse events (AEs; all grade/grade ≥3) occurred in 1012/556 (99%/55%) patients; serious AEs were reported in 366 patients (36%). The most common grade ≥3 AEs were diarrhoea (14%) and rash (9%). Any-cause AEs leading to dose reduction were reported in 412 (40%) patients. Treatment discontinuation due to afatinib-related AEs occurred in 54 patients (5%). **Conclusion:** In this combined analysis of two large, prospective 'real-world' afatinib studies in EGFR TKI-naïve patient populations, which included patients treated with afatinib in later lines, patients with ECOG PS 2, patients with brain metastases, and patients with uncommon mutations, safety data were consistent with previous results seen in the LUX-Lung 3, 6, and 7 studies. Efficacy findings are also encouraging, with a median TTSP of 14.6 months.

P1.15 THYMOMA/OTHER THORACIC MALIGNANCIES
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.15-01 PROGNOSTIC FACTORS AND LONG-TERM OUTCOMES AFTER PULMONARY METASTASECTOMY FROM RENAL CELL CARCINOMA

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Background: Treatment of pulmonary metastases from renal cell carcinoma (RCC) remains controversial. However, some studies revealed potential survival benefits of pulmonary metastasectomy (PM) in these patients. We evaluate our experience analyzing surgical results, postoperative outcomes, and prognostic factors in patients receiving PM for RCC. **Method:** Using a prospective database, we retrospectively reviewed data from 133 patients who underwent PM for RCC between 1998 and 2018. There were 93 men (median age, 62 years, range, 29-80). Surgery included 104 wedge/segmentectomies (78.2%), 28 lobectomy/bilobectomy (21.0%), one pneumonectomy (0.8%). Twenty-one patients (15.8%) received a redo-metastasectomy. A single metastasis or 2-3 metastases were removed in 42 patients (31.6%) each; in 91 patients (68.4%) 4 or more metastases were removed. Lymphadenectomy was performed in 84 patients (63.2%): 58/84 (69.1%) were pN0, and 26/84 (30.9%) were pN+. **Result:** Complete resection was achieved in 124 patients (93.2%). Mortality was nil. We had only minor complications occurring in 23 patients (18.0%). After a median follow-up of 2.5 years (range, 0.03-13.3 years), 102 patients (76.7%) were alive. Five and 10-year survival were 57% and 53%, respectively. Disease-free interval was <12 months in 39 patients (29.4%); between 12 and 36 months in 33 (24.8%), and >36 month in 61 (45.8%), respectively. DFI and complete resection did not influence survival rate. Number of resected metastases influenced long-term outcome (60% for less 3 metastases versus 32% for 4 or more, log-rank test: p=.02). Patients with nodal involvement had a poor survival (58% for N0 versus 29% for N+, p=.01). At multivariate analysis, both number of resected metastases and nodal involvement were independent prognostic factors [p=.03 (95% CI: 0,66-8,46) and p=.001 (CI: 0,57-6,35), respectively]. **Conclusion:** PM may be a promising treatment for metastatic RCC allowing a good long-term survival rate. Nodal involvement and a number of resected metastases equal or more than 4 are predictors of poor survival.

Keywords: pulmonary metastasis, renal metastasis

P1.15-02 ROLE OF MTOR INHIBITOR EVEROLIMUS IN THE TREATMENT OF METASTATIC THYMIC EPITHELIAL TUMORS

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Background: Optimal treatment for metastatic thymic epithelial tumors (TETs) after progression on platinum-based chemotherapy has yet to be determined. There is emerging evidence to support the use of mTOR inhibitor everolimus in this setting including the recent phase II study by Zucali et al. However, patient selection and identifying predictors of response remains a challenge. Here, we describe a single-center experience with everolimus in TETs and molecular markers associated with response to therapy using a computational biological model (CBM). **Method:** Data on all patients with advanced TETs who were prescribed everolimus at our institution were retrospectively abstracted from the electronic medical record. Time to treatment failure (TTF) and overall survival (OS) were calculated. Solid Tumor Actionable Mutation Panel (STAMP), a targeted next generation sequencing (NGS) panel, was run on each TET and the results were computationally matched to a cohort of genomically similar TET patients from The Cancer Genome Atlas (TCGA). CBM was used to examine key genomic alterations of TETs correlated with response on everolimus. Responders were defined as having TTF > 6 months. **Result:** Thirteen patients with TETs, including ten thymomas (T) and three thymic carcinomas (TC) treated with everolimus, were included. All patients had been heavily pre-treated with an average of three prior lines of therapy. Three patients discontinued treatment due to adverse events. The average TTF was 10.8 months in T and 2.6 months in TC with median OS of 205 months (T) and 67.8 months (TC). Molecular data was available for 11 of 13 patients and identified mutations in *MAP2K*, *HRAS* and *NF1* as key molecular features associated with a response to everolimus. CBM accurately predicted response in 9 of 11 genomically similar TCGA tumors to our patient cohort. **Conclusion:** Patients with previously treated metastatic TETs appear to benefit from everolimus. Molecular testing of these tumors using targeted NGS panel revealed an association with several key genes, which may help to guide patient selection in the future.

Keywords: thymic epithelial tumors, Everolimus

P1.15-03 CABOZANTINIB AND R428 INHIBIT THE GROWTH OF ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

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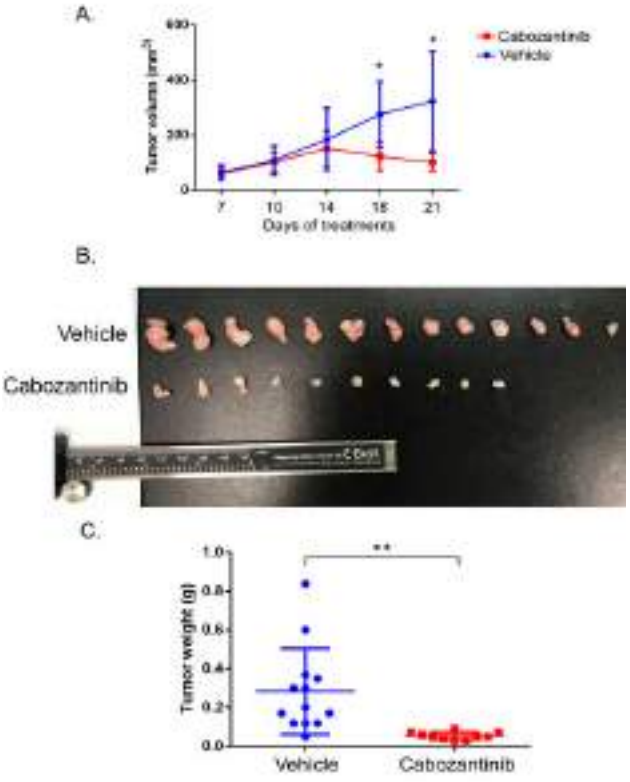
Background: Esophageal squamous cell carcinoma (ESCC) is a deadly disease for which no effective targeted therapeutic agent has been approved. Both AXL and c-MET have been reported to be independent prognostic factors for ESCC. Thus, inhibitors of AXL/c-MET might have great potential as targeted therapy for ESCC. We evaluated the efficacy of AXL/c-MET selective inhibitors, R428 (BGM324) and cabozantinib (XL184) in ESCC cell and mouse xenograft models. **Method:** The cytotoxicities of R428, BMS-777607 and cabozantinib in CE81T and KYSE-70 cells were determined by MTT survival assay. The effect of each inhibitor on migration activity of ESCC cells was analyzed by wound healing assay. ESCC xenograft models were established by injecting KYSE70 cells with matrigel into the upper back region of NOD-SCID male mice followed by treatment with vehicle control, R428 (50 mg/kg/day), cisplatin (1.0 mg/kg) or cabozantinib (30 mg/kg/day) for the indicated number of days. **Result:** We demonstrated both R428 and cabozantinib significantly inhibit the growth of CE81T and KYSE-70 ESCC cells. R428 but not cabozantinib had a synergistically cytotoxic effect in combination with cisplatin in ESCC cells. Meanwhile, both R428 and cabozantinib inhibited ESCC cell migration by wound-healing assay. In ESCC xenograft models, R428 alone significantly inhibited ESCC tumor growth compared to the vehicle; however, no synergistic effect with cisplatin was observed. Notably, the dramatic efficacy of cabozantinib alone was observed in the mice xenograft model. **Conclusion:** Our study demonstrated that both cabozantinib and R428 inhibit ESCC

growth in cell and xenograft models. The results reveal the great potential of using cabozantinib for targeted therapy of ESCC.



Keywords: esophageal cancer, Targeted therapy, cabozantinib

P1.15-04 CHEST WALL RESECTION AND RECONSTRUCTION FOR THORACIC WALL MALIGNANCIES: INDUCTION THERAPY REDUCES RECURRENCE RATES

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Background: Chest wall resections are associated with significant morbidity. The present analysis reports a the outcome of a large series of chest wall tumor resections. **Method:** Patients with primary and secondary chest wall malignancies undergoing resection and reconstruction were retrieved from our institutional database. Clinical and pathological parameter were correlated with long-term outcome **Result:** The study includes 169 patients, who underwent chest wall resection and reconstruction for primary or secondary chest wall tumors between 1999 and 2018. The median age was 60 (range 10-87) years. 48 (28%) were primary tumors, whereas 121 (72%) were secondary tumors. Primary malignancies were predominantly sarcomas 39 (23%). For secondary malignancies, the largest subgroups were non-small cell lung cancer 65 (38%), breast cancer 24 (14%), and mesothelioma 20 (12%). Resection margins were free in 103 (61%), R1 in 60 (36%), R2 in 4 (2%). Perioperative complications occurred in 67 patients (40%). The 30-days mortality was 4% (n=7). 46 patients (27%) received preoperative chemotherapy, 52 patients (31%) preoperative radiotherapy. The median follow-up time was 21 (range 0-218) months. The median OS was 44 months (95% confidence interval (CI): 33-55 months[SI1]). At the time of last follow-up 71% (n=120) of the patients were recurrent. Local recurrence rate was significantly lower in patients receiving preoperative therapy (16%) compared to patients receiving postoperative therapy (42%) or pre- and postoperative therapy (44%) (p=0.01). In patients receiving a preoperative chemotherapy, a R0 resection was significantly more often achieved (77%) than in patients receiving no preoperative chemotherapy (56%) (p=0.02). Preoperative radiotherapy had no influence on R0 resection (p=0.2). Defect size and resection status had no influence on OS (p=0.4 and p=0.8, respectively). **Conclusion:** Surgical therapy is the cornerstone for the treatment of primary and secondary chest wall malignancies and can be performed with reasonable morbidity. Induction chemo- and/or radiotherapy improves the probability of free resection margin and has positive influence in survival.

Keywords: Multimodal Therapy, Thoracic wall, Reconstruction

P1.15-05 GENOMIC VARIATION LANDSCAPE OF THYMOMA AND THYMIC CARCINOMA IN CHINESE PATIENTS

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Background: Thymoma and thymic carcinoma (TC) are rare diseases of thymus with relatively good prognosis. Though pathological sub-types of thymoma and TC show clear differences on clinical characteristics, morphology, molecular markers, and prognosis, little is known on either the etiology or the molecular mechanism of the two tumor types. **Method:** In this study, 27 thymoma and thymic carcinoma patients with most common thymic epithelial tumor subtypes were enrolled, including 2 type A, 6 type AB, 3 type B1, 1 type B1/B2, 5 type B2, 2 type B2/B3, 5 type B3, and 3 type TC patients in total. The Masaoka stage status of the cohort was 15 stage I, 5 stage II, 3 stage III, and 4 stage IV patients. DNA samples extracted from the frozen tissues were sequenced using a 500-gene NGS panel. **Result:** Forty-seven non-synonymous somatic variants in 38 genes were identified from the sequencing data. The average tumor mutation burden was low (0.83 mut/MB), which was consistent with the previous findings in the TCGA thymic epithelial tumor cohort study (0.48 mut/MB). The KEGG pathway enrichment analysis showed that the function of the mutated genes was closely related to cancer signaling pathways: 15 genes in "pathway in cancer", 9 in "Ras signaling pathway", and 10 in "PI3K-Akt signaling pathway". *GTF2I* L424H mutation was observed in one type A (50% of type A), six type AB (100% of type AB), and four type B (25% of type B) samples. We observed the significantly higher *GTF2I* mutant prevalence on type B samples in our cohort than that in the TCGA cohort (p=0.024). *NF1* and *ATM* were highly mutated genes in our cohort. Three type B samples had *NF1* mutations (D1067V, P1087L, and G1090*). Two type B and one type A samples had *ATM* mutations (S169F, P424H, and R493G). Neither *NF1* nor *ATM* was identified as frequently mutated genes in the TCGA cohort. One *KRAS* (A59del) and one *NRAS* (Q61K) mutations were detected in two type AB samples respectively. No *KIT* or *EGFR* mutation was found. **Conclusion:** This study provided a comprehensive somatic mutation landscape of thymic epithelia tumor in a Chinese cohort. We compared our data to the TCGA cohort, most of which were Caucasian people. We identified higher mutation prevalence of *GTF2I* on type B samples in the Chinese cohort. Moreover, *NF1* and *ATM* mutations were found to be highly mutated in our cohort but not in the TCGA cohort.

Keywords: mutation, thymic epithelial tumor, THYMOMA

P1.15-06 RESECTION OF THORACIC PARAGANGLIOMAS: A MULTICENTER EXPERIENCE

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Background: Paragangliomas are chromaffin cell tumor arising from the sympathetic ganglia. Approximately 2% of paragangliomas occur in the thoracic cavity. Surgical resection is an effective treatment with most cases being curative. Tumor recurrence and long-term prognosis data remain scarce. We described our 14-year experience of complete resections. **Method:** We analyzed surgical characteristics and outcomes from our multicenter cohort of 17 patients with complete paraganglioma resection. We performed a retrospective review from May 2004 to August 2018 across three institutions. Perioperative data were collected using all available medical records from diagnosis to date. Description of baseline demographics, surgical outcomes, complications and survival rates were included in the analysis. Data are reported as mean ± standard deviation (SD) where applicable. **Result:** A total

of 17 patients underwent resection of thoracic paraganglioma. Baseline demographics, operative characteristics and outcomes are presented in Table 1. Mean age at the time of surgery was 46.8 ± 17.2 with ages ranging from 15 to 76 years. Sixty-five percent of patients were male. Eleven patients (64.7%) had the tumor arising from the left atrium, 3 (17.6%) from the mediastinum, 2 (11.8%) from the aorta, and one (5.9%) from both the left and right atria. Eight (47%) patients underwent cardiac autotransplant technique for a better resection approach. Additionally, 2 patients had a concomitant aortic valve and a pulmonic valve replacement, respectively. Complications included tamponade, right ventricular failure requiring RVAD, left ventricular failure requiring IABP, bi-ventricular failure requiring both RVAD and IABP, junctional bradycardia, tracheostomy, and vocal cord paralysis. Recurrence of the tumor presented in three patients (17.6%). One-year, five-year and ten-year survival was 92.3%, 87.5% and 75%, respectively.

Table 1: Results

Total N=17	n (%)
Age (Mean, years)*	46.8 +/- 17.2
Male Gender	11 (64.7)
Race:	
Caucasian	9 (52.9)
African American	7 (41.2)
Hispanic	1 (5.9)
Preoperative Chemotherapy	1 (5.9)
Tumor location:	
Left atrium	11 (64.7)
Left and right atrium	1 (5.9)
Mediastinum	3 (17.6)
Aorta	2 (11.8)
Surgical Procedure:	
Autotransplant	8 (47)
Valve replacement:	
- Aortic	1 (50)
- Pulmonic	1 (50)
Area of Reconstruction:	
Left Atrium	8 (47)
Left and right atrium	2 (11.8)
Right Ventricle and Pulmonary Artery	1 (5.9)
Aorta	1 (5.9)
Left main coronary artery	1 (5.9)
Postoperative Complications:	
Tamponade	2 (11.8)
Right Ventricular Heart Failure (RVAD)	1 (5.9)
Left Ventricular Heart Failure (IABP)	1 (5.9)
Bi-ventricular Heart Failure	1 (5.9)
Junctional Bradycardia	1 (5.9)
Tracheostomy (ventilator dependence)	1 (5.9)
Vocal cord paralysis	1 (5.9)
Postoperative Outcomes:	
Recurrent tumor	3 (17.6)
Deceased	1 (5.9)

Conclusion: Thoracic paragangliomas are rare and surgically challenging tumors due to their anatomical proximity with surrounding structures. Complete surgical excision is the elective treatment. Surgical mortality is reasonable for this complex disease and long-term outcomes are favorable in patients with complete resection.

Keywords: Paraganglionoma, Cardiac tumors, Cardiothoracic surgery

P1.15-07 COMBINED AORTIC ARCH RESECTION FOR THYMIC CANCER USING TOTAL REROUTING OF SUPRA-ARCH VESSELS

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Background: Surgery for aortic arch involvement in thymic cancer cases is challenging, and generally requires provision of extracorporeal circulation with circulatory arrest or use of a cerebral protection technique. With the aim to reduce morbidity, we developed a novel surgical technique that includes total rerouting of supra-arch vessels under a beating heart condition. **Method:** With our technique, the tumor and aortic arch are accessed through a median sternotomy and lateral thoracotomy. The proximal portion of a trifurcation graft is anastomosed to the ascending aorta with a side-clamping technique under a cardiopulmonary bypass, then the 3 distal branches of the graft are sequentially anastomosed to supra-aortic vessels. Next, the ascending aorta distal to the anastomosis of the trifurcated graft and descending aorta are clamped, with perfusion of the heart performed via the femoral and right axillary arteries. Finally, the tumor is resected along with the aortic arch and involved organs, followed by reconstruction of the arch with a tube graft. **Result:** Case 1: A 61-year-old male, diagnosed with cStage III (cT4N0M0) thymic cancer with invasion to the aortic arch, underwent concurrent chemoradiotherapy with carboplatin and paclitaxel, after which complete resection of thymic cancer was performed with total aortic arch replacement and a left lobectomy using our new technique. Operative and CPB times were 738 and 130 minutes, respectively, and blood loss was 4210 ml. The patient was extubated on postoperative day (POD) 1. After an uneventful postoperative course, he was discharged on POD 45 and free of recurrence 8 months later. Case 2: A 45-year-old male diagnosed with cStage IVa (cT4N0M1a) thymic cancer with malignant pericardial effusion underwent chemotherapy with carboplatin and paclitaxel, followed by S-1 administration. Liver dysfunction developed due to chemotherapy and surgery was considered. Thoracoscopic findings ruled out pericardial dissemination, thus complete resection of thymic cancer combined with total aortic arch replacement, a left pneumonectomy, and right pulmonary reconstruction were performed. Operative and CPB times were 958 and 254 minutes, respectively, and blood loss was 7980 ml. Extubation was done on POD 2. After an uneventful postoperative course, the patient was discharged on POD 45 and free of recurrence 2 years later. **Conclusion:** Total arch replacement with total rerouting of the supra-arch vessels under a beating heart condition is effective for thymic cancer patients with aortic involvement. Our novel method has potential to avoid side-effects associated with deep hypothermic circulatory arrest and ischemia-reperfusion injury.

Keywords: thymic cancer, aortic arch resection, surgical technique

P1.15-08 OUTCOMES OF T4 ESOPHAGEAL CANCER TREATED WITH NEOADJUVANT CHEMORADIATION FOLLOWED BY SURGERY AND DEFINITIVE CHEMORADIATION: A META-ANALYSIS

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Background: The optimal treatment approach for T4 esophageal squamous cell carcinoma (SCC) is not well-established. We aim to perform a meta-analysis to determine the outcomes of T4 esophageal SCC treated with two approaches: neoadjuvant chemoradiation followed by surgery (NCRT-S) and definitive chemoradiation (DCRT). **Method:** We searched databases for eligible studies. Studies that evaluated the outcomes of patients with T4 any N M0 esophageal SCC treated with NCRT-S or DCRT were included. Our study outcomes of interests were overall survival (OS), rates of fistula formation and treatment-related death. The pooled estimates of outcomes were calculated using the logistic-normal random effects model. The differences in outcomes between the two treatment groups were examined using the Chi Square test. **Result:** Four prospective and fourteen retrospective studies including 875 patients were identified. The pooled estimates of 1-, 2-, 3-, 4- and 5-year OS were 61% (95% confidence interval (CI), 48%-72%), 38% (95% CI, 26%-51%), 31% (95% CI, 22%-42%), 26% (95% CI, 16%-39%) and 23% (95% CI, 15%-33%) for NCRT-S group and 40% (95% CI, 33%-47%), 23% (95% CI, 15%-32%),

17% (95% CI, 10%-27%), 16% (95% CI, 8%-30%) and 14% (95% CI, 7%-24%) for DCRT group, respectively. The OS of patients treated with NCRT-S were significantly improved compared with those treated with DCRT at 1 year (P= 0.004) and 3 years (P= 0.035). The rate of fistula formation was lower in NCRT-S group compared with DCRT (4% (95% CI, 1%-14%) versus (vs) 12% (95% CI, 7%-19%); P = 0.06). The rates of treatment-related death were similar between NCRT-S and DCRT groups (3% (95% CI, 1%-6%) vs 3% (95% CI, 1%-9%); P= 0.891). **Conclusion:** NCRT-S was associated with improved OS and lower fistula rate in the treatment of T4 esophageal SCC compared with DCRT. The rates of treatment-related death were similarly low in both groups. Randomized controlled trials are warranted to confirm these findings.

Keywords: T4 esophageal cancer, chemoradiation, surgery

P1.15-09 THE IMPACT OF MINIMAL INVASIVE ESOPHAGECTOMY AND NEOADJUVANT CHEMORADIOTHERAPY FOR ESOPHAGEAL MALIGNANCY: A NATIONWIDE DATABASE ANALYSIS

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Background: Squamous cell carcinoma is the predominant histologic subtype of esophageal cancer in Asia pacific. Radical surgery provides the most realistic chance of cure from cancer of the esophagus. Multimodality treatment, including radiotherapy, chemotherapy and surgery is superior to surgery alone for patients with resectable adenocarcinoma of the esophagus. Recent advances in thoracoscopic surgery have made it possible to perform esophagectomy via minimal invasive surgery. The objective of this study was to evaluate the survival of esophageal squamous malignancy, received minimally invasive esophagectomy, with or without neoadjuvant chemoradiotherapy. **Method:** From 2010 to 2016, all patients received esophagectomy for esophageal malignancy, in Taiwan, were enrolled into this study. The demographic and outcome data for these patients were retrospectively examined. Logistic regression analysis was used to identify the factors associated with survival. **Result:** Total 3957 patients received esophagectomy, 2946 of these were performed by minimal invasive method. About 56.8% patients received neoadjuvant chemoradiotherapy. The overall five years survival of all stage patients was 35.9%. The patients, who received minimal invasive esophagectomy, had better five years survival of 37.7%. Stage III patients treated with or without adjuvant chemoradiotherapy, the five years survival was 29.2 and 31.8%. Stage IV patients treated with or without adjuvant chemoradiotherapy, the five years survival was 8.8 and 13.4%. **Conclusion:** Minimal invasive esophagectomy had better survival in stage I/II patients. Better survival was also noted in stage III/IV patients, when neoadjuvant chemoradiotherapy was applied.

Keywords: esophagectomy, chemoradiotherapy, Esophagus

P1.15-10 TRABECTEDIN HAS LIMITED CLINICAL ACTIVITY IN PRETREATED PATIENTS WITH PLEURAL MESOTHELIOMA

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Background: In mesothelioma, chemotherapy with pemetrexed is effective but after progression the options of treatment have limited efficacy. Tumor associated macrophages are necessary for the growth of mesothelial tumors. Trabectedin is a tetrahydroisoquinoline alkaloid used for the treatment of sarcomas and ovarian cancer. Trabectedin interacts with the DNA double helix and interfere with the binding of transcription factors and polymerases, reprogramming gene expression in cancer and microenvironment cells. Therefore, we evaluated the effect of trabectedin in patients with mesothelioma after progression to standard treatments. **Method:** We retrospectively identified 9 patients treated with trabectedin between 2017 and 2019. A continuous infusion of 1.5 mg/m^2 of trabectedin was administrated in 24h every 21 days. According to RECIST criteria, overall survival (OS) and progression free survival (PFS) were calculated using Kaplan-Meier estimation. **Result:** Seven of the 9 patients were male. The median age was 64 years (range 44-77). There were 6 epithelioid, 1 sarcomatoid and 2 biphasic mesotheliomas. The stage at diagnosis was III in 3 patients and IVB in 6 patients. Pleurectomy/decortication was performed in 5 patients, 4 patients received biopsy. The number of previous lines of chemotherapy was 1 in 4 patients, 2 in 2 subjects and 3 in 3 remaining. The median number of cycles was 3 (range 1-6). A grade 2 increase of transaminase was observed in 1 patient and a patient developed an atrial flutter with an heartrate of 180 during treatment. Two patients experienced G3 fatigue and fever. There were not G3-4 hematological toxicities but a G3 increase of creatine kinase was observed in 1 patient. Seven patients experienced a disease progression with a median PFS of 1.8 months (95%CI 1.55-2.05). The median OS was 5 months (95%CI 2.42-7.57). There were not significant differences in PFS and OS in relation to age, histology, sex, performance status, across patients treated with one or more lines of chemotherapy and between those who received pleurectomy **Conclusion:** Trabectedin in pre-treated mesothelioma patients is feasible with a moderate toxicity but there is no meaningful clinical activity for this agent according to the previous report of ATREUS trial.

Keywords: Trabectedin, pre-treated, Mesothelioma

P1.15-11 INTRATHORACIC NEUROGENIC TUMORS: CLINICAL, PATHOLOGICAL, AND LONG-TERM OUTCOMES

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Background: Intrathoracic neurogenic tumors are uncommon neoplasms arising from nerve tissues. We report our single-center experience in treating this rare intrathoracic neurogenic tumors. **Method:** We retrospectively analyzed the clinical, surgical and pathological records of patients receiving the resection of an intrathoracic neurogenic tumor between May 1998 and December 2018. **Result:** There were 82 patients (24 females) with an average age of 53 years (29 to 75 years). Mean diameter was 32 mm, ranging from 12 mm to 68 mm. Histology included 42 benign schwannomas, 7 malignant schwannomas, 15 neurinomas, 14 neurilemmomas, and 4 paragangliomas. 55 were located in the posterior mediastinum, 13 in the thoracic inlet, 7 in the anterior mediastinum, 4 in the lung parenchyma, and 3 in the chest wall. Symptoms were seen in 51 patients (62.2%) and including cough in 23, dyspnea in 15, neurologic symptoms in 11, and wheezing in 2. In 3 patients (3.6%), the tumor showed an intraspinal extension. Tumor resection was made by thoracotomy in 42 (51.2%) cases and thoracoscopy in 40 (48.8%). Resection was complete in 80 patients (97.6%). Postoperative radiotherapy was administerd in 2 cases. Mortality was nil. Morbidity rate occurred in 4 patients (4.8%) and included 2 prolonged air leaks, 1 hemothorax, and 1 chylothorax. Five-year survival was 97% in an average follow-up of 4.9 years. No recurrence occurred during the follow-up period neither for malignant nor for benign tumors. **Conclusion:** The treatment of choice for thoracic neurogenic tumors is complete resection. Long-term prognosis is favorable both for malignant and benign neurogenic tumors.

Keywords: mediastinum, neurogenic tumors

P1.15-12 A DIFFERENT ASPECT TO TUMOR SIZE DILEMMA IN THYMOMA'S TNM STAGING CLASSIFICATION

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Background: Thymic epithelial tumors including thymomas are relatively rare thoracic neoplasms; though thymomas are the most common tumors of anterior mediastinum in adults. Among the TNM classifications of many solid tumors, tumor size is included in definition of T descriptor and as a key for staging it plays an important role in predicting prognosis and affects clinical decision making. However, TNM or the other classifications of thymomas do not take tumor size into consideration. **Method:** Between 2004 and 2018, 204 consecutive patients with thymic epithelial tumors underwent surgical resection in Department of Thoracic Surgery, Ankara University Medical School. One hundred and forty-three patients with thymoma were included in the study. When survival analysis

was performed, sixteen cases were excluded due to missing datas of either survival and/or tumor diameter. Remaining 127 patients were classified into two groups: a. largest tumor diameter (LTD), b. mean tumor diameter (largest diameter+shortest diameter/2) (MTD). Then each were divided into three subgroups (LTDa/ MTDa ≤5cm; LTDb/ MTDb 5.1-10 cm; LTDc/ MTDc >10 cm). LTDa, LTDb and LTDc subgroups contained 47 (37%), 60 (47.3%) and 20 (15.7%) patients; while MTDa, MTDb and MTDc subgroups had 66 (52%), 56 (44.1%) and 5 (3.9%) patients respectively. **Result:** There were 78 males and 65 females, with a mean age of 49.6 years (10-78). Results of the survival analysis according LTD and MTD subgroups are shown in Table 1. In survival analysis, there were significant differences in the presence of MG, resection status (R0 vs R1), T status and the Masaoka-Koga staging (p=0.018, p=0.001, p=0.015, p = 0.003), respectively. In survival analysis for MTD subgroups, survival decreased as the tumour size increased. In LTD group, the only difference which was close to statistical significance was in R0 group for 10 years OS (p=0.051). Table 1: 10-year survival according to tumor diameter groups

	Largest Tumor Diameter (LTD)			Mean Tumor Diameter* (MTD)		
	≤5cm	5.1-10cm	p value	≤5cm	5.1-10cm	p value
10 years overall survival (%) (LTD:107 (48/59) patients, MTD:122 (66/56))	87.6	80	0.246	91.2	74.8	0.088
10 years disease-free survival (%) (LTD:94 (40/54) patients, MTD:107 (56/51))	75.5	56.5	0.113	82.6	41.9	0.052
10 years overall survival in R0 resection (%) (LTD:91 (37/54) patients, MTD:104 (53/51))	95.2	81.1	0.051	96.8	75.9	0.027
10 years disease-free survival in R0 resection (%) (LTD:82 (34/48) patients, MTD:93 (48/45))	75.2	57.7	0.159	82.4	43.1	0.095

Conclusion: In this study, complete resection was the most powerful prognostic factor for thymoma as reported by Ruffini et al. Though complet resection is associated with better survival, tumor size is an essential factor on decision of complete resection. Therefore, the largest or mean tumor size should be a criterion in the thymoma TNM staging system.

Keywords: Size, staging, THYMOMA

P1.15-13 SUBXIPHOID UNIPORTAL THORACOSCOPIC THYMECTOMY WITHOUT CARBON DIOXIDE INSUFFLATION IN THE PATIENTS WITH THYMOMA

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Background: Thymectomy is the most important treatment for anterior mediastinal mass and myasthenia gravis. Until now, different surgical approaches have been described to perform thymectomy, from median sternotomy to robotic thymectomy. But there is no consensus on the best approach of thymectomy. Depending on approach to perform thymectomy, the advantages and disadvantages are different. Currently, the lateral intercostal approach in video-assisted thoracoscopic surgery thymectomy (VATS thymectomy) is the most frequently performed surgical approach for thymectomy. But this approach has difficulty to identify the contralateral phrenic nerve and intercostal nerve impairment. Recently, to overcome shortcomings of VATS thymectomy, subxiphoid single-port thymectomy (SPT) was introduced. We have performed modified subxiphoid SPT using our own manufacturing sternal retractor without carbon dioxide insufflation under one-lung ventilation. We report the initial operative results of modified subxiphoid SPT. **Method:** Subjects of this study were patients who underwent thymectomy or extended thymectomy at Inje University Haeundae Paik Hospital between July 2016 and November 2018. We reviewed the medical records of these patients retrospectively. Indication of thymectomy is anterior mediastinal mass without tumor invasion. In our department, we performed thymectomy for anterior mediastinal mass in the absence of myasthenia gravis. And extended thymectomy, which involves the removal of all adipose tissue involve anterior to the phrenic nerve, was performed for myasthenia gravis. Subxiphoid uniportal thoracoscopic thymectomy was attempted first in July 2016. From this time, thymectomy for anterior mediastinal mass or extended thymectomy for MG were preformed via SPT with sternal retraction. All surgical procedures were performed by a single surgeon. 29 patients who underwent thymectomy or extended thymectomy were enrolled. Information of patient demographics, intraoperative, postoperative data were collected and retrospectively evaluated. **Result:** The patient's demographics and results of operative outcome of subxiphoid SPT are presented in table 1.

Table 1

	Thymectomy	Extended thymectomy
No. of patients	21	8
Age (years)	55.23±13.04	44.62±16.47
Sex (male/female)	10/11	3/5
BMI	24.72±3.60	24.87±3.57
Mass size(cm)	3.85±1.73	2.13±0.38
Operative time (min)	143.57±51.96	184.38±43.30
Blood loss in operation(ml)	246.90±262.76	183.75±147.45
Drain after operation(ml)	488.67±308.05	1506.13±1203.80
Duration of chest tube(day)	2.81±1.12	5.00±2.39
HD after operation (day)	6.05±2.87	8.38±2.39
Conversion to other approach	3	0

Conclusion: The benefit of subxipohid approach with sternal retraction is that it makes it easier to identify the contra-lateral phrenic nerve. Also, our procedure has 3 advantages when compared with carbon dioxide insufflation subxiphoid single-port thymectomy. First, because we do not insufflate carbon dioxide, there is no need to worry about hypotension. Second, we do not use air tight trocar, so we use more instruments and have more flexibility in them. Finally, sternum retraction provides more optimal space for the surgery. Single-port thymectomy through the subxiphoidal incision using sternal retractor under one-lung ventilation without carbon dioxide insufflation was feasible.

Keywords: THYMOMA, Subxiphoidal incision, Without CO2 insufflation

P1.16 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.16-01 COMPLICATIONS ASSOCIATED WITH LUNG BIOPSIES IN PATIENTS WITH LUNG CANCER: A POPULATION BASED ANALYSIS

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Background: The discovery of molecular biomarkers that guide management of lung cancer has led to increasing frequency and amounts of tissue required for repeat lung biopsies.This has coincided with increased emphasis on patient safety and reporting on adverse events over the past two decades. The safety of repeat lung biopsies in patients with lung cancer has only been studied in small cohorts. We analyzed hospital-acquired adverse events for patients with lung cancer undergoing lung biopsies in the National Hospital Discharge Survey (NHDS) database from 2001- 2010. **Method:** NHDS collects clinical information on patients discharged from non-Federal short-stay United States hospitals. Demographics, diagnoses, procedures, and mortality data were extracted using ICD-9 codes. The Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicators (PSIs) were utilized to identify hospital-acquired adverse events. Weighted analyses were performed using SAS version 9.4. **Result:** An estimated 540,747 patients with lung cancer underwent lung biopsy during the study period and were included in the analysis; 61% were >65 years, 46% female, 65% white. Biopsy approaches included bronchoscopic (60%), percutaneous (33%), and surgical (7%). The number of lung biopsies increased over the study period, from 51,221 in 2001, to 63,239 in 2010 (P<0.001). Overall, 159,683 (30%) patients suffered ≥1-PSI event during their hospitalization, including an 11% incidence of pneumothorax. Incidence of PSI varied by biopsy type: bronchoscopic (26%), percutaneous (34%), surgical (39%). The proportion of patients experiencing ≥1 PSI event increased from 24% in 2001, to 38% in 2010 (P<0.001). Patients with ≥1 PSI experienced higher in-hospital mortality (14.5% vs 3.2%, adjusted odds ratio, 5.9, 95% CI 3.9 – 8.9; P<0.001), and prolonged length-of-stay (11.6 vs 8.1 days; P<0.001). **Conclusion:** The frequency of lung biopsies performed in lung cancer patients has increased in recent years, as has the rate of documented complications in this selected inpatient cohort. The increased rate of complications may be due to increased attention to and reporting of adverse events in this era focusing on patient safety, which has implications for policy makers and funding authorities. Investigators, sponsors, patients and regulatory authorities should be aware of the risks associated with repeat biopsies as they design, oversee, and analyze clinical trials. Non-invasive assessment of tumor biology, such as cell-free DNA, may help mitigate these risks.

Keyword: patient safety indicator

P1.16-02 THE REAL-WORLD RISK OF BRAIN METASTASES IN STAGE 3 LUNG CANCER PATIENTS IN THE ERA OF PET AND MRI STAGING

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Background: Brain metastases (BMs) are a common site of recurrence in Stage 3 NSCLC following definitive chemoradiation. In small-cell lung cancer, prophylactic cranial irradiation (PCI) was historically offered to improve overall survival (OS). Studies of PCI in NSCLC failed to show OS benefit; many were based on a 30% 2-year risk of CNS metastases, using data from the era prior to routine brain imaging at staging. An increasing preference for stereotactic radiosurgery(SRS) over WBRT for BMs may also affect outcomes. The purpose of this study was to review surveillance, incidence, and treatment patterns of BMs in patients with stage 3 NSCLC at our institution. **Method:** In this IRB approved study, we retrospectively reviewed stage 3A/3B NSCLC patients treated at Stanford from 2008-2018. Of 279 patients, 163 received radiation with curative intent, and had complete data regarding pathology, staging, imaging, radiation and follow-up. **Result:** Ninety-seven patients had adenocarcinoma, 54 squamous, and12 other histology (usually large-cell neuro-endocrine). Two patients received PCI; neither developed BMs. For all patients, median survival was 50 months (95%CI:30, 61). Patients with adenocarcinoma had significantly longer survival than squamous (53 v. 24 months, p=0.0119). 37 patients (22.7%) developed BMs, with 2-year cumulative incidence of 17.1% (95%CI:11.6%, 23.5%). Patients with adenocarcinoma had higher cumulative incidence of BM at 2 years, 21.9%, versus squamous 7.9%, and other histology 21.7%(p=0.0295). Of 37 BM patients, 18 presented with one BM, 8 with 2-3, and 11 had >3 BMs. Seventeen patients had asymptomatic BMs discovered at re-staging for systemic recurrence, 3 patients had asymptomatic BMs on surveillance MRI, 14 had BMs on MRI ordered for neurologic symptoms, 3 had symptoms and pre-scheduled surveillance MRI confirmed BM. Twenty-nine patients received SRS for first BM, 3 received WBRT, 5 had no treatment. Time from first BM to death was not different between adeno and squamous histology (21.0 v. 16.5 months, p=0.6050) or symptomatic v. asymptomatic BMs (18 v. 21 months, p=0.8273). **Conclusion:** Patients with stage 3A/3B NSCLC treated at our institution have a lower 2-year incidence of BMs than historically reported, but higher than recently reported in the PACIFIC study (11.8%, 25-month median follow-up). Suspicion for BM should remain high in this population. Our experience suggests imaging at the time of systemic recurrence or neurologic symptoms may capture the majority of brain metastases. Routine surveillance MRI may capture more asymptomatic metastasis, though impact on overall survival remains unclear.

Keywords: Brain metastases, Stage 3 NSCLC, surveillance MRI

P1.16-03 INCIDENCE AND RISK FACTORS OF METACHRONOUS NON-PULMONARY MALIGNANCIES IN RESECTED LUNG ADENOCARCINOMA

P. Kneuertz[1], D. D'Souza[1], M. Richardson[1], M. Abdel-Rasoul[2], S. Moffatt-Bruce[1], R. Merritt[1]

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Background: Patients with non-small cell lung cancers have an increased risk of developing second primary lung cancers (SPLC). However, little is known about the development of non-pulmonary cancers (NPC) in patients with long-term survival after complete resection. We analyzed our experience with resected lung adenocarcinoma patients to assess the incidence and factors associated with metachronous malignancies. **Method:** Surveillance records of 326 patients with primary lung adenocarcinoma who underwent complete staging followed by lobectomy between 2011-2017 at a single center were reviewed. Median follow-up time was 42 months. Metachronous NPCs were distinguished from distant metastases by pathologic correlation of histology and immunohistochemistry. The association of patient/tumor factors and mutation status with NPC was assessed. **Result:** The cohort included 275 (84.4%) smokers, and 51 (15.6%) never smokers, with a median age of 65 years. The majority of patients were pathologic stage-I (72.4%) or stage-II (19.6%). KRAS (38%) and EGFR (17.8%) were the most commonly observed mutations. Metachronous NPC were detected in 30 patients (9.2%) and SPLC in 13 patients (4%), after a median interval of 14 months [IQR: 6.8–44] and 36 months [IQR: 27–60], respectively. Highest incidence of NPCs was seen in patients having EGFR tumor mutations (EGFR+ 17.2% vs. EGFR- 7.5%, p=0.020) and former smokers (former smokers 14.8% vs. never smokers 7.8% vs. active smokers 3.8%, p=0.005). Metachronous breast and GI cancers were frequently seen in patients with EGFR+ lung cancers (Table). Controlling for age, gender, and smoking status, EGFR mutation in resected lung adenocarcinoma was associated with 2.6 times greater odds (95% CI: 1.1-6.3, p=0.028) of metachronous NPC.

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Metachronous Non-pulmonary Cancers (NPC) in Resected Lung Adenocarcinoma based on EGFR Mutation Status		
NPC Type	EGFR Positive (N=58)	EGFR Negative (N=268)
Brain	0 (0%)	2 (0.8%)
Head/Neck		
Laryngeal	0 (0%)	1 (0.4%)
Thyroid	0 (0 %)	1 (0.4%)
Breast	4 (6.9%)	5 (1.9%)
GI		
Anal	2 (3.5%)	0 (0.0%)
Colorectal	1 (1.7%)	3 (1.1%)
Hepatocellular Carcinoma	1 (1.7%	1 (0.4%)
GU		
Bladder	0 (0%)	2 (0.8%)
Prostate	0 (0%)	1 (0.4%)
Renal Cell	0 (0 %)	1 (0.4%)
Skin/Soft Tissue Sarcoma		
Skin	1 (1.7%)	2 (0.8%)
Leiomyosarcoma	1 (1.7%)	0 (0.0%)
Liposarcoma	0 (0%)	1 (0.4%)
Total*	10 (17.2%)	20 (7.5%)
*P-value comparing incidence of any NPC's between EGFR groups = 0.020		

Conclusion: Metachronous non-pulmonary malignancies can be frequently detected in patients during active surveillance of resected lung adenocarcinoma. Besides smoking as a known risk factor, patients with EGFR mutated tumors may be at particular risk. Germline mutations of EGFR positive lung adenocarcinoma patients should be further explored.

Keywords: Second Primary, Other Malignancy, EGFR

P1.16-04 REAL WORLD EXPERIENCE OF USING COMPREHENSIVE GENOMIC PROFILING OF PLASMA CIRCULATING TUMOR DNA

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[1]*Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Henan/China,* [2]*University of California Davis Comprehensive Cancer Center, Sacramento/United States of America,* [3]*Foundation Medicine, Cambridge/United States of America,* [4]*University of California Davis, Department of Public Health Sciences, Davis/United States of America,* [5]*University of California Davis Department of Pathology, Sacramento/United States of America*

Background: The clinical application of molecular biomarker assays has revolutionized cancer diagnosis and treatment, enabling the current era of precision lung cancer care. Increasingly, comprehensive genomic profiling (CGP) by next generation sequencing has been used in the clinic. We here summarize our initial experience in using tissue- and blood-based tumor genomic profiling assays. **Method:** This retrospective chart review included consecutive cases from patients with locally advanced or metastatic lung cancer seen at an academic institution between January 2014 and March 2019. A total of 596 archival tumor specimens and 128 blood samples were subjected to tissue- and plasma-based, hybrid capture-based next generation sequencing assays, respectively. Maximum somatic allele frequency (MSAF) was used to quantify the fraction of circulating tumor DNA in the plasma cell free DNA. Survival was calculated by the Kaplan-Meier method. **Result:** We found that plasma cell free DNA (cfDNA) assay significantly reduced the sample acquisition time and test failure rate (Table below). All patients who failed tissue assay due to insufficient tissue or DNA and were willing to undergo liquid biopsy had a successful test result. Reasons for 38 patients who had liquid biopsy only are summarized below. In 117 (19.6%) identified patients with either EGFR-mutant or ALK-rearranged NSCLC tumors, median survival has improved compared to those patients diagnosed before 2014 (N=103) (48.9 vs 30.0 months, hazard ratio 0.43, 95% CI 0.31-0.60; p<0.0001). Furthermore, plasma ctDNA CGP identified suspicious germline mutations in ~16% cases.

Specimen Type	Tumor	Plasma cfDNA	P value
Genomic Assay	FoundationOne or CDx	F-ACT or FoundationOne Liquid	
All cases	596	128	
Sample acquisition time (mean with 95% CI; days)	9.9 (8.79-10.95)	1.3 (0.17-2.49)	<0.0001
Test time (mean with 95% CI; days)	13.0 (12.55-13.53)	14.7 (13.24-16.15)	<0.01
Total test time (mean with 95% CI; days)	22.9 (21.66-24.07)	16.0 (14.19-17.85)	<0.0001
No. (%) Failure cases	114 (19.1%)	4 (3.1%)	
Reasons for liquid biopsy only:		N=38	
Tissue insufficient		11 (29%)	
Resistance evaluation		10 (26%)	
No record		6 (18%)	
Limited panel		7 (16%)	
Refused biopsy or too ill		4 (11%)	

Conclusion: In our experience, the adoption of CGP with subsequent, effective targeted therapy has shown improved median survival in patients with NSCLC. CGP of plasma ctDNA is particularly useful when patients have insufficient tumor specimens and can unveil germline mutations which need further confirmation. A prospective concordance study is planned to compare the FoundationOne CDx and FoundationOne Liquid in patients with advanced NSCLC.

Keywords: circulating tumor DNA, NSCLC, genomic profiling

P1.16-05 INCIDENCE AND OUTCOME OF MULTIPLE PRIMARY CANCERS (MPC) IN A SERIES OF LUNG CANCER (LC) PATIENTS

S. Cedres, A. Hernando-Calvo, P. Iranzo, A. Callejo, N. Pardo Aranda, A. Navarro, A. Martinez-Marti, J.D. Assaf, J.M. Miquel, G. Rodriguez, V. Monton, A. Pedrola, C. Viaplana, C. Carbonell, M. Sanso, R. Dienstmann, R. Amat, A. Vivancos, E. Felip

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Background: The number of cancer survivors has increased as a result of significant progress in prevention, diagnosis and treatment of malignant tumors. The risk of developing a second neoplasm, after treatment of an initial primary cancer, is increasing and indeed lung cancer represents a commonly diagnosed second primary malignancy. This study investigates the co-occurrence of MPC among patients (p) diagnosed with lung cancer (LC). **Method:** Review of clinical data of all consecutive patients with histologically confirmed LC visited at our institution between October 2017 and August 2018 **Result:** Out of 1386 p with LC, two primary cancers occurred in 206 cases (15%), including 41 p (3%) with three primary cancers. Patients with MPC were predominantly males (67%), smokers (88%), statin users (40%) and 28% had known family history. Second cancer was detected in a routine follow-up in 62%, whereas 27% were symptomatic patients. Median age at the first tumor diagnosis was 61 years (27-85). LC occurred as first neoplasm in 34% of the cases, as subsequent neoplasm in 41% and as two consecutive primary

neoplasm in 25%. The most common primary cancer was LC in 34%, followed by breast (16%), colorectal (15%), prostate (9%), bladder (8%) and head and neck (6%). Treatment received for the first cancer included surgery in 80%, chemotherapy in 47% and radiotherapy in 32%. As a second tumor LC represented 41%, followed by bladder (19%), colorectal (10%), prostate (9%) and breast (7%). Surgery was performed in 70% of the cases with a second cancer. Regarding only patients with LC as two primary tumours (first and second tumour), 25 pts (89%) were not metastatic at second tumour, surgery was performed in 82% and 7 pts (24%) developed a third tumour. Overall, median time of diagnosis between the first and the second neoplasm was 4.2 years (CI95% 3.2-5.2), without significant differences if primary tumor was LC or another neoplasm (p=0.82). Smoking was associated with a shorter time of the second neoplasm diagnosis (3.8 years vs 7.9 years for non-smokers, p=0.09), whereas taking statins exhibited longer time of diagnosis of the second neoplasm (5.1 vs 3.3 year, p=0.05). With a median follow up of 7.3 years after diagnosis of the first neoplasm, the 5-year survival rate was 97.2% (94.8-99.7%). **Conclusion:** In our series, the frequency of the MPC co-occurrence among LC p is 15%, indicating that surveillance strategies are recommended. Many p are treated with curative intent. Moreover, smoking and taking statins influences the time interval between tumors

Keywords: cancer survivor, multiple primary cancer, Lung cancer

P1.16-06 EARLY CHANGES IN PULMONARY FUNCTION ARE ASSOCIATED WITH DEVELOPMENT OF PNEUMONITIS IN NSCLC PATIENTS RECEIVING IMMUNE CHECKPOINT BLOCKADE

J. Reuss, K. Suresh, K. Psoter, P. Forde, J. Naidoo

Johns Hopkins University School of Medicine, Baltimore/United States of America

Background: Checkpoint inhibitor pneumonitis (CIP) is an immune-related adverse event of immune checkpoint inhibitors (ICI). Pulmonary function test (PFT) changes have been noted in patients receiving drugs such as bleomycin, and PFTs are routinely used to monitor for lung toxicity in such patients. We retrospectively analyzed PFTs in ICI-treated non-small cell lung cancer (NSCLC) patients to identify PFT changes associated with ICI use, and determine whether CIP modified this association. **Method:** The study cohort included NSCLC patients who were treated with PD-(L)1 ICI as standard-of-care or part of a clinical trial at Johns Hopkins from 1/2007 - 7/2017 and had ≥1 PFT in the year preceding and/or following ICI initiation. The primary outcomes of interest were forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. Linear regression based on generalized estimating equations (GEE) was used to evaluate changes overall and by CIP status (CIP+: Patients who develop CIP, CIP-: Patients who do not develop CIP). **Result:** A total of 58 patients (43 CIP-, 15 CIP+) were included. Median age was 66y and 96% of patients were current/former smokers. 52% had adenocarcinoma and 45% had squamous histology. 75% had stage III/IV disease at initial diagnosis. Patients received single agent PD-(L)1 ICI (77%), ipilimumab+nivolumab (ipi/nivo) (12%), and novel PD-(L)1 ICI (10%). Compared to CIP- patients, CIP+ patients were more likely to have squamous histology (67% vs. 34%) and receive ipi/nivo (27% vs 7%). In the overall study cohort, ICI initiation was associated with a 0.335L reduction in FEV1 (95% CI: -0.713, 0.042), 0.747L reduction in FVC (-1.21, -0.28), and 0.061 increase in FEV1/FVC (0.006, 0.116) consistent with restrictive lung physiology. Compared to CIP- patients, CIP+ patients had a 0.35L (-0.724, 0.013) lower FEV1 and 0.516L (-1.06, 0.02) lower FVC, while FEV1/FVC did not differ (-0.07, 0.07). The rate of change of FEV1/FVC over time was significantly higher among patients with vs without CIP (p<0.05). **Conclusion:** Our data suggest that initiation of PD-(L)1 ICI is associated with progressively restrictive lung function changes on PFTs (increased FEV1/FVC) irrespective of CIP development. Furthermore, our results indicate that patients who eventually develop CIP may have an altered respiratory physiology prior to ICI initiation, with longitudinal changes in lung function that differ when compared to CIP- patients who receive checkpoint blockade. To further characterize PFT changes associated with CIP, a prospective study assessing serial PFTs in NSCLC patients receiving ICIs is underway.

Keywords: Non-Small Cell Lung Cancer, Pulmonary Function Tests (PFTs), pneumonitis

P1.16-07 REAL WORLD EVIDENCE OF THE IMPACT OF IMMUNOTHERAPY IN PATIENTS WITH ADVANCED LUNG CANCER

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Background: PD-1 axis inhibitors have become a standard treatment modality in the management of advanced lung cancer. Novel Natural Language Processing (NLP) and Artificial Intelligence (AI) technology enables automated extraction of real-world data at greater scale than current manual chart abstraction processes, which can be used to further explore the impact of these agents in the general population irrespective of PDL1 tumour expression. **Method:** Patients diagnosed with stage IIIB/IV lung cancer at the Princess Margaret Cancer Centre between 2015 and 2018 were reviewed using the DARWEN™ NLP and AI data abstraction platform developed by Pentavere. Data extracted include patient age, smoking status, ECOG performance status, tumour histology, biomarker status, PDL1 expression, sites of metastases, treatment information and survival. **Result:** Of 615 patients with accessible electronic pathology records, 540 (87.8%) had NSCLC and 280 (51.8%) of those received systemic therapy and were included in the analysis. 86 (30.7%) were EGFR sensitizing mutation positive, 18 (6.4%) ALK rearranged, PDL1>50%/1-49/<1/unknown in 21/8/10/61%. Almost one third (31.7%) of those that received treatment received immunotherapy for any line of therapy (12.1% first-line). Chemotherapy was used first-line in 56.1% and targeted therapy in 36.1% of those receiving systemic therapy Patients that were more likely to receive immunotherapy any line were smokers (OR: 2.7, 95% CI: 1.43-5.10, p=0.002) with a higher number of metastatic sites (OR: 1.23, 95% CI: 1.06-1.43, p=0.005). Those with EGFR sensitizing mutation and ALK rearrangement were less likely to be given immunotherapy (OR: 0.07, 95% CI: 0.03-0.19, p<0.001 and OR: 0.11, 95% CI: 0.01-0.84, p=0.03 respectively). There was no difference in the rates of immunotherapy being given in those with PDL1>50%/1-49/<1 (52/52/44%, p=0.8). Using Cox regression analyses after controlling for ALK, EGFR, PD-L1, age, sex, baseline ECOG, smoking status and number of metastatic sites, patients that received immunotherapy at any point had longer survival (HR: 0.28, 95%CI: 0.12-0.67, p=0.004) in a complete case analysis. **Conclusion:** Novel NLP and AI technologies like DARWEN™ gives clinicians access to previously unavailable information on real world treatment strategies and outcomes. Increasing uptake of immunotherapy may further improve outcomes for patients with this challenging to treat cancer. This study demonstrates that the benefit of immunotherapy seen in clinical trials can be translated into the general advanced lung cancer population. Larger population studies will be needed to further analyze the impact of new treatments in the real world and will be facilitated by automated data abstraction to rapidly generate large datasets.

Keywords: Real world evidence, immune therapy, Artificial Intelligence

P1.16-08 INTEGRATION OF DURVALUMAB INTO THE TREATMENT OF STAGE III NON-SMALL CELL LUNG CANCER: REAL-WORLD CONSIDERATIONS

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Background: In 2017, the PACIFIC study demonstrated improvement in progression free survival, leading to FDA approval for the treatment of unresectable stage III non-small cell lung cancer (NSCLC) that has not progressed following concurrent platinum based chemoradiation (CRT). This study reports on practice patterns during the first year of adaptation of immunotherapy into the treatment paradigm for stage III NSCLC at a NCI designated Comprehensive Cancer Center. **Method:** This retrospective study captured patients (pts) with unresectable NSCLC treated from 09/2017-10/2018 who referred to radiation oncology for definitive treatment. Clinical and treatment characteristics were extracted, including radiation dose parameters and information regarding durvalumab administration. **Result:** 48 pts with locally advanced NSCLC were referred for definitive

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radiation therapy. 17% were not eligible for concurrent CRT: of these, 6 received 60 Gy hypofractionated radiation alone, and 2 received 60-64 Gy with conventional fractionation. Forty (83%) received concurrent CRT (80% carboplatin/paclitaxel, 10% cisplatin/etoposide, 10% platinum/pemetrexed). Of the patients undergoing CRT, 32% did not go on to receive durvalumab due to the following factors: 25% due to unresolved grade 3 or higher toxicities, 25% due to relative contraindications to immunotherapy, 17% were lost to follow up, 8% due to disease progression, 8% due to active illicit drug use, 8% due to large tumor and potential risk for pneumonitis, and 8% received nivolumab. Twenty-seven (68% of pts receiving CRT, 56% of all referred pts) went on to receive durvalumab after completion of CRT. For these pts, the radiation dose parameters were as follows: median total dose of 60 Gy (range 60-66 Gy), median lung V20 of 22.7% (range 5.4-31.5%), median lung mean dose of 13.9 Gy (range 5.3-19.5 Gy), and median heart mean dose of 12.9 Gy (range .715 – 29.9 Gy). The median time from completion of radiation to start of durvalumab was 36 days (range 11-84). Restaging imaging with CT chest after completion of CRT was obtained at a median time point of 35 days. The median number of cycles of durvalumab was 5 (range 1-20). Of pts receiving durvalumab, 37% stopped before 1 year; 40% due to disease progression, 50% due to intolerable side effects, and 10% were lost to follow up. **Conclusion:** Conclusions: Durvalumab was successfully integrated in a rapid fashion into the treatment paradigm for stage III NSCLC in this single institution experience, however only 56% of referred pts were ultimately able to receive durvalumab.

Keywords: Clinical, durvalumab, NSCLC

P1.16-09 POST-PROGRESSION OUTCOMES AFTER PEMBROLIZUMAB IN PATIENTS WITH NSCLC AND HIGH PD-L1 EXPRESSION: REAL-WORLD DATA FROM A EUROPEAN COHORT

G. Metro[1], D. Signorelli[2], J. Rey-Cobo[3], M. Banini[1], P. Economopoulou[4], G. Lo Russo[2], P. Baxevanos[5], F. Roila[6], A. De Toma[2], G. Banna[7], A. Christopoulou[8], B. Jimenez[9], A. Collazo-Lorduy[9], H. Linardou[10], A. Calles Blanco[11], D. Galetta[12], A. Addeo[13], A. Camerini[14], P. Kosmidis[15], M. Garassino[16], G. Mountzios[17]

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Background: Real-world data regarding treatment patterns and clinical outcomes after progression on first-line pembrolizumab (pembro) monotherapy among NSCLC patients are lacking. **Method:** A comprehensive clinicopathological database of 173 consecutive patients with NSCLC and PD-L1>50% treated with first-line pembro in 14 centers in Italy, Spain, Greece and Switzerland was retrospectively created and post-progression patterns and outcomes were recorded. Analysis was performed using the SAS 9.3 software. **Result:** Main clinicopathological features are summarized in Table 1. Median TPS score for PD-L1 expression was 70%. Median duration of pembro treatment was 6.1 months (range: 0.2-20.8). Thirty patients (17.4%) received pembro despite having non-metastatic disease (stage I-IIIC), as deemed medically inoperable or ineligible for definite chemo-radiotherapy. At data cut-off (10th April 2019), 100 patients (58%) had stopped treatment due to disease progression, 9 (5%) due to toxicity, 3 (2%) for other reasons and 61 (35%) were still on treatment. Best response to pembro was CR, PR, SD and PD in 2%, 34%, 20% and 24% respectively, while in 11.6% death occurred in the absence of documented PD. Among patients who progressed (N=100), in 18 cases pembro was continued beyond progression, as considered to confer clinical benefit. Among patients who discontinued pembro (N=94), 47% received any second-line chemotherapy and 53% received no further treatment. Main chemotherapy regimens were carboplatin with either pemetrexed (16%) or gemcitabine (9%) or paclitaxel (7%), cisplatin-pemetrexed (7%) and gemcitabine monotherapy (9%). Best response to chemotherapy was CR, PR, SD and PD in 2%, 30%, 11% and 32% respectively. After a median follow-up of 11.2 months, median OS was 13.5 months (range: 0.16-25.8+). Table 1: Main clinicopathological characteristics of the patient cohort.

		N=173	%
COUNTRY OF ORIGIN	Italy	98	56.7
	Greece	32	18.5
	Switzerland	27	15.6
	Spain	16	9.2
SEX	Male	112	64.7
	Female	61	35.3
AGE Median (Range) yrs		68 (19-86)	
SMOKING STATUS	Current	66	38.2
	Former	86	49.7
	Never	18	10.4
	Unknown	3	1,7
PERFORMANCE STATUS	0	50	28.9
	1	80	46.2
	2	41	23.7
	3	2	1.2
HISTOLOGY	Adeno	116	67.1
	Squamous	37	21.4
	Large Cell	2	1.2
	Pleiomorphic	3	1.7
	Sarcomatoid	7	4.0
	Poorly differenti-ated/ Undifferen-tiated	8	4.6
SITE OF METASTASIS	Bone	74	49.7
	Intrapulmonary/ Contralateral Lung	72	48.3
	Adrenal	43	28.9
	Brain	30	20.1
	Liver	23	15.4
	Other	63	36.4
TNM STAGE AT DIAGNOSIS (AJCCC v.8)	I	2	1.2
	II	2	1.2
	III	26	15.0
	IV	142	82.1
	Unknown	1	0.5
STEROID USE	Yes	48	27.7
	No	105	60.7
	Unknown	20	11.6

Conclusion: Real-world data in a large retrospective cohort, indirectly compared to Keynote 024, suggest that: 1) Due to it's favorable toxicity profile, pembro is also an option in earlier stages in frail (PS=2 or medically inoperable stage I-III) patients, 2) One in five patients continues pembro beyond progression due to clinical benefit and 3) More than half of patients who progress do not receive any second-line treatment, mainly due to clinical deterioration.

Keywords: Pembrolizumab, Real world data, post-progression outcomes

P1.16-10 REAL-WORLD EFFICACY OF FIRST-LINE PEMBROLIZUMAB IN PATIENTS WITH ADVANCED PD-L1 HIGH NON-SMALL CELL LUNG CANCER IN ARGENTINA

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Background: Pembrolizumab monotherapy is a standard first-line (1L) treatment regimen for patients (pts) with non-small cell lung cancer (NSCLC) and a PD-L1 tumor proportion score (TPS) ≥ 50%. We aimed to study the clinical efficacy and toxicity of this approach in the real-world setting in Argentina. **Method:** We conducted a retrospective, multicenter study. Patients with metastatic NSCLC and a PD-L1 TPS ≥ 50% treated in 1L with at least one dose of pembrolizumab monotherapy, from December 2016 to February 2019, were included. Data was collected from clinical records, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) were estimated. Cox regression model was performed for uni- and multivariate analysis. **Result:** A total of 53 pts were included. Median age (range) was 68 years (35-88), 33 (62.3%) were male, and 46 pts (86.7%) were smokers. Most tumors were lung adenocarcinoma (N=47, 88.7%), median (IQR) PD-L1 TPS was 79% (60-87.5) and 22 tumors (41.5%) had a TPS ≥ 75%. *EGFR/ALK/ROS1* mutations/fusions were not detected. Brain (N=10; 18.9%), liver (N=5 (9.4%) and bone (N=15; 28.3%) metastasis were present at baseline. Performance status (PS) score was 0-1 in 46 pts (86.8%) and 7 pts (13.2%) had PS 2. Six pts received baseline corticosteroid treatment. The ORR with pembrolizumab was 41.5% (95% CI: 28.1-55.8), median PD-L1 TPS (mTPS) was significantly higher in responders (mTPS 74% vs 67%, P = 0.04). Grade ≥ 3 immune-related adverse events occurred in 7 pts (13.2%) and 10 (18.9%) required systemic therapy with steroids. With a median-follow up of 12.9 months (95% CI: 8.4-17.6), median PFS and median OS were not reached. The estimated percentage of patients alive and without progression at 6 and 12 months was 64.8% and 55.8%. The estimated percentage of patients alive at 6 and 12 months was 77.5% and 69.4%. Median PFS and OS for patients with PS 2 was 2.4 months (95% CI: 1.7-3.1) and 4.5 months (95% CI: 3.1-6.0), respectively. After adjusting for PS, a PDL1 TPS score ≥ 75% was independently associated with improved PFS in multivariate analysis [HR 0.28 (95% CI: 0.09-0.92); P = 0.03) but not with OS. PS score equal to 2 was independently associated with decreased OS [HR 4.52 (95% CI: 1.06-19.28); P = 0.04] in multivariate analysis. **Conclusion:** Pembrolizumab monotherapy is tolerable and confers durable clinical benefit for patients with tumors expressing high levels of PD-L1 in the real world clinical setting. The optimal first-line immunotherapy approach for patients with PS 2 in this setting warrants further studies.

Keywords: Immunotherapy, real-world, Efficacy

P1.16-11 A DYAD-BASED MINDFULNESS CANCER RECOVERY PROGRAM FOR SURVIVORS AND FAMILY MEMBERS TO REDUCE LUNG CANCER SYMPTOMS

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Background: Although the five-year survival rate for individuals with NSCLC stages I-IIIa, is increasing, excessive symptom burden remains a distressing problem that negatively impacts quality of life. Our long-term goal is to improve clinical outcomes for survivors of localized lung cancer (NSCLC; stages I–IIIa). The study objective is to test a tailored intervention, *Breathe Easier*, which encompasses meditation, varying levels of yoga, and breathing exercises to evaluate feasibility and preliminary effects for survivors and family members (dyads). **Method:** A community-based participatory research approach was used to adapt a mindfulness-based cancer recovery program. Using a prospective, one-group, repeated measures, mixed method design, this study collected feasibility and preliminary data to test the hypothesis that survivors and family members (dyads) who receive an 8-week intervention will demonstrate (a) less dyspnea, (b) less fatigue, (c) improved sleep quality and quantity, (d) improved exercise tolerance and (e) less stress immediately after the intervention. The intervention known as *"Breathe Easier"* consisted of breathing exercises, individual and partner sitting, standing and floor yoga movements, meditations and participant interaction.The outcome variables were measured pre and immediately post intervention by the FACIT Dyspnea Short Form (Parts 1 and 2), FACIT Fatigue Scale v.4. Pittsburgh Sleep Quality Index, 6-Minute Walk Test, and the Perceived Stress Scale v.4. Post-intervention qualitative interviews were conducted. Descriptive statistics were obtained for five quantitative feasibility measures (recruitment, retention, intervention dose, adherence, acceptability). Thematic analysis was used to interpret the qualitative data. **Result:** In six iterations of the intervention,164 survivors were reached, and 32 dyads enrolled (62 participants; 20% recruitment and 94% retention rates). Survivors were 44% male and 62% African American. Among all, 74% were not current smokers, 22% used oxygen, and 71% completed a six-minute walk test post-intervention. Adherence was demonstrated by good attendance and exceeding expectations on home assignments for breathing exercises and meditations. All participants practiced gentle movements (yoga), meeting approximately 80% of expectations. Survivors reported completing daily home assignments slightly more than family members. All agreed that the intervention materials were easy to use, learning yoga and breathing exercises helped, and involving a family member was important. For each outcome variable, differences in survivors versus partners were calculated. Survivors had less dyspnea and perceived stress over time. Both groups had improved fatigue and sleep scores. Interview data enriched the understanding of feasibility and preliminary outcome measures. Six themes illustrated participants' experiences: (1) Learning to Breathe Easier, (2) Enhanced Closeness with Committed Partners, (3) Stretching, Releasing Tension, and Feeling Energized, (4) Interacting with Others as Beneficial, (5) Refocused on Living, and (6) Sustainability as a Decision. **Conclusion:** Recruitment, retention, adherence, and acceptability demonstrated strong feasibility. Preliminary outcome data indicate benefits over time for both survivors and family members.

Keywords: lung neoplasm, mindfulness, dyads

P1.16-12 AN ANALYSIS OF HEALTHCARE USE AND THE COST ASSOCIATED TO END-OF-LIFE CARE OF LUNG CANCER PATIENTS IN A SPANISH HOSPITAL

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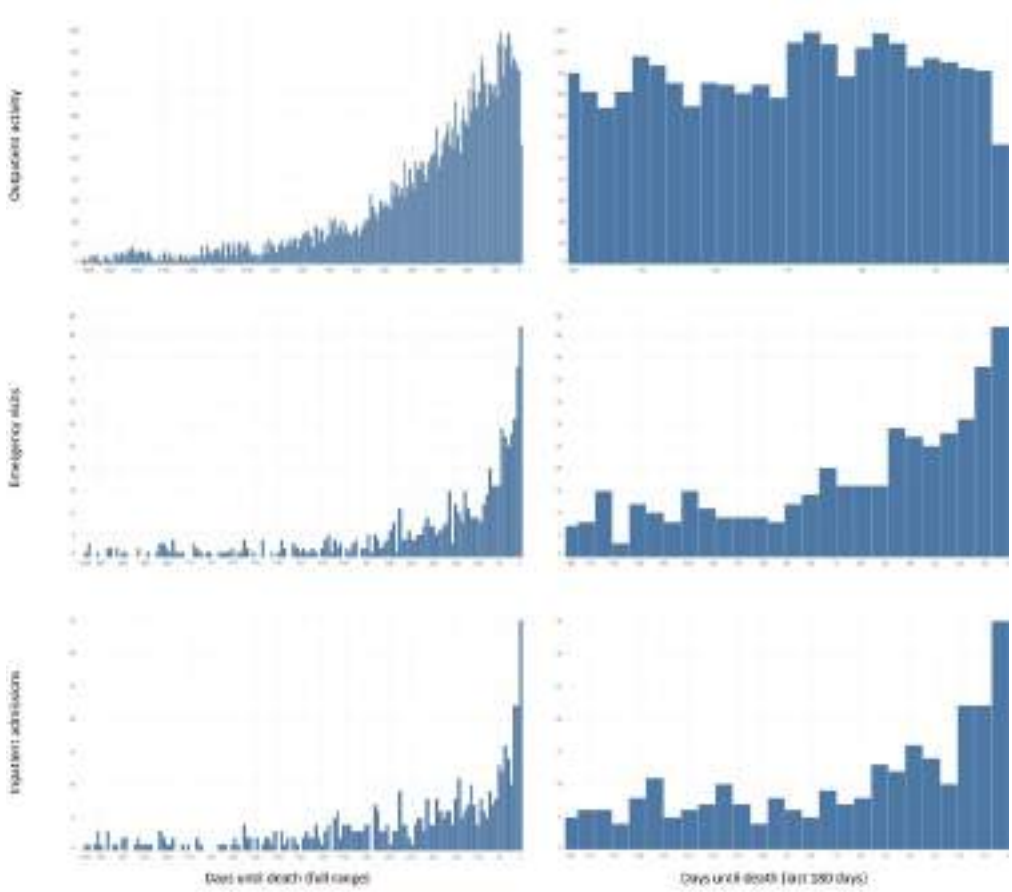
Background: Despite various studies have demonstrated that the consumption of healthcare services by cancer patients, and therefore healthcare costs, increases during the end-of-life period, there are insufficient studies which focus specifically on lung cancer. Thus we aim to study the consumption of healthcare services and its cost in end-of-life lung cancer patients attended in the Puerta de Hierro University Hospital, Spain. **Method:** The Cross Industry Standard Process for Data Mining (CRISP-DM) was applied to integrate and analyze activity data extracted from the Electronic Patient Record (EPR) and clinical data of lung cancer patients from a previous study. A cohort of 224 deceased patients, diagnosed between 01/01/2009 and 31/12/2016, was analyzed to determine the use of healthcare services together with the time-related distribution of such use and associated cost during the end-of-life period. **Result:** Overall, 82% of the patients received outpatient care, 68% received emergency service care, 53% experienced some period of hospitalization during the last 30 days of their life, and 38% of the patients died during hospitalization. The cost of hospitalization amounted to 88% of the total (excluding the cost of outpatient administered medication and radiotherapy treatment), with the cost of emergency services and consultations being 2.3% and 9.6%, respectively. In total, 58% of the healthcare assistance cost occurred during the last 6 months of life, and 21% in the last 30 days. The costs during the last 30 days represented 36% of the cost during the last 6 months.

Variable	Total	Variable	Total
Number of patients	224 (100%)	Number of patients	224 (100%)
Gender		Stage at diagnosis	
Male	187 (83.5%)	IA	7 (3.1%)
Female	37 (16.5%)	IB	13 (5.8%)
Age at diagnosis (years)		IIA	12 (5.4%)
Mean (SD)	65.3 (10.0)	IIB	9 (4.0%)
Median (Min.-Max.)	66 (31-92)	IIIA	50 (22.3%)
Race		IIIB	46 (20.5%)
Caucasian	217 (96.9%)	IV	87 (38.8%)
African	4 (1.8%)	With a history of cancer in first degree family	
Latin American	3 (1.3%)	Yes	41 (18.3%)
Tobacco use		No	63 (28.1%)
Ex-smoker (>1 year)	151 (67.4%)	Unknown	120 (53.6%)
Cigarettes per day. Mean (SD)	28.7 (13.4)	Personal history of cancer	
Cigarettes per day. Median (P25-P75)	28 (20-40)	Yes	45 (20.1%)
Active smoker	54 (24.1%)	No	150 (67.0%)
Cigarettes per day. Mean (SD)	27.9 (13.6)	Unknown	29 (12.9%)
Cigarettes per day. Median (P25-P75)	23.5 (20-40)	ECOG-PS at diagnosis	
Never-smoker	17 (7.6%)	0	104 (46.4%)
Unknown	2 (0.9%)	1	87 (38.8%)
Histology		2	24 (10.7%)
Adenocarcinoma	101 (45.1%)	3	5 (2.2%)
Squamous cell	89 (39.7%)	4	1 (0.4%)
Large-cell carcinoma	19 (8.5%)	Unknown	3 (1.3%)
Not Specified/Undifferentiated	5 (2.2%)	Charlson Comorbidity Index	
Small-cell carcinoma	4 (1.8%)	1-2	10 (4.5%)
Others	6 (2.7%)	3-4	26 (11.6%)
Survival after diagnosis (days)		5-8	62 (27.7%)
Mean (SD)	453.0 (487.6)	>8	89 (39.3%)
Median (P25-P75)	308.5 (130-578.5)	Unknown	37 (16.5%)

Table 1 – Characteristics of the patient cohort analyzed



Conclusion: Integrating activity data from EPR and clinical structured data from lung cancer patients and applying CRISP-DM has allowed us to describe end-of-life healthcare which could be used to plan resources and improve the quality of care in these patients.

Keywords: lung cancer costs, end-of-life, Data Science

POSTERS

P1.16-13 DEVELOPMENT OF A VETERANS AFFAIRS BASED COMPREHENSIVE LUNG CANCER SURVIVORSHIP PROGRAM

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Background: Symptoms of depression and poor exercise tolerance are common in patients with lung cancer and negatively impact patients' quality of life and decrease survival[1]. Cardiorespiratory fitness is inversely correlated with survival in lung cancer patients[2], and interventions that improve depression have been shown to increase survival in these patients[1]. We have developed a comprehensive lung cancer survivorship program (LCSP) at the Durham Veterans Administration Medical Center to address symptoms of depression, anxiety, dyspnea, physical debility, and tobacco abuse in veterans with lung cancer. The objective of the program is to alleviate symptoms and improve quality of while potentially impacting longevity through these interventions. **Method:** The LCSP is a 4 part tele-health based program with interventions targeted at depression, tobacco abuse, physical debility, and radiographic surveillance for recurrence. The initial visit is conducted with a mental health PA and an exercise physiologist and consists of a mental health (MH) assessment, depression screen, respiratory symptom, quality of life assessment, 6 min walk, and tobacco use assessment. Medications for depression or COPD may be prescribed or modified and the exercise program is explained and demonstrated to the patient. Patients are followed weekly for 12 weeks with 60 min MH visits and 30 min pulmonary rehabilitation appointments depending which components of the program they are participating in. There is also a video tablet option available for interested patients. At the end of the 12 week program, patients return for an in-person clinic appointment for a final assessment and to complete a repeat set of assessment metrics collected during the initial visit. Patients with ongoing mental health concerns are referred for continued care with a local mental health provider. **Result:** Program enrollment began in January 2019. 71% of referred patients agree to participate. 91% of participants are male, most patients are in the 7thor 8thdecade of life, and 91% are stage I with one stage III non-small lung cancer. All patients are participating in pulmonary rehabilitation, but only 37% have accepted mental health intervention despite 82% of patients carrying a mental health diagnosis (Table 1).

Table 1. Baseline Patient Characteristics

	Number	Percentage
Smoking Status		
Current	2	18
Former	8	82
Never	1	9
Fried Frailty Index		
Non-frail	3	33
Pre-frail	5	45
Frail	1	11
Mental Health Status		
HADS Score $\geq$ 8	6	54
PHQ-9 $\geq$ 5	6	54
Psychiatric Diagnosis	9	82
COPD Status		
No Diagnosis	2	18
Mild	1	9
Moderate	6	54
Severe	2	18

Conclusion: Patients with lung cancer are accepting of home based pulmonary rehabilitation even among elderly patients with poor performance status. Assistance with mental health support is not commonly engaged by this population, despite higher than anticipated rates of depression and post-traumatic stress disorder. Future work will examine the interaction between exercise performance and symptoms of depression.

Keywords: pulmonary rehabilitation, mental health, survivorship

P1.16-14 EFFECTS OF AN ARTIFICIAL INTELLIGENCE (AI) SYSTEM ON CLINICAL TRIAL ENROLLMENT IN LUNG CANCER

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Background: Clinical trials offer cancer patients access to the latest promising therapies and improve the overall quality and safety of cancer care. However, few patients participate, due in part to the time and effort associated with traditional manual ad hoc screening methods. IBM Watson Health's Clinical Trials Matching (CTM) is an artificial intelligence (AI) system that employs natural language processing to abstract patient and trial data from unstructured sources and machine learning to match patients to trials. This study compared the clinical trial enrollment rates of lung cancer patients before and after deployment of CTM. **Method:** CTM was trained for lung cancer and adopted in an academic outpatient oncology clinic using a phased implementation approach beginning July 2018. Clinical trials included ~42 therapeutic, supportive care, and observational trials. Clinical research coordinators validated Watson-derived clinical trial matches on the day prior to patient clinic visits. Oncologists were provided with a list of potentially eligible trials for each patient to facilitate evaluation at point of care. The average monthly enrollment rates for therapeutic trials were compared 6 months before and after CTM deployment. Average enrollment rates per active clinical trial were reported. **Result:** Clinical trial matches were validated and delivered to lung oncology providers in 69% (1818/2637) of patients' visits during the 6-month phased implementation. Enrollment of patients in lung cancer therapeutic clinical trials occurred at a rate of 3.83 patients/month after CTM deployment, as compared to 1.83 patients/month prior to CTM deployment; a 109% enrollment increase. When adjusted for the average number of active clinical trials before (30) and after (39) CTM implementation, the enrollment was 0.097 patients/trial using CTM, compared to 0.061 patients/trial using traditional methods; a 58.4% enrollment increase. **Conclusion:** Use of IBM Watson Health's Clinical Trials Matching (CTM) system with screening coordinators facilitated an increase in clinical trial enrollment and promoted awareness of clinical trial opportunities within the lung oncology practice.

Keywords: Lung cancer, Artificial Intelligence, clinical trial matching

P1.16-15 RATES OF SYSTEMIC ANTICANCER THERAPY (SACT) FOR ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) IN THE US, 2011–2018

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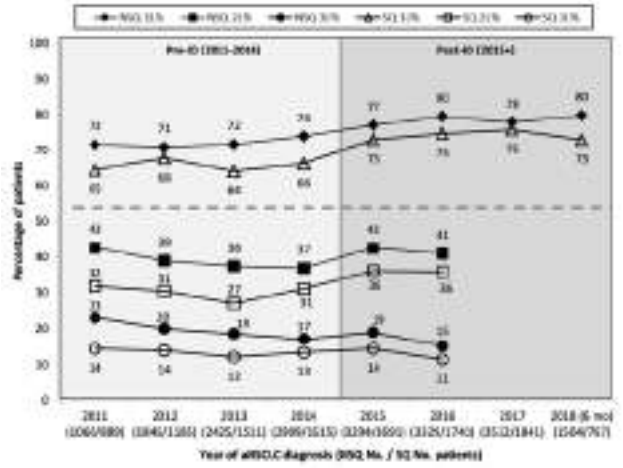
Background: The SACT options for aNSCLC continue to increase each year with approvals of more effective therapies that improve long-term outcomes, such as immunotherapies (IO). Our aim was to examine trends in SACT rates from 2011-2018 for patients with aNSCLC and no known EGFR/ALK aberrations at US community oncology practices. **Method:** We used the nationwide Flatiron Health EHR-derived database (data cutoff: 31Jan2019), which incorporates oncologist-defined, rule-based lines of therapy. Adults with aNSCLC diagnosis date from Jan2011-Jun2018, inclusive, with recorded EHR activity $\leq$90 days after diagnosis, were eligible. Patients with known EGFR/ALK-positive tumors, or nonsquamous histology (NSQ) with unknown or untested EGFR/ALK status, were excluded. We summarized no-treatment and first-line (1L) SACT rates as a proportion of aNSCLC diagnosed from 2011-2018, while limiting 2L and 3L SACT rates to aNSCLC diagnoses from 2011-2016

in order to have sufficient follow-up. Results were stratified by NSQ and squamous (SQ) histology, as well as by pre-IO and post-IO years of aNSCLC diagnosis, defined broadly as 2011-2014 and 2015+, respectively, based on the earliest IO approval for 2L therapy in Mar2015. **Result:** The figure depicts 1L, 2L, and 3L SACT rates by year of aNSCLC diagnosis for EGFR/ALK-negative NSQ and for SQ. For NSQ, the pre-IO and post-IO no-treatment rates were 28% (2286/8246) and 22% (2520/11,639), respectively. For SQ, the pre-IO and post-IO no-treatment rates were 34% (1781/5200) and 26% (1549/6040).



Conclusion: For both EGFR/ALK-negative NSQ and SQ aNSCLC, 1L SACT rates are trending upward, with no-treatment rates showing substantial drops in the post-IO (versus pre-IO) period. The 2L and 3L SACT rates are variable for both NSQ and SQ; and SACT rates for NSQ tend to be substantially greater than for SQ across all lines of therapy and years of diagnosis.

Keywords: real-world treatment rates, Immunotherapy, advanced NSCLC

P1.16-16 LUNG CANCER CONTROL IN SUB-SAHARAN AFRICA: EXPERIENCE AT AMPATH ONCOLOGY IN WESTERN KENYA

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Background: Objective To find out the cause for the under-diagnosis of Lung Cancer (LC) at AMPATH by using community engagement and high-risk screening at the TB clinics. Methods FGDs with community cough monitors in counties were done due to overlap of LC and TB presentations. **Method:** Consequently through establishing a multinational-lung cancer control program (MLCCP) to improve diagnosis and patient journey for lung cancer patients in our settings, we classified patients with symptomatic lung disease (chest pain, cough, SOB, weight loss, hemoptysis) and negative gene expert/negative sputum for AAFB as high-risk for further evaluation. CT scans were done for anyone with a chest mass/lesion and Image-guided biopsy offered. **Result:** s Jan 2018-Mar 2019, 331 high risk clients were evaluated. 214 with masses CT scans of which 205 were lung and 9 were mediastinal. 131/214 had biopsy, of which 83 (60 LC, 23 secondary mets) while 48 were other conditions.These included: Lung Fibrosis, Aspergillosis, Chronic granulomatous inflammation, TB, Thymoma, viral histiocytosis, Granuloma and unconfirmed diagnosis For the biopsied lung masses-131/214, 60 had confirmed LC. This represented 45.8% of those biopsied. Male to Female ratio was 1:1, median age at diagnosis was 62 with 55-74 age range accounting for 73.2% of LC cases. The mean duration of symptoms was 8 months, range of 1 to 12 months. >50% of the cancer patients made 7-10 hospital visits before diagnosis, with 25% making more than 14 visits. NSCLC accounted for 92.2% of the diagnosis with SCLC 7.8%. Adenocarcinoma was the commonest diagnosed histological sub-type at 66% of NSCLC. Majority of the patients were diagnosed at stage IV, 78.1% with only three patients diagnosed in stage II. 39% (25/64) patients are alive and on follow-up. **Conclusion:** Early detection is key. Poor referral patterns and lack of LC knowledge and diagnostic skills by HC professionals causes late stage at diagnosis. Patients do not present Late. Community engagement and embedding simple protocols for prompt referrals/diagnostic work-up in TB control programs may lead to improved outcomes. Prevention measures should also be rolled out. Cough monitors were essential to improving the LC patient's journey. *MLCCP is a Multi-National Lung Cancer Control Program with Dr. Asirwa the overall PI for Kenya, Tanzania, Swaziland and South Africa. Funding for the program has been provided by Bristol Myers Squib Foundation (BMSF) *MLCCP Team is the Kenyan Team for this Western Kenya Program Component

Keywords: Lung cancer, AMPATH, SUB-SAHARAN AFRICA

P1.16-17 GETTING TO KNOW OUR WEAPONS BETTER. ANALYZE FROM REAL LIFE DATA FROM LEÓN, SPAIN

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Background: The way immunotherapy alters the tumor environment is perceived but still not completely known. Although clinical trials revealed good results, data from real life settings is still lacking. We reviewed patients treated with immunotherapy at our center. **Method:** We retrospectively reviewed 83 lung cancer patients treated with immunotherapy at our Hospital between September 2015 and July 2018.75 patientsreceived immunotherapy after previous treatment. Data was obtained from medical records. Primary endpoint was to report immunotherapy efficacy and safety in the 75 pretreated patients with advanced NSCLC of our everyday clinical practice. Secondary aim was to analyze efficacy according to immune related toxicity and other basal features. **Result:** 60 were men, 15 women. Median age 66 years (range 48-84). 50 were former smokers, 23 still smoking, 2 were never smokers. 44 were adenocarcinomas, 26 squamous cell carcinoma, 5 NOS. 18 were stage III, 57 stage IV. 36 had at least one metastatic organ. 11 had liver while 10 had brain metastases. PDL1 was assessed in 12: <1%, 3; 1-49%, 3; >50%, 6. 3 were EGFR-positive, 3 ALK+, 2 KRAS+. Median number of lines was 1 (range=1-5). Best response to any previous treatment was stable disease (SD) 38.7% (n=29); partial response (PR) 36% (n=27); complete response 2.7% (n=2). 71 patients received Nivolumab vs 4 Pembrolizumab. Best response to immunotherapy was PR 21.3% (n=16) with SD 34.7% (n=26). Median number of cycles was 10 (range=1-77). 68 (90.7%) were PS<=1 before immunotherapy while 43 (57.3) still PS<=1 after. Median overall survival (OS) was 18 months (95%CI 7.03-28.69). Median progression free survival (PFS) was 4 months (95%CI 2.52-5.47). OS were higher in former smokers (median OS: 31 months vs 14 p<0.05); in PS<=1 before immunotherapy (median OS: 22 months vs 6 p<0.05) and in those with any grade of toxicity (mean 29 months vs 13 p<0.05). 42.7% (n=32) had any grade of immune-related toxicity (80% <=grade 2). Skin rash and hypothyroidism were the most common toxicities. 32% (n=24) needed corticosteroids to control toxicity. Immunotherapy stopping reasons were progression 47 (62.6%) and toxicity 9 (12%). 33.3% (n=24) received treatment after progression. Best response to treatment after immunotherapy was PR 38.1% (n= 8) with 90.5% disease control rate. 37 (49.3%) patients died at data cut-off. **Conclusion:** Compared with previous publications we had less treatment-related toxicity but the same discontinuation due to it. Best response and PFS is similar while median OS is slightly higher in our center. After immunotherapy we obtained better disease control with chemotherapy. Toxicity was related with better OS as in previous works.

Keywords: NSCLC, Immunotherapy in pretreated patients, Real world data

P1.16-18 PLEURAL MALIGNANT EFFUSION. IS IT POSSIBLE TO PREDICT RECURRENCE AFTER PALLIATIVE PLEURAL PROCEDURE?

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Background: Malignant pleural effusion (MPE) accounts for several hospital admissions. MPE recurs rapidly in a considerable number

of patients. Since MPE is associated with poor survival, a detailed prognosis may help to recognize patients with at higher risk of recurrence, aiming to individualize treatment strategies. However, there have been few studies that evaluated factors, including systemic therapy, associated with MPE recurrence. The aim of this study was to recognize risk factors of recurrence in symptomatic patients only, who required a pleural approach. **Method:** A prospectively assembled database was analyzed to search for patients with symptomatic MPE. The obtained data included basic demographics, primary tumor site, performance status, neutrophil/lymphocyte ratio (NLR) and platelets/lymphocyte ratio. Metastatic sites were also evaluated, which was defined as presence of any numbers of metastasis at each organ. Regarding the postoperative period, we analyzed pleural effusion recurrence, the palliative approach used, in addition to the biochemical profile of pleural fluid. Pleural thickening and pulmonary infiltrate were also described. Systemic treatment was evaluated. Patients were classified into three groups at MPE diagnosis: systemic treatment-naïve patients, patients who received first-line systemic treatment and patients receiving second-line systemic treatment or further therapy. The quantitative variables without definite cutoff points were submitted to the ROC (Receiver Operating Characteristic) curve, using a sub-sample of 50% of the recorded cases. Cutoff points were defined as the ones with sensitivity and specificity values >0.80. Univariate and multiple Cox regression models were used to evaluate the risk of recurrence (HR) and their respective 95% confidence intervals (95%CI). **Result:** Of the 288 analyzed patients, the most frequent main procedure was pleurodesis (43.1%). Disease recurrence occurred in 58 patients (20.1%). Recurrence-free survival was 73.3% at 12 months. Patients submitted to the pleurodesis procedure had a longer recurrence-free survival of 84.6%, with HR = 0.33 (95%CI = 0.17 - 0.63) when compared to patients who underwent the pleural drainage. Regarding the chemotherapy lines of treatment, Cox univariate analysis showed that the risk of recurrence for those submitted to the 1st line of palliative CT was HR = 3.19 (95% CI = 1.32 - 7.70) and for the 2nd line of palliative CT, HR = 7.32 (95% CI = 3.34 - 16.07) when compared to the systemic treatment-naïve patients. The independent factors for recurrence-free survival were procedure and chemotherapy lines. Patients who were submitted to pleurodesis had a protective factor for recurrence, with an HR = 0.34 (95% CI = 0.15 - 0.74, p = 0.007). On the other hand, patients submitted to the 1st and 2nd line of palliative CT had, respectively, an HR risk = 2.81 (95% CI = 1.10-7.28, p = 0.034) and HR = 3.23 (95% CI = 1.33 - 7.84, p = 0.010). **Conclusion:** Patients receiving the first or second line of systemic treatment have a higher risk of MPE recurrence when compared to patients who underwent MPE treatment before starting the systemic treatment. The definitive treatment of MPE, such as pleurodesis, was associated with a lower risk of MPE recurrence.

Keywords: pleural malignant effusion, Recurrence, palliative

P1.16-19 UNDERSTANDING PHYSICIAN BARRIERS IN THE MANAGEMENT OF LUNG CANCER IN NEPAL. CAN EDUCATIONAL INTERVENTION MAKE A DIFFERENCE?

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Background: Lung cancer is the leading cause of cancer morbidity and mortality for both men and women in Nepal. A majority of patients present with advanced or metastatic disease and some patients are never referred to an oncologist for further treatment after diagnosis. Many factors contribute to this, but diagnostic delay, lack of prompt referral and nihilistic attitude towards lung cancer seem to be most important. Potentially, a lack of oncology training and exposure contributes to this. Herein, we evaluated the physician related factors contributing to the current scenario of lung cancer treatment in Nepal and whether oncology education could make a difference. **Method:** A prospective pilot survey among residents and faculty from 10 medical colleges with Internal Medicine programs across Nepal was performed. A structured, self-administered questionnaire focusing on physician's behavior, practice, and attitude towards lung cancer was used. The questionnaire was distributed by e-mail to each site and a printed copy given to participants. **Result:** 74 participants responded to the survey questionnaire. Only 3 out of 10 Internal Medicine programs had a compulsory oncology rotation in their residency program. Multiple factors contributed to delay in diagnosis of lung cancer. 66 participants (91.6%) responded that they gave empirical anti-tubercular drugs(ATT) to patients with a non-resolving consolidative mass before they began evaluation for lung cancer; 22 % deferred CT scan before ATT. Multiple courses of antibiotics was a common practice in 62.5% participants. Misattribution of existing symptoms was common. 83.3% agreed that they treated smokers with respiratory symptoms initially as COPD with no consideration of lung cancer while 72.2% did not consider lung carcinoma in a middle-aged, never-smoker female with non-resolving consolidative mass. A paired t-test was used to analyze the responses among participants with oncology education during their residency with those who did not have an oncology rotation and was statistically significant (p= 0.001). We also discovered that 36.1% of participants don't refer elderly patients with lung cancer to an oncologist because they think lung cancer treatment is usually futile, toxic and does not help the patient. **Conclusion:** Lung cancer remains a neglected disease in Nepal. There is an urgent need to overcome physician related barriers by oncology education for physicians and in training programs for early diagnosis and treatment of lung cancer for potential improvement in survival and quality of life in patients with lung cancers.

Keywords: physician barriers, Lung cancer, Educational intervention

P1.16-20 TRIAL IN PROGRESS: CARDIAC TOXICITY IN PATIENTS UNDERGOING CURATIVE INTENT RADIOTHERAPY FOR LUNG CANCER

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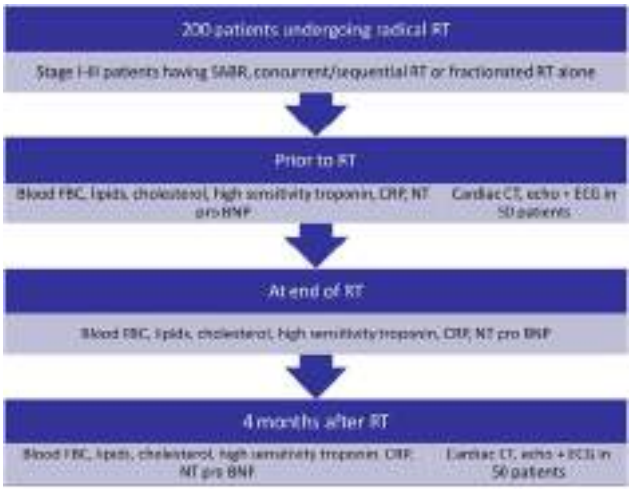
Background: The cardiotoxic effects of radiotherapy (RT) in long term survivors of breast cancer or lymphoma are well documented. Post-mortem studies and animal models have shown that RT causes fibrosis of cardiac structures leading to a wide variety of cardiac pathology. RTOG 0617 has highlighted a link between survival and cardiac dose and has led to a number of studies of cardiac toxicity in lung cancer patients. It is difficult to draw conclusions on cardiac dose constraints from available studies due to their retrospective nature and heterogeneity. We present an ongoing multicentre retrospective data mining study and prospective trial of cardiac biomarkers and imaging in patients undergoing radical lung RT, the aim of which is to define cardiac dose contraints leading to cardiac sparing treatment strategies. **Method:** Retrospective Validation Image based data mining results for heart substructures will be validated using a larger cohort. We will obtain data from Public Health England on cardiac risk factors, hospital admissions and cause of death for these patients to conduct a multivariate survival analysis. Clinical Trial (NCT03645317) A prospective study will collect cardiac risk factors (Qrisk 3), detailed cardiac imaging (CT and echocardiogram), ECG and cardiac blood biomarkers to evaluate effect of the radiotherapy on the heart. Figure 1 shows an overview of the clinical trial.



Result: Over 4000 patients treated with curative intent RT from 1/1/2010 to 30/12/206 have been identified. Details on 600 patients have been obtained and will be presented at WCLC 2019. Fifty-two

patients (9%) had cardiac events following RT. The prospective trial is due to open in May 2019 **Conclusion:** Studies of cardiac toxicity in lung RT have so far mainly been heterogeneous and retrospective. We describe a package of work incorporating large retrospective datasets with prospective imaging and blood biomarker collection to define cardiac dose parameters. This will improve the outcomes of lung cancer patients treated with radical radiotherapy by limiting heart dose and reducing cardiac events.

Keywords: cardiac toxicity, cardiac imaging, radiotherapy

P1.16-21 DOES AGE AFFECT WHAT PATIENTS VALUE WHEN CONSIDERING LUNG CANCER TREATMENTS? EVIDENCE FROM A NATIONAL SURVEY

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Background: Few studies have explored how values vary with patients' lung cancer treatment experience. Due to the rapidly increasing number of treatments for lung cancer, we sought to demonstrate a simple values-elicitation method and explore how values differ across age. **Method:** The values of patients and caregivers with small cell (SCLC) and non-small cell lung cancer (NSCLC) inclusive of all stages were explored using a simple values elicitation exercise developed in partnership with diverse stakeholder advisory boards. Respondents were presented with five treatment characteristics, including progression free survival (PFS), short-term side effects (ST-SE), long-term side effects (LT-SE), and mode of administration. All characteristics and plausible outcomes were described. Values were elicited using a simple three-point Likert scale spanning not important, somewhat important, and very important, which were scored as 0, 5, and 10 respectively. Data came from a national survey completed in partnership with LUNGevity and other partners. Differences in values were explored between patients and caregivers, as well as across patients' self-reported age with two sample t-tests. **Result:** Among 793 eligible respondents, 556 were patients (70%) with 77% NSCLC, 11% SCLC, 12% unknown subtype and 233 were caregivers (30%). The average patient age was 58.4 years (y) (SD = 12.3), with 235 (42%) < 60y and 321 (58%) ≥60y. PFS was the most important attribute for respondents, but was undervalued by caregivers compared to patients (mean score (MS): 8.1 v 8.6, P = 0.014). Caregivers overvalued the importance of ST-SE (MS: 7.0 v 6.1, P < 0.001), LT-SE (MS: 8.4 v 7.6, P = 0.001), and mode of administration (MS: 6.9 v 6.1, P = 0.006). PFS was the most important attribute and valued similarly among younger vs. older patients (MS: 8.7 v 8.6, P = 0.76). However, ST-SE (MS: 6.4 v 5.8, P = 0.042) and LT-SE (MS: 8.0 v 7.4, P = 0.018) were more important among patients < 60y vs. ≥60y, respectively. **Conclusion:** Among patients with lung cancer, progression free survival was highly valued regardless of patient age. Older patients value short term and long term side effects differently as compared to younger patients.

P1.16-22 REDUCED DELAYS IN DIAGNOSTIC PATHWAYS FOR NON-SMALL CELL LUNG CANCER AFTER LOCAL AND NATIONAL INTERVENTIONS

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Background: Patients with non-small cell lung cancer (NSCLC) may experience progression and stage shift due to delays in a complex and time-consuming diagnostic work-up. We have analyzed the impact of both a local and national intervention on total time to treatment (TTT) for a population-based cohort of NSCLC patients. **Method:** All patients diagnosed with NSCLC at a county hospital in Kristiansand, Norway, 2007-2016 were reviewed. The period 2007-12 before the interventions was defined as baseline. Local bottlenecks in the diagnostic pathways were identified and a new, locally developed diagnostic algorithm introduced from 2013. From 2015 National diagnostic cancer pathways were implemented and local adjustments were made accordingly. TTT defined as time from referral of the primary physician to treatment was compared in the three diagnostic time periods; baseline period (2007-12), local initiative (2013-14) and the national initiative (2015-16). Multivariable quantile regression was used to correct for possible confounding factors. **Result:** A total of 780 NSCLC patients were included in the study. The median TTT decreased from 46 days in the first period to 35 days in the last period. Among patients treated with curative intent the median TTT decreased by 21 days, from 64 to 43 days (p<0.001) while the mean number of procedures increased from 3,5 to 3,9. In median regression analysis, the local intervention was associated with a reduction of 7.7 days (95% CI 3.2, 12.3) in TTT, while the national intervention had a reduction of 14.9 days (95% CI 10.2, 19.6) compared to the baseline group. Examining the 75thand 90thpercentile, the last period had 22 days and 27 days shorter TTT than the first period, respectively. Covariates associated with longer TTT were stage I (21.3 days compared to stage IV), use of PET-CT (10.6 days), diagnostic procedure at external hospital (13.0 days), and additional number of diagnostic procedures (5.3 days per procedure). **Conclusion:** Both interventions, the local and national initiatives introduced to this population significantly reduced TTT in NSCLC despite more diagnostic procedures being added to the work-up. The effect was most pronounced among patients with disease available for curative treatment.

Keywords: Non-Small Cell Lung Cancer, delay, intervention

P1.16-23 COMPARISON OF ELECTRONIC AND TRADITIONAL THORACIC DRAINAGE SYSTEMS FOR POSTOPERATIVE CHEST TUBE MANAGEMENT AFTER PULMONARY RESECTION

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Background: The objective of this study was to evaluate whether a electronic thoracic drainage system (ECD) is clinically useful compared with a traditional thoracic drainage system (TTD) in chest tube management following lung lung resection. **Method:** Patients scheduled to undergo wedge, segmentectomy or lobectomy were prospectively randomized before surgery to ECD group or TTD group. A stratification randomization was performed sequentially. The primary end point was the duration of chest tube placement. The secondary endpoint was daily activity of both groups **Result:** No statistically significant differences were found between groups ECD and TTD with regard to the duration of chest tube placement (2.0 vs 3.0 days) and duration of hospitalization in wedge resection sub group, or frequency of postoperative adverse events (1% vs 2%; P=0.361). In subgroup analyses of segemetectoy and lobectomy patients, the duration of chest tube placement(median, 2.5 vs 4.0 days; P=0.045) and duration of hospitalization (median 3.0vs 5.2 days; P=0.048) were significantly different between subgroups. **Conclusion:** The use of a digital thoracic drainage system did not shorten the duration of chest tube placement in comparison to a traditional thoracic drainage system in wedge group. However, in anatomic resection, the chest tube duration and hospitalization was significantly in ECD group

Keyword: VATS, electronic drainage system,daily activity

P1.16-24 DETECTION OF PLASMA T790M MUTATION AFTER THE FIRST GENERATION EGFR-TKI RESISTANCE OF NON-SMALL CELL LUNG CANCER IN THE REAL WORLD

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Background: The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has shown efficacy in mutation non-small cell lung cancer(NSCLC), but acquired resistance is inevitable. It has been confirmed that the secondary EGFR Thr790Met (T790M) mutation accounted for about 50% at acquired resistance in tumor tissue. The third generation EGFR-TKI had significantly efficacy in T790M positive NSCLC . The purpose of this study was to investigate the

positive rate of plasma T790M mutation and its relationship among the clinical characteristics and the frequency of T790M mutation in acquired resistance after first line EGFR- TKI treatment in the real world. **Method:** Patients were recruited prospective from September 2017 to June 2018.The eligibility criteria of the trial included:1. Older than 18 years, histologically confirmed NSCLC stageIIIB/IV, EGFR mutation positive; 2.Had progressive disease (PD) after first generation EGFR-TKI by RECIST, PFS>3months; 3.excluded patients who had recevied the third generation TKI treatment. All patients take 10 ml of blood, and detected the T790M gene by amplification refractory mutation system(ARMS). The study was approved by the Ethics Committee of Taizhou Hospital, ethical batch number: 201637. **Result:** 189 patients are in the analysis (Table 1). The overall plasma T790M mutation rate was 36.51 % (69/189). The positive rate of T790M mutation after the failure of first generation EGFR-TKI treatment was not correlated with the patient's age, sex and the type of first generation TKI drugs. However, it is related to the mutation type of EGFR in baseline and the mode of progression according to Wu YL et al. reports. The frequency of T790M mutation among patients with initial exon 19 deletion mutation, exon 21 L858R point mutation, and other mutations were 45.44%, 26.19% and 33.33%. The mutation rate of T790M in 19del mutant patients was higher than that of L858R mutation and other mutations (p=0.026). The frequency of T790M mutation in local progression patients was 50% after the first generation EGFR TKI was resistant to drug, when in gradual progression was 26.92%, and in dramatic progression was 38.10%. The frequency of T790M mutation of patients with local progression was significantly higher (p=0.031).

Table 1 Univariate analysis of the association between patients' characteristics and plasma T790M status.

Characteristics	NO.	Plasma T790M mutation states		P value
		Positive (+)	Negative(-)	
Age(yr)				
≤60	64	25(39.1%)	39(60.9%)	P=0.438
>60	125	44(35.2%)	81(64.8%)	
Sex				
Male	64	27(42.19%)	37(57.81%)	P=0.246
Female	125	42(33.6%)	83(66.4%)	
Baseline EGFR mutation status				
19-del	99	45(45.45%)	54(54.55%)	P=0.026
21-L858R	84	22(26.19%)	62(73.91%)	
others	6	2(33.33%)	4(66.67%)	
First generation TKI				
Lcotinib	96	28(29.17%)	68(70.83%)	P=0.074
Gefitinib	90	39(43.33%)	51(56.67%)	
Erlotinib	3	2(66.67%)	1(33.33%)	
Disease progression modes				
Gradual progression	78	21(26.92%)	57(73.08%)	P=0.031
Local progression	48	24(50%)	24(50%)	
Dramatic progression	63	24(38.10%)	39(61.90%)	

Conclusion: The overall plasma T790M mutation rate was 36.51% after first generation of EGFR-TKI acquired resistance of NSCLC in the real world. The frequency of T790M mutation with initial mutation of 19 Del was higher than that of L858R mutation, and local progression was higher than gradual progression and dramatic progression.

Keywords: Plasma EGFR Thr790Met (T790M), Acquired resistance

P1.16-25 IMPACT OF PIRFENIDONE ON THE RISK SCORING SYSTEM OF POSTOPERATIVE ACUTE EXACERBATION OF INTERSTITIAL PNEUMONIA IN LUNG CANCER

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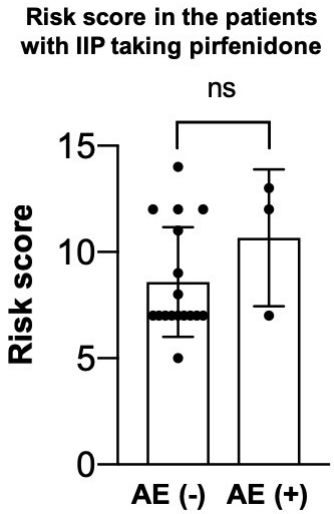
Background: Acute exacerbation (AE) of idiopathic interstitial pneumonia (IIP) is a life-threatening complication of lung cancer resection. There has been an increasing number of studies about postoperative AE of IIP in recent years. A few of these have reported that perioperative oral administration of pirfenidone reduces the occurrence of AE in patients with IIP. Furthermore, a large cohort study conducted by the Japanese Association for Chest Surgeons (JACS) proposed risk factors for postoperative AE in IIP patients which can predict the incidence of AE following an operation. JACS risk score included seven factors (sex, history of AE, surgical procedure, usual interstitial pneumonia pattern, steroid use, KL-6, %VC) and classified patients into three groups: low risk (risk score: 0-10), intermediate risk (risk score: 11-14) and high risk (risk score: 15-22). The objective of present study is to investigate the validity of those risk factors for patients with IIP who are taking pirfenidone. **Method:** We retrospectively analyzed 1626 consecutive lung cancer patients who had undergone lung resection at our institution from January 2010 to December 2018. The patients who underwent lung resection since 2016 onward were administered pirfenidone from 4 weeks before operation to 4 weeks after operation. **Result:** Out of 1626 patients, 125 patients (7.7%) had IIP. Twenty patients (16%) took pirfenidone and 105 patients (84%) did not take pirfenidone. Of the patients taking pirfenidone, three patients (15%) contracted AE of IIP after lung resection within 30 postoperative days. No significant difference was identified in JACS risk score between AE (+) group taking pirfenidone and AE (-) group taking pirfenidone (10.7 ± 3.2 versus 8.6 ± 2.6, p = 0.74). In the AE (+) group taking pirfenidone, there were significant higher rates of patients having increased serum levels of KL-6 or having reached pathological stageII-IV (UICC 8th) (p = 0.01, p = 0.04, respectively). Of the patients not taking pirfenidone, seven patients (6.7%) contracted AE of IIP. No significant difference was identified in incidence of postoperative AE between the group of patients taking pirfenidone and the group not taking pirfenidone (p = 0.21).



Conclusion: In the patients taking pirfenidone, there was no significant difference in the risk score between AE (+) group and AE (-) group.

Keywords: Lung cancer, idiopathic interstitial pneumonia, pirfenidone

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P1.16-26 EPITHELIAL GROWTH FACTOR RECEPTOR MUTATION PATTERN IN NON-SMALL CELL LUNG CANCER OF XUANWEI REGION IN SOUTHWESTERN CHINA

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Background: The incidence and mortality rate of lung cancer in Xuanwei region are among the highest in China. A previous study reported that non-smoking female lung cancer patients in Xuanwei exhibit different EGFR mutation patterns compared with the patterns seen elsewhere in Asia. A unique environment, ethnic group and certain susceptible population may have certain genetic background. Investigating EGFR mutation distribution of NSCLC patients in Yunnan province especially in Xuanwei region is meaningful. **Method:** A meta-analysis was conducted to identify the distinctive pattern of EGFR mutations in NSCLC patients in Xuanwei. Electronic databases were comprehensively searched and relevant literature with data were retrieved. The odds ratios (OR) for each EGFR mutation between Xuanwei and other regions were calculated, and the absolute incidence of EGFR mutations in Xuanwei was pooled. Subgroup analyses were performed for different EGFR mutation subtypes. **Result:** Five relevant studies with a total of 1,058 NSCLC patients from Yunnan province in southwestern China were conducted. 337 were from Xuanwei and 721 were from other regions; The overall EGFR mutation rate across studies ranged from 34.90% to 55.56%(Table 1). The results revealed a higher incidence of uncommon EGFR mutations (p<0.001), but a lower incidence of common EGFR mutations (p<0.001) in Xuanwei region compared with other regions. The pooled incidence of uncommon and common EGFR mutations in Xuanwei were 62.7% and 37.3%, respectively (Table 2). More specifically, compared with other areas, patients from Xuanwei harbored a higher frequency of exon 20 S768I (P<0.001) and exon 18 G719X + 20 S768I mutations (P<0.05), but had a lower frequency of 19 deletion (p<0.001)(Table 3).

Table 1 Characteristics of the included studies.

Publication year	Region	Study type	Number of patients			EGFR mutation			Female (%)	Age (years)	Smoker (%)	Adenocarcinoma (%)	Stage	Lymph node metastasis (%)	Scores Of AHRQ
			Xuanwei	non-Xuanwei	Total	Yes	No	Rate							
2017	China, Yunnan	Retro	63	384	447	156	291	34.90%	44.97%	<65 (69.4%); 65-75 (23.5%); >75 (7.2%)	47.43%	86.58%	I , II , III, IV	NG	10
2016	China, Yunnan	Retro	90	168	258	124	134	48.06%	52.33%	<=60 (68.6%); >60 (31.4%)	27.13%	87.60%	I , II , III, IV	29.07%	11
2016	China, Yunnan	Retro	81	169	250	131	119	52.40%	NG	NG	NG	NG	NG	NG	10
2016	China, Xuanwei	Retro	63	NA	63	35	28	55.56%	42.86%	<50 (54.0%); >=50 (46.0%)	39.68%	84.13%	NG	17.46%	10
2013	China, Xuanwei	Retro	40	NA	40	14	26	35.00%	NG	46.5±10	0	80.00%	NG	NG	10

Abbreviations: Retro , Retrospective study ; EGFR, Epidermal growth factor receptor; NA , Not Available; NG, Not given; AHRQ, Agency for Healthcare Research and Quality.

Table 2 Incidence of common and uncommon mutation in Xuanwei.

			Xuanwei				META			
			Yes	No	Tatal	Rate	Rate	LL	UL	*P*-value
Common mutation	Zhou et al.[14]	2017	8	19	27	29.63%	0.296	0.124	0.469	
	Chen et al.[12]	2016	14	37	51	27.45%	0.275	0.152	0.397	
	Yang et al.[15]	2016	21	22	43	48.84%	0.488	0.339	0.638	
	Yang et al.[17]	2016	16	19	35	45.71%	0.457	0.292	0.622	
	Hosgood et al.[18]	2013	6	8	14	42.86%	0.429	0.169	0.688	
	Overall		65	105	170		**0.373**	**0.301**	**0.444**	**<0.001**
Uncommon mutation	Zhou et al.[14]	2017	19	8	27	70.37%	0.704	0.531	0.876	
	Chen et al.[12]	2016	37	14	51	72.55%	0.725	0.603	0.848	
	Yang et al.[15]	2016	22	21	43	51.16%	0.512	0.362	0.661	
	Yang et al.[17]	2016	19	16	35	54.29%	0.543	0.378	0.708	
	Hosgood et al.[18]	2013	8	6	14	57.14%	0.571	0.312	0.831	
	Overall		105	65	170		**0.627**	**0.556**	**0.699**	**<0.001**

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Mutation type		Zhou et al. 2017[R6]		Chen et al. 2016[R5]		Yang et al. 2016[R9]		Yang et al. 2016[R7]		Hosgood et al. 2013[R8]		META			Xuanwei META	
		Xuanwei	Non-Xuanwei	Xuanwei	Non-Xuanwei	Xuanwei	Non-Xuanwei	Xuanwei	N A	Xuanwei	N A	OR	95% CI	Pvalue	Rate	95% CI
common mutation	19 deletion	18.50%	45.00%	7.80%	49.30%	13.95%	39.77%	14.30%		28.57%		**0.186**	**(0.103-0.335)**	**<0.001**	0.125	(0.075-0.174)
	21 L858R	11.10%	33.30%	19.60%	37.00%	34.88%	35.23%	31.40%		14.29%		0.517	(0.238-1.124)	0.096	0.220	(0.129-0.311)
	18 G719X	22.20%	3.90%	7.80%	1.40%	9.30%	7.95%	14.30%		50.00%		3.420	(0.966-12.112)	0.057	0.157	(0.067-0.246)
	20 T790M	0	2.30%	0	0	4.65%	4.55%	2.90%		0		0.956	(0.239-3.819)	0.949	0.0083	(0-0.0345)
	20 S768I	11.10%	3.10%	3.90%	2.70%	23.26%	1.14%	17.10%		0		**5.052**	**(1.057-24.156)**	**0.042**	0.1009	(0.0296-0.2008)
	20 insertion	0	3.90%	2.00%	0	0	0	0		7.14%		1.212	(0.246-5.985)	0.813	0.0037	(0-0.026)
	21 L816Q	3.70%	2.30%	2.00%	2.70%	0	0	0		0		1.165	(0.251-5.411)	0.845	0.0049	(0-0.0283)
	18 G719X + 20 S768I	18.40%	1.60%	45.10%	4.10%	9.30%	3.41%	17.10%		0		**10.60**	**(4.669-24.095)**	**<0.001**	0.1632	(0.0412-0.3351)
uncommon mutation	18 G719X + 20 G779C	0	0	2.00%	0	0	0	0		0		3.587	(0.438-29.364)	0.234	0.0012	(0-0.0201)
	18 G719X + 21 L816Q	0	0.80%	2.00%	1.40%	0	0	0		0		1.595	(0.248-10.265)	0.623	0.0012	(0-0.0201)
	18 G719X + 21 L858R	3.70%	0	0	0	0	0	0		0		4.104	(0.566-29.746)	0.162	0.0005	(0-0.0174)
	18 G719X + 21 L858R + S768I	3.70%	0	0	0	0	0	0		0		4.104	(0.566-29.746)	0.162	0.0005	(0-0.0174)
	19 deletion + 21 L858R	0	0.80%	2.00%	0	0	4.55%	0		0		0.827	(0.184-3.721)	0.805	0.0012	(0-0.0201)
	19 deletion + 20 T790M	0	2.30%	0	0	0	0	0		0		1.049	(0.149-7.368)	0.962	0	0
	20 S768I + 20 T790M	**7.40%**	**0.00%**	0	0	0	0	0		0		5.960	(0.943-37.657)	0.058	0.0017	(0-0.0214)
	20 S768I +20 insertion	0	0	3.90%	1.40%	0	0	0		0		2.597	(0.492-13.719)	0.261	0.0036	(0-0.0259)
	20 S768I + 21 L858R	0	0.80%	2.00%	0	0	0	0		0		2.583	(0.391-17.043)	0.324	0.0005	(0-0.0174)
	20 T790M + 21 L858R	0	0	0	0	4.65%	3.41%	2.90%		0		1.669	(0.401-6.937)	0.481	0.0083	(0-0.0345)

Abbreviations: Retro , Retrospective study ; EGFR, Epidermal growth factor receptor; NA , Not Available; CI, confidence interval.

Conclusion: To summarize, Xuanwei patients carrying EGFR mutations exhibit distinct EGFR mutation spectrum compared with other regions, with higher uncommon mutations but lower common mutations. The Xuanwei pattern provides an important model to study the etiology or risk factor for EGFR uncommon mutations.

Keywords: EGFR mutation, Lung cancer, Xuanwei

P1.16-27 RISK FACTORS ASSOCIATED WITH A SECOND PRIMARY LUNG CANCER (SPLC) IN PATIENTS (PTS) WITH AN INITIAL PRIMARY LUNG CANCER (IPLC)

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Background: The risk for development of a SPLC after treatment of an IPLC is around 1% to 2% per pt per year. The aim of this study was to characterize the risk factors associated with the development of a SPLC. **Method:** Pts registered in the Karmanos Cancer Institute Tumor Registry diagnosed with an IPLC between 2000 and 2017 were included in this study. Pts with an IPLC who later developed a SPLC were matched for age, histology and stage to pts with an IPLC who did not develop a SPLC. SPLC was defined as a second lung cancer with a different pathology or if the same pathology, anatomically, molecularly, or chronologically distinct. Six variables including: stage at IPLC, histology, family history, surgery as a primary treatment for IPLC, and smoking history (determined by pack years, and continued tobacco use after first diagnosis) were reviewed. Logistic and Cox regression analyses were performed to determine the relationship of these characteristics with the development of a SPLC, and their association with overall survival (OS). **Result:** 121 pts with IPLC who later developed an SPLC were identified and compared to 120 pts with IPLC who did not develop a SPLC. Logistic regression analyses did not show that stage at first diagnosis, histology, family history, smoking history, and continued tobacco use after first diagnosis to be relevant for increased risk of SPLC (Table 1). Pts who were primarily treated with surgical resection had a significantly higher probability of developing a SPLC (Odds Ratio, 0.24; 95% CI, 0.12 to 0.48; p<0.001, see Table 1). Pts who did not have surgical resection as their primary mode of treatment for IPLC had a significantly higher hazard of death than those who received surgical resection (Hazard Ratio, 3.02; 95% CI, 1.99 to 4.57; p<0.001).

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Table 1. Univariable and multivariable logistic regression analysis for risk factors associated with second diagnosis

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Smoking status after treatment				
Yes	Reference		Reference	
No	0.775 (0.440,1.356)	0.373	0.743 (0.378,1.442)	0.383
Histology				
Small Cell Carcinoma	Reference		Reference	
Adenocarcinoma	1.000 (0.343,2.912)	>0.99	0.537 (0.140,1.925)	0.346
Squamous Cell Carcinoma	1.000 (0.339,2.948)	>0.99	0.514 (0.134,1.848)	0.313
Other NSCLC	1.062 (0.318,3.554)	0.921	0.717 (0.161,3.071)	0.654
Family History				
Yes	Reference		Reference	
No	1.051 (0.544,2.028)	0.882	0.927 (0.441,1.941)	0.841
Smoking history at first diagnosis, pack year				
Nonsmoker	Reference		Reference	
Light Smoker	1.538 (0.368,7.144)	0.562	2.106 (0.399,11.944)	0.383
Heavy Smoker(>30)	2.364 (0.719,9.099)	0.172	2.549 (0.642,11.140)	0.188
Stage at first diagnosis				
Localized	Reference		Reference	
Regional	1.042 (0.612,1.775)	0.880	1.244 (0.631,2.494)	0.532
Distant	0.737 (0.281,1.875)	0.524	1.243 (0.364,4.247)	0.726
Surgery after 1st diagnosis				
Yes	Reference		Reference	
No	0.257 (0.146,0.444)	***<0.001***	0.243 (0.119,0.481)	***<0.001***

OR, odds ratio; CI, confidence interval

Conclusion: Based on our findings, pts who had surgical resection for an IPLC were found to have improved OS and a higher possibility of developing a SPLC. Stage at first diagnosis of IPLC, histology, family history, smoking history and continued use of tobacco after first diagnosis did not correlate with increased risk for SPLC. These results warrant further investigation and if confirmed could have an impact on surveillance recommendations post resection of initial lung cancers.

Keywords: second lung cancer, survivorship

P1.16-28 THE HUMANISTIC BURDEN OF ALK+ NSCLC: FINDINGS FROM THE ALKCONNECT PATIENT INSIGHT NETWORK AND RESEARCH PLATFORM

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Background: The ALKConnect Patient Insight Network (www.alkconnect.com) is a patient-centered online registry that provides support to and collects information from patients living with Anaplastic Lymphoma Kinase-Positive (ALK+) Non-Small Cell Lung Cancer (NSCLC). The objectives of this study were to: (1) describe the characteristics of patients in ALKConnect; (2) quantify patients' preferences, ALK+ NSCLC symptom burden, and health-related quality of life (HRQoL); and (3) determine whether disease treatment and employment status were associated with HRQoL. **Method:** Study inclusion criteria were US adults (18 years or older) living with ALK+ NSCLC who have internet access, and willingness to answer e-surveys. Cross-sectional 'real-world' data that were collected included demographics, disease history and status, comorbidities, treatments, patient preferences, and HRQoL (MD Anderson Symptom Inventory lung cancer module [MDASI-LC]), reported as symptom severity and interference in activities of daily living (walking, activity, work, relations with others, enjoyment, and mood) caused by symptoms. Data were reported descriptively overall and by subgroups of interest (e.g., treatments, employment status) where sample sizes permitted. Associations between patient treatment history and employment status and HRQoL were analyzed. **Result:** Data for 104 patients were available. Median age was 53.0 years (range 22-90), 67.3% were female, 84.0% were White (n=84), 12.0% were Asian (n=12), and 40.0% (n=40) were employed. Most patients were treated with ALK tyrosine kinase inhibitors (TKIs) (83.7% [n=87] ALK TKI only). Among treatment-associated preferences, preventing disease progression, shrinking tumor size, and maintaining HRQoL were perceived to be the most important treatment attributes. An additional 3-month delay in disease progression was perceived to be meaningful by 57.7% (n=60) of patients. MDASI-LC inventory data (from n=75 patients) showed that the most bothersome patient-reported symptoms were fatigue, sleep disturbance, drowsiness, difficulty remembering, and constipation. Interference on patient HRQoL was greatest for work and activity. Statistically-significant associations were observed between HRQoL and treatment with ALK TKIs (Symptom Severity p=0.0062, Interference p=0.0016), number of prior ALK TKIs (Symptom Severity p=0.1487, Interference p=0.0137), and employment status (Symptom Severity p=0.0201, Interference p=0.0210). **Conclusion:** ALKConnect gathered humanistic burden data directly from patients with ALK+ NSCLC. Participants reported that the most burdensome symptoms were fatigue, sleep disturbance, and drowsiness, and that symptoms interfered most with work and general activity. A 3-month delay in cancer progression and HRQoL were important treatment attributes. Patients' HRQoL was positively associated with ALK TKI treatment and the ability to maintain employment status, suggesting that these aspects may be important for ALK+ NSCLC patients' well-being.

Keywords: Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer, humanistic burden, Health-related quality of life

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P1.16-29 PROFILING IMMUNE-RELATED ADVERSE EVENTS (IRAES) IN PATIENTS WITH ANTI-PD-1 FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune-related adverse events (irAEs) are frequently observed during anti-programmed death-1 antibody therapy. We previously reported that patients with irAEs were associated with clinical efficacy. However, little is known about which irAEs are related with clinical efficacy in patients with non-small cell lung cancer (NSCLC). This study aimed to evaluate the correlations between different irAEs and treatment response. **Method:** Patients with advanced NSCLC who received nivolumab or pembrolizumab monotherapy at our hospital (n=154) from January 2016 to April 2018 were included in this study. Subjects were categorized into the irAE-incident group (with irAEs group) or non-irAE-incident group (without irAEs group), specific for each irAE. We evaluated the objective response rate (ORR), time to treatment failure (TTF), progression-free survival (PFS), and overall survival (OS) in each group. **Result:** The categorization of irAEs identified 51 cases of skin reactions (31%), 16 of infusion reactions (10%), 19 of pneumonitis (12%), 21 of thyroid dysfunction (14%), and 10 of hepatitis (6%). In the with/without skin reaction groups, the ORRs were 57% (29 cases)/19% (20 cases) (p<.001), median TTFs (months) were 8.7/2.8 (p<.001), median PFSs were 12.9/3.4 months (p<.001), and median OSs were NR/11.4 months (p<.001), respectively. In the with/without infusion reaction groups, the ORRs were 56% (9 cases)/29% (40 cases) (p=.05), median TTFs were 7.6/3.7 months (p=.11), median PFSs were 11.1/4.1 months (p=.045), and median OSs were NR/14.8 months (p<.001), respectively. In the with/without pneumonitis groups, the ORRs were 63% (12 cases)/27% (37 cases) (p=.004), median TTFs were 4.4/3.7 months (p=.44), median PFSs were 18.9/4.1 months (p=.02), and median OSs were NR/14.8 months (p=.09), respectively. In the with/without thyroid dysfunction groups, the ORRs were 52% (11 cases)/29% (38 cases) (p=.08), median TTFs were 7.4/3.7 months (p=.63), median PFSs were 8.7/4.2 months (p=0.22), and median OSs were 11.8/15.9 months (p=.84), respectively. In the with/without hepatitis groups, the ORRs were 40% (4 cases)/31% (45 cases) (p=.82), median TTFs were 2.7/4.1 months (p=.42), median PFSs were 6.4/4.20 months (p=.70), and median OSs were NR/15.6 months (p=.43). The PFS was significantly longer in patients with skin reactions, infusion reactions, and pneumonitis than that in those without, whereas the OS was significantly longer in patients with skin and infusion reactions than that in those without. **Conclusion:** The development of skin and infusion reactions during nivolumab or pembrolizumab monotherapy for NSCLC might be strongly associated with improved clinical efficacy, and clinical benefits should be validated through large-scale prospective analysis.

Keywords: NSCLC, Anti-PD-1 antibody, irAEs

P1.16-30 IMPACT OF PATIENT TKI COPAYMENTS ON INSURANCE EXPENDITURE IN ADVANCED EGFR OR ALK POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: To influence treatment choice and control expenditures, insurance plans impose cost sharing policies for expensive oral tyrosine kinase inhibitors (TKIs). We evaluated the effect of patient TKI copayments on insurance expenditures among patients with EGFR and ALK positive advanced NSCLC receiving TKIs. **Method:** We identified EGFR+ and ALK+ NSCLC patients in the Washington State SEER registry using natural language processing on registry pathology reports, followed by manual confirmation of molecular test results. We linked registry records with commercial and Medicare claims. Eligible patients had stage IV NSCLC diagnosed between 01/01/2010 and 12/31/2016, EGFR exon 19 deletions or L858R mutations, or ALK + by FISH, ≥ 12 months of insurance enrollment, survival of ≥6 months, and ≥ 1 pharmacy claims for EGFR or ALK TKIs with FDA approval in the study period. We estimated monthly TKI copayments by subtracting the drug amount paid from the amount allowed by insurance in pharmacy claims. We used claims to calculate lifetime total and drug costs from the insurance perspective. Covariates included sociodemographic characteristics, insurance type, comorbidity, mutation type, and receipt of chemotherapy and immunotherapy. We used generalized linear models with gamma family and log link to estimate the adjusted effect of TKI copayment of $0 vs. above $0 on insurer expenditures in 2016 US dollars. **Result:** Of 103 eligible patients, median age was 69; 66% were female; 72% were White, median household income was $69,951; 54% had Medicare, 85% were EGFR+, and 51% received chemotherapy or immunotherapy. Mean monthly TKI copayment was $312 (range= $0 to $5,913). Mean total and drug reimbursements were $234,294 and $114,253. Table 1 shows the adjusted effect of TKI copayments on insurance expenditures. **Conclusion:** Higher TKI copayments were not associated with lower insurance expenditures. Eliminating TKI copayments would reduce patient financial burden and not adversely impact insurer spending.

Table 1. Effect of Patient TKI Copayments on Insurance Expenditures, Adjusted for Age, Race, Comorbidity, Insurance Type, Mutation Type, Receipt of Chemotherapy and Immunotherapy (EGFR TKIs: erlotinib, gefitinib, afatinib, osimertinib; ALK TKIs: crizotinib, alectinib, ceritinib, brigatinib).

TKI Copayment (n=103)	Adjusted Mean Total Expenditure (95% CI)	P value	Adjusted Mean Drug Expenditure (95% CI)	P value
$0 (n=82)	$230,989 ($188,958; $273,019)	Ref.	$110,171 ($88,150; $132,194)	Ref.
Above $0 (n=21)	$264,963 ($182,424; $347,502)	0.44	$132,707 ($83,206; $182,208)	0.38

Keyword: Copayment; Insurance; Cost.

P1.16-31 BODY MASS INDEX RELATING TO PATIENT-REPORTED SYMPTOMS IN FIRST-LINE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Patient-reported outcomes (PROs) provide information on patient treatment experience. Our aim in this analysis was to assess the longitudinal relationship between body mass index (BMI) with patient-reported symptom severity and interference during treatment. **Method:** Between May 1, 2017 and December 7, 2018, patients with mNSCLC at a single institution were enrolled in a real-world Advanced Non-Small Cell Lung Holistic Registry (ANCHoR) and completed the MDASI-LC prior to start of therapy and at routine clinic visits. MDASI-LC consists of 16 symptom severity and 6 symptom interference items rated on 0-10 scales (0 = no symptom or interference, 10 = worst imaginable symptom or complete interference). BMI was measured at the same schedule as MDASI-LC. Mixed-effects models were used to examine the longitudinal association between BMI and symptom levels during treatment. **Result:** 103 patients completed the MDASI-LC prior to start of therapy and at least 2 follow-up assessments. Mean patient age was 64.3 years (standard deviation = 11.5) and 50% were males. 22% of patients received chemotherapy (CTX), 34% immunotherapy (IM), 23% CTX+IM or angiogenesis inhibitor, and 20% targeted therapy. The median pre-treatment BMI was 25.2 (inter quartile range, 5.2). BMI did not change during treatment and no significant difference was found among treatment groups. Compared with the obese group (BMI≥30), the overweight group (25≤BMI<30) experienced lowest levels of fatigue (estimation(est)=-1.23, standard error (SE)=0.49, p=0.016), disturbed sleep (est=-1.66, SE=0.49, p=0.002), distress (est=-0.90, SE=0.40, p=0.030) and less interference on mood (est=-1.03, SE=0.46, p=0.030) and interference with walking (est=-1.50, SE=0.51, p=0.005). The normal group (BMI<25) demonstrated lower levels of fatigue (est=-1.05, standard error (SE)=0.47, p=0.032) and disturbed sleep (est=-1.15, SE=0.47, p=0.018), compared with the obese group. **Conclusion:** For patients with mNSCLC, obesity was

related with higher symptom burden during active treatment. This analysis provides pilot data for future studies on balanced weight control and patients' wellbeing during cancer treatment.

Keywords: BMI, symptom burden, real-world evidence

P1.16-32 EMPOWERING LUNG CANCER SURVIVORS AND FAMILY MEMBERS TO "BREATHE EASIER": ADAPTATION AND EVALUATION OF A M-HEALTH INTERVENTION

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Background: Survivors of lung cancer often experience a myriad of symptoms that have devastating effects on their physical and psychological functioning such as dyspnea, fatigue, and stress. To combat these symptoms, the American College of Chest Physicians has recommended the use of complementary therapies. Mindfulness-based Cancer Recovery (MBCR) can empower survivors, and family members who often cope with their own health problems and the stress related to caring for a survivor. Our goal is to deliver a tailored, culturally sensitive, MBCR intervention to survivors and family members via a mHealth app. **Method:** This research was comprised of four phases. Phase I was the development and testing of an 8-week in-person intervention called *Breathe Easier* with survivors and family members (dyads). Phase II adapted *Breathe Easier* into a mHealth app prototype utilizing user-centered design. Phase III was a focus-group evaluation of the usability and acceptance of the mHealth app prototype by survivors and family members. Phase IV was comprised of additional interviews with an African-American subset of survivors and family members to assess the cultural sensitivity of the mHealth app. **Result:** Findings from the in-person intervention (n = 62) showed that all agreed the intervention materials were acceptable, different levels of yoga, breathing exercises, and meditations helped them, and involving a family member was important. Preliminary analyses showed survivors had less dyspnea and perceived stress over time (T1 vs T2). Both groups had improved fatigue and sleep scores. Findings from the mHealth app design and acceptance evaluation were organized into two primary categories: usefulness and ease of use. User-friendly design recommendations included aesthetic appeal, navigation layout, and display of content. Furthermore, potential health outcomes, privacy concerns, and comparison to in-person interventions also influenced app usefulness and acceptance. Lastly, findings from our cultural sensitivity assessment demonstrated that the mHealth app was culturally sensitive for African-Americans, but some changes were recommended. **Conclusion:** MBCR interventions hold great promise for improving the lives of racially diverse survivors of lung cancer and family members. An mHealth app will increase accessibility. However, special consideration of app design is needed to ensure future acceptance and longer-term usage.

Keyword: lung neoplasm, mindfulness, m-health application

P1.16-33 FROM A SYSTEMATIC REVIEW TO REAL WORLD EVIDENCE: INTEGRATING GENDER AS A CLINICAL RISK FACTOR IN NSCLC

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Background: Gender-based disparities in NSCLC experience have been widely discussed in the literature. The recognition of gender as a confounder in clinical practice remains uncertain. Confirming its impact on prognosis encourages personalized interventions in an effort to improve survival for NSCLC patients. Since best prevention programs are derived from findings established from multiple-evidence based analysis, the influence of gender on the observed disparities in NSCLC was explored using worldwide evidence and single institute experience. A systematic review was initially carried out to synthesize the evidence on a global scale to confirm the influence of gender-discrepancies in NSCLC incidence rates. Findings were compared and contrasted using a single cancer institute to highlight potential trends related to the different data. **Method:** We identified relevant articles published in English using Medline between 1996 and 2016. Pooled standardized-incidence data was analyzed using a semi-parametric longitudinal regression model to estimate changes in NSCLC incidence as a function of time, histology and gender. A heat map was also designed to illustrate the global trend of NSCLC captured in the published articles. Findings of this review were evaluated to confirm the influence of gender on NSCLC trends and outcomes using a single center record. A retrospective analysis was performed using the Glans-Look Database (GLD) for patients diagnosed between 1999 and 2015. The Kaplan-Meier estimator of cumulative survival was conducted to analyze treatment outcomes of patients using SPSS and R. Statistical significance was set at 95% confidence level ($p < 0.05$). **Result:** Our systematic review demonstrated gender-based disparities over time, and the main effect of gender on incidence rates is significant ($p=0.01$). Visualizing global trends of NSCLC's histology confirm that women are prone to develop ADC. GLD data verifies the influence of gender, where women were more prone to develop ADC (49%), and the relative changes of its rate over 15 years increased significantly compared to men (58% vs 32%, $P<0.02$). Survival rates were also predisposed by gender, where female ADC mOS exceeded that of males in overall comparisons (17.6 vs. 12.2, $p=0.047$). **Conclusion:** Our findings serve as a basis to resolve the inherent controversies in the research, and highlight the importance of gender as a clinical risk factor. Therefore, it is important to include gender as a prognostic tool to improve screening programs and promote tailored therapies for better outcomes. Biological, social, or a combination of factors could also influence the differences observed and warrant further investigation.

Keyword: #NSCLC #Gender #Prognosis #Risk

P1.16-34 ASSOCIATION BETWEEN SKIN REACTIONS AND CLINICAL BENEFIT IN PATIENTS TREATED WITH ANTI-PD-1 TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Anti-Programmed death-1 antibody is now standard therapy for advanced non-small cell lung cancer (NSCLC). However, immune-related adverse events (irAEs) including skin reactions are frequently observed. In melanoma, skin reactions and clinical efficacy are reportedly associated. However, little is known about this association in NSCLC. In addition, predictive markers of irAEs remain unknown. This study aimed to evaluate whether skin reactions correlate with clinical efficacy and identify potential clinical biomarkers that may meaningfully and conveniently predict skin reactions following treatment. **Method:** We retrospectively surveyed patients with advanced NSCLC who received nivolumab or pembrolizumab monotherapy at Sendai Kousei Hospital (n=155) between January 2016 and April 2018. The patients were categorized into two groups based on the development of skin reactions during treatment. Treatment efficacy was evaluated in each group, and predictive markers of skin reactions were determined. Furthermore, we also conducted 6-week landmark analysis to assess the association between early skin reactions and clinical benefit. **Result:** In the cohort of 155 patients (median [range] age, 68 [31-88] years; 117 men [75%], 38 women [25%]), skin reactions were observed in 52 (33%) patients. The median duration of onset of skin reactions was 6.4 weeks. The overall response rate (ORR) was significantly higher in patients with skin reactions than that in those without (57% vs. 19%; P<.001). The median progression free survivals (PFSs) were 12.9(95% confidence interval (CI), 8.5–not reached(NR)) and 3.4 (95% CI, 2.5-4.1) (P<.001) months, whereas the median overall survivals (OS) were NR (95% CI, 17.4-NR) and 11.4 months (95% CI, 8.8-15.6) (P<.001) in patients with and without skin reactions, respectively. In 6-week landmark analysis, the ORR was significantly higher in patients with skin reactions than that in those without (28 of 49 patients [57.1%] vs. 20 of 106 patients [18.9%]; P <.001), and the development of skin reactions was significantly associated with increased PFS (with skin reactions median PFS = 10.3 months, 95% CI, 5.6-NR ; without, median PFS = 4.2 months, 95% CI, 3.6-5.9; P=.045). Furthermore, multivariate analysis revealed that pre-existing rheumatoid factor (RF) was an independent predictor of skin reactions (odds ratio, 3.39; 95% CI, 1.56–7.33; P=.003). **Conclusion:** The development of

skin reactions was associated with clinical benefit in patients treated with nivolumab and pembrolizumab for NSCLC. Pre-existing RF also served as an independent predictor of skin reactions. Further studies with large patient samples are necessary to validate these findings.

Keywords: irAE, Anti-PD-1 treatment, advanced non-small cell lung cancer

P1.16-35 THE PROGNOSTIC IMPACT OF SARCOPENIA ON THE CLINICAL OUTCOME OF THORACIC SURGERY FOR NON-SMALL CELL LUNG CANCER IN ELDERLY PATIENTS

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Background: The elderly patients who undergo surgery for non-small cell lung cancer (NSCLC) is increasing in Japan whereas they are at high risk for surgery because of weakness of physical strength and increased comorbidity. Skeltal muscle depletion, referred to as sarcopenia, has recently been identified as a risk factor of poor clinical outcomes after surgery in the patients with various malignancies including NSCLC. We investigated the impact of sarcopenia on the clinical outcome of thoracic surgery for NSCLC in elderly patients. **Method:** We enrolled 259 patients over 65 years old with NSCLC who underwent pulmonary resection (lobectomy or segmentectomy) without any induction treatment before surgery in our hospital during 2012 to 2015. Sarcopenia was assessed by the psoas muscle mass index (PMI, cm^2/m^2) using the computed tomography imaging at the third lumbar vertebra level before surgery. Postoperative complications, which were observed within 30days after surgery, were classified according to Clavien-Dindo classification. Overall survival (OS) was evaluated by the Kaplan-Meier method with log-rank test (univariate analyses) and by the cox proportional hazard model (multivariate analyses). **Result:** Median age was 73 years old (65 - 92). One hundred fifty-five (60%) patients were male. Two hundred nine (81%) patients were cStage0 or I. Fifty-seven (22%) patients were squamous cell carcinoma (SCC). Postoperative pneumonia, arrhythmia, and delirium were observed in 17 (7%), 35 (14%) and 17 (7%) patients, respectively. Median follow-up was 48.7 months (range 3.0 – 79.6). Using the cutoff values as previously reported, 179 (69%) and 80 (31%) patients were diagnosed as sarcopenic and non-sarcopenic, respectively. Male and ever smoker were significantly more frequent in the sarcopenic patients than the non-sarcopenic patients (P < 0.001 and P = 0.018, respectively). The sarcopenic patients showed the trend of high incidence of Postoperative complications, however, there was no significant difference in OS between the sarcopenic and non-sarcopenic patients. Next, we performed the subgroup analysis to elucidate the prognostic factors only in the elderly sarcopenic patients. Among 179 sarcopenic patients, multivariate analysis including statistically significant factors in the univariate analysis revealed that the patients with restrictive lung disease, advanced cStage, postoperative pneumonia and delirium were inferior in OS [Hazard Ratio, 11.1, 3.6, 5.3 and 4.6; 95% confidence interval, 1.6 to 68.1, 1.1 to 13.0, 1.4 to 20.0 and 1.1 to 16.5; P= 0.011, 0.037, 0.017 and 0.041], suggesting the importance of the intensive perioperative management to avoid complications. **Conclusion:** Perioperative complications are significantly associated with the prognosis of the sarcopenic elderly patients with NSCLC. Intensive perioperative management is mandatory for NSCLC patients with sarcopenia to improve the clinical outcome after thoracic surgery.

Keywords: sarcopenia, elderly patient, Non-Small Cell Lung Cancer

P1.16-36 TREATMENT PATTERNS AMONG PATIENTS WITH EGFRM NSCLC TREATED IN THE US COMMUNITY ONCOLOGY SETTING

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Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy is associated with improved outcomes in patients with EGFR mutation-positive (EGFRm) non-small cell lung cancer (NSCLC). Despite initial responses, most patients develop resistance. Little is known about treatment following first-line (1L) TKIs. This study aimed to understand real world treatment patterns, T790M testing rates, and disposition of EGFRm patients following availability of newer TKIs. **Method:** Adult patients with EGFRm stage IV NSCLC treated between Dec 1, 2015 and Aug 31, 2017, were retrospectively identified from the US Oncology Network's iKnowMed℠ (iKM) electronic health record. Patient characteristics, treatment patterns, and T790M testing data were obtained via programmatic database abstraction and supplemented with chart review. **Result:** 308 patients were identified during the study period. Median age at diagnosis was 69 years, 67% were female, 63% Caucasian, 49% never smokers and 59% with ECOG performance status 0–1. Nearly all patients (n=302; 98%) received treatment with a TKI, 80% (n=246) with a TKI as 1L therapy. The most frequently used TKIs as 1L monotherapy were erlotinib (n=204; 66%), afatinib (n=27; 9%), and gefitinib (n=3; 1%). Combination chemotherapy with or without a TKI was used in 24% of patients. Among all patients treated with a 1L TKI, 19% (n=47) were tested for the T790M mutation after 1L TKI, and 34% (n=16) were positive. The most common 2L therapies in patients who received a 1L TKI (n=44 patients) were pemetrexed-based chemotherapy (n=20; 45%), afatinib (n=7; 16%), and osimertinib (n=7; 16%). Among all patients who received a 1L TKI, 15% (n=41) had died, 18% (n=51) were still alive and on TKI therapy, 12% (n=29) went on to receive subsequent therapy, and 53% (n=149) stopped their TKI and received no subsequent therapy at the end of the follow-up period. **Conclusion:** The majority of patients with EGFRm advanced NSCLC received 1L TKI therapy, most often with erlotinib. Following 1L TKI, less than 20% of patients were tested for T790M, and most did not receive any subsequent therapy following TKI. As understanding of resistance mechanisms in mutation-driven lung cancer is rapidly evolving, and as ongoing studies evaluate optimal treatments, it is imperative to integrate this information into clinical practice.

Keywords: treatment patterns, NSCLC, EGFR

P1.16-37 CORRELATION BETWEEN THE ACTUAL MEASUREMENT VALUE AFTER LUNG LOBECTOMY AND THE PREDICTED VALUE OF FORCED EXPIRATORY VOLUME IN 1 SECOND

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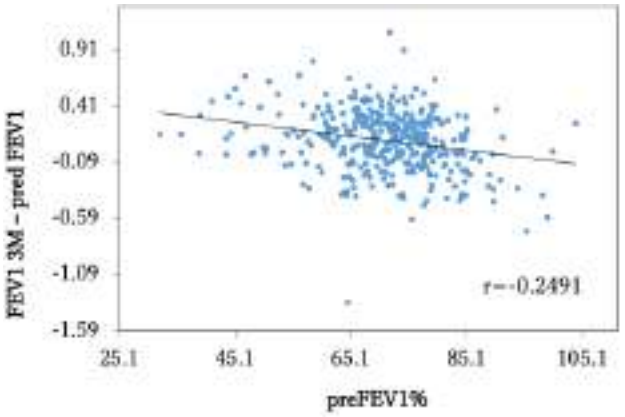
Background: It is important to accurately predict postoperative respiratory function to safely perform lung resection without impairing the postoperative quality of life (QOL), particularly for patients with a significant ventilatory defect. To easily predict the vital capacity (VC) and forced expiratory volume in one second (FEV1), the number of pulmonary segments remaining after lung resection are divided by the total number of pulmonary segments (predicted value of FEV1). **Method:** We performed a retrospective review of 386 consecutive lobectomies performed from June 2011 to December 2018 at the Ehime University Hospital. On the basis of the preoperative values of FEV1%, we made 4 groups: FEV1%< 50% (n=16), FEV1% ≥50% but <60% (n=29), FEV1% ≥60% but <70% (n=109), and FEV1% ≥70% (n=232). We compared the difference between the predicted value of FEV1 and the actual measurement value three months after the lobectomy. **Result:** The scattergram in Fig 1. shows the correlation between the preoperative FEV1% and the predicted value of FEV1 in all cases. A weak but negative correlation (r=-0.2491) was found between them. Furthermore, in the FEV1% <50% group, the actual measurement value of FEV1 three months after the lobectomy was 253.9 mL larger than the predicted value

and was 146.6 mL, 124.8 mL, and 70.4 mL in the FEV1 ≥50% but <60%, FEV1 ≥60% but <70%, and FEV1 ≥70% groups, respectively.



Conclusion: Although this method is convenient and useful in predicting the postoperative respiratory function, it tends to be generally underestimated, especially in patients with a significant ventilatory defect. These results suggest that it is necessary to be careful not to indicate an operable patient as being inoperable on the basis of the predicted FEV1.

Keywords: actual measurement value three months after the lobectomy, forced expiratory volume in one second, predicted value of FEV1

P1.16-38 RACIAL DISPARITIES IN LONG-TERM SURVIVAL AFTER SURGICAL RESECTION IN THE US

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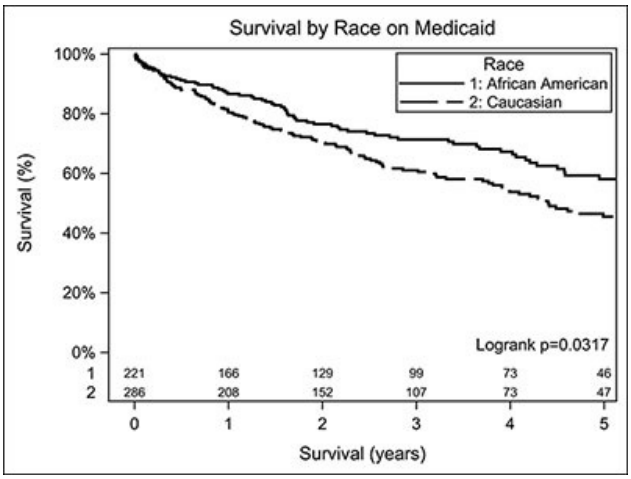
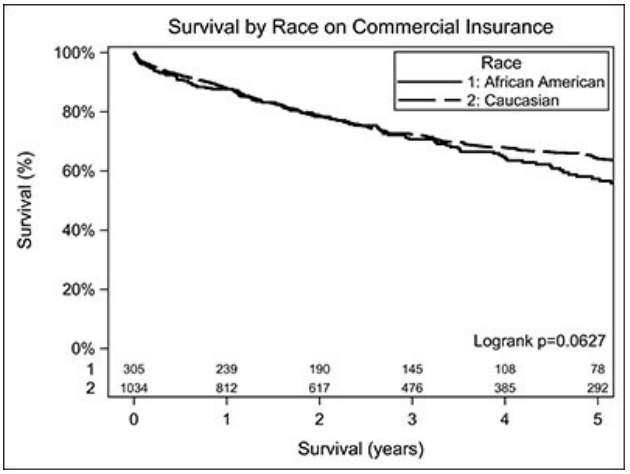
Background: Racial disparities exist in US lung cancer care, including delayed access, lower use of invasive procedures such as curative-intent surgery, and worse surgical outcomes in African-Americans compared to Caucasians. We investigated if racial disparities persist in non-small cell lung cancer (NSCLC) patients who received curative-intent resection in a population-based cohort. **Method:** We examined all patients from a prospective population-based cohort who underwent curative-intent resections for lung cancer from 12 hospitals across 7 healthcare systems from 2009-2018. We compared overall survival (OS) by race and adjusted for age, sex, smoking status, family history, tumor histology, and clinical stage. We used Chi-square tests, Kaplan-Meier plots, and Cox proportional hazards modeling, reporting unadjusted and adjusted hazard ratios (aHR) with 95% confidence intervals. **Result:** Of the 3,418 patients, 78% were Caucasian, 22% were African-American; 42% had Medicare,15% Medicaid, 39% commercial insurance, and 3% were uninsured. Caucasians were older (mean age 67.8 vs. 64.1; p=<0.0001). African-Americans were more likely to be active smokers (p=0.0017), have adenocarcinoma histology (p=0.0167), and less likely to be clinical stage I (p=0.0453). Median follow-up time in censored patients was 3.4 years. Overall, we found no differences in OS by race (unadjusted HR: 0.97 [0.88-1.08]; aHR: 0.998 [0.87-1.15]). However, stratified by insurance, we found significant differences (p=0.0251). Among patients with Medicaid insurance, African-Americans had significantly better OS (aHR: 0.73 [0.55-0.97]) than Caucasians but among patients with commercial insurance, African-Americans had significantly worse OS (aHR: 1.26 [1.02-1.57]).





Conclusion: When all patients receive curative-intent surgical resection, racial disparities in NSCLC survival may be reduced, but differences in the impact of race on survival by type of insurance suggest residual and complex disparities in both access and quality of care. Further exploration of the interaction between race, socio-economic factors, and the mechanisms of lung cancer outcome disparities is warranted.

Keyword: racial disparities, insurance, survival

P1.16-39 ONCOLOGY EMERGENCIES IN PATIENTS WITH LUNG CANCER: EXPERIENCE OF ONE HOSPITAL

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Background: Oncological emergencies (OE) are common conditions associated with significant morbidity and mortality. Individuals with malignancy may present with a cancer-related emergency; for many, this will be their initial manifestation of cancer (about 23%). Patients with lung cancer are the type of cancer patient who are most often admitted to emergency departments due to OE. The aim of this study was to characterize the OE like superior vena cava syndrome and metastatic spinal cord compression (MSCC) in patients with lung cancer, at our hospital. **Method:** a retrospective review was undertaken to assess the number and the outcomes of patients admitted from 2015 to 2018 with lung cancer who had superior vena cava syndrome and MSCC. **Result:** in this 4-year period there were 455 new patients with the diagnosis of lung cancer, and 31 had an OE: n= 15 (48%) had superior vena cava syndrome and n = 16 (52%) had MSCC. The median age was 66 years old and 90% were man. The histological diagnostics was adenocarcinoma in 48% (n=14), small cell lung cancer in 34% (n=10) and squamous cell carcinoma in 18% (n=4). In 61% (n=19) of the patients the OE was the first manifestation of cancer, and lead to the diagnosis. In the others, the median time between the diagnosis and the emergency was 6 month (0-56 month). Of this, 36% (n=4) were in the first-line chemotherapy, 36%

(n=4) in the second-line chemotherapy and 18% (n=2) in the third-line chemotherapy. MSCC was the most frequent OE with 46% (n=16) of the patients, followed by superior vena cava syndrome (43%; n=15). 63% of the patients with MSCC, when the diagnosis was performed had lost the ability to walk; 50% had paraparesis, 25% paraplegia and only one presented with sphincter incontinence. 69% (n=11) of the patients with MSCC were treated with radiotherapy; 44% (n=7) underwent surgery and/or radiotherapy; 13% (n=2) were treated with steroids in combination with radiotherapy. 14 patients who were presented with superior vena cava syndrome (93%) were treated with radiotherapy. After the OE only 13 patients (37%; n=8 (62%) in superior vena cava syndrome and n=5 (38%) in MSCC) initiated or restarted systemic treatment for lung cancer. In this group disease progression was observed in a median time of 2 month after OE (0-31 months). Only 2 patients with MSCC who had lost the ability to walk regain it. 71% (n=21) of patients were dead 3 months after the OE. Only 4 patients (25%) with MSCC and 6 (40%) with superior vena cava syndrome were alive after 3 months of OE. **Conclusion:** OE causes severe morbidity and compromised survival and can be the initial manifestation of lung cancer. We need to be aware of this situation because the this OE have the potential to progress rapidly; therefore, prompt, accurate diagnosis and institution of appropriate treatment are essential to achieve favorable outcomes.

Keywords: Oncology emergency, superior vena cava syndrome, metastatic spinal cord compression

P1.16-40 REAL-WORLD NEUROCOGNITIVE FUNCTION IN LUNG CANCER: INITIAL RESULTS OF THE PRO-LONG STUDY

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Background: Changes in neuro-cognitive function (NCF) as a result of treatment and disease have been repeatedly reported in cancer patients. However, contradictions exist on the prevalence and extent of impairment. Evidence in the lung cancer population is very limited. We here report the initial results of NCF in non-small cell lung (NSCLC) cancer patients receiving radiotherapy and/or systemic therapy in the PRO-Long study. **Method:** PRO-Long is a monocentric, prospective, longitudinal study, investigating the effect of first-line chemotherapy, radiotherapy and/or immunotherapy on patient-reported health-related quality of life (HRQoL), toxicity, functional exercise capacity (6-minute walking test – 6MWT) and NCF in locally-advanced and metastatic NSCLC patients. HRQoL and toxicity data are collected with patient-reported outcome measurements (PROMs). NCF data is collected with the Reys-Osterrieth Complex Figure Test (ROCF), Hopkins Verbal Learning Test-Revidsed (HVLT-R) free recall, delayed recall and recognition; Trail Making Test (TMT) A and B, Controlled Oral Word Association Test (COWA), Wechsler Adult Intelligence Scale (WAIS) digit span and the Stroop Color and Word Test (SCWT). Demographic data are collected at baseline; outcome data (survival, local and loco-regional control and metastatic relapse) during follow-up. NCF data is collected pre-treatment, and 2-3 months, 6 and 12 months after the end of treatment in patients receiving chemo- and/or radiotherapy or after start of immunotherapy. The mixed model approach was applied to determine statistical significance ($p < 0.05$). Meaningful clinical important difference (MCID) in NCF is defined as a decline greater than one standard deviation from baseline. **Result:** Between January 2016 and December 2018, 50 patients (mean age: 63) were recruited. The majority was male (60%), had locally-advanced disease (54%) and received chemotherapy with (50%) or without (24%) radiotherapy. NCF data is available of 49, 28, 16 and 10 patients at baseline, 2-3 months, 6 months and 1 year respectively. So far no significant decline was found in any NCF test. At 2-3 and 6 months after treatment, 42% and 34% of patients had a MCID decline in one or more tests. NCF decline was mostly detected in the HVLT-R free recall test, respectively 15 and 23% at 2-3 and 6 months. **Conclusion:** The initial data suggest that systemic treatment, all or not combined with radiotherapy may result in a clinically meaningful NCF decline in locally-advanced and metastatic NSCLC patients. Particularly, immediate recall seems to be affected. Updated results will be presented.

Keywords: Neuro-cognitive function, Real world data

P1.16-41 TIMING, SITES, AND CORRELATES OF LUNG CANCER RECURRENCE: THE MISSING PIECES IN NATIONAL DATASETS

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Background: Because national datasets do not collect relevant data, few studies have analyzed the timing, sites, and correlates of lung cancer recurrence. We therefore employed an institutional tumor registry to obtain information on this critical, intermediary disease outcome. **Method:** From the UT Southwestern Tumor Registry, we identified cases or primary and/or recurrent lung cancer diagnosed January 1, 2000, to December 31, 2017. For cases with recurrent disease, we recorded site, timing, and case characteristics (including gender, age, race, histology, and primary treatment). Associations between these factors were evaluated using univariable and multivariable random-effect logistic regression models. We estimated time to recurrence using Kaplan-Meier methods. We used univariable and multivariable marginal Cox regression models were to assess the association between time to recurrence and case characteristics. **Result:** A total of 1,619 stage 1-3 lung cancer cases from 1,549 patients were analyzed. Of these, 466 patients (30%) had recurrent lung cancer. In multivariable analyses, both race (P=0.02) and primary treatment (P<0.001) significantly correlated with recurrence. Among recurrent cases, patient age (P=0.02) and TNM staging (P=0.001) significantly correlated with timing of recurrence. The most common type of first recurrence was distant disease, most frequently central nervous system (94/162, 58%). The development of distant recurrent disease was associated with race (P=0.01), histology (P=0.004), and primary treatment (P=0.03). **Conclusion:** In this single-center analysis of early stage and locally advanced in lung cancer, approximately one-third of cases develop recurrent disease, most commonly at distant metastatic sites. Central nervous system was the most frequent site of distant recurrence, accounting for more than half of cases. Race, TNM stage, and primary treatment were associated with the timing and site of recurrent disease. These findings have potential relevance to post-treatment clinical and radiographic surveillance.

Keywords: Recurrence, Clinical surveillance, Single-center analysis

P1.16-42 REAL-WORLD TRENDS IN SYSTEMIC ANTICANCER THERAPY (SACT) FOR SQUAMOUS ADVANCED NSCLC (ANSCLC) IN THE US, 2011–2018

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Background: The SACT options for aNSCLC continue to increase each year with approvals of more effective therapies that improve long-term outcomes, as seen with immunotherapies (IO). Our aim was to examine real-world trends in SACT distribution and sequence from first- to second-line (1L-2L) for squamous aNSCLC from 2011-2018 at US community oncology practices. **Method:** This study used the nationwide Flatiron Health de-identified, EHR-derived database (cutoff: 31Jan2019). Eligible patients were adults who initiated 1L SACT from Jan2011-Jun2018 for aNSCLC with squamous histology, excluding patients with known EGFR/ALK-positive tumors. Descriptive analyses included patients receiving ≥1 SACT dose, assigning all SACT regimens to mutually exclusive classes in hierarchical order (combination regimens assigned by highest component), from highest to lowest: (1) PD1/PD-L1 inhibitor (anti-PD1/L1)-based, (2) EGFR/ALK TKI-based, (3) platinum-based chemotherapy combination with vascular endothelial growth factor inhibitor (PBC+VEGF), (4) PBC only, (5) single agent chemotherapy, (6) others. The 2L regimens were examined for patients with 1L SACT initiation only through 2017 to enable sufficient follow-up. Results were stratified by years and by pre-IO and post-IO years of 1L initiation, defined as 2011-2014 and 2015-2018, respectively, based on the earliest IO approval for 2L therapy in Mar2015. **Result:** For 1L therapy, in the pre-IO period, most patients were prescribed PBC (80%), and post-IO, most patients were prescribed PBC (68%) or anti-PD1/L1 (21%). Among patients prescribed 1L therapy, the percentages who received 2L therapy were 44%-53% following 1L PBC and 25%-37% following 1L anti-PD1/L1, with 19% of 2017 1L anti-PD1/L1 starts still on 1L therapy (table).

SACT prescribing for squamous aNSCLC by 1L initiation year, including 1L and three most common 2L regimens overall

1L Regimen	2011 (n=476)	2012 (n=769)	2013 (n=924)	2014 (n=1044)	2015 (n=1240)	2016 (n=1327)	2017 (n=1374)	2018(¼) (n=634)
PBC, n(%)	383(81)	594(77)	756(82)	851(82)	939(76)	939(71)	848(62)	388(61)
Still on 1L[a]	3%	3%	4%	5%	4%	5%	6%	--
Rec'd 2L[a]	50%	49%	44%	45%	52%	52%	53%	--
Anti-PD1/L1[b]	1%	2%	4%	24%	67%	74%	80%	--
PBC[b]	44%	37%	36%	25%	14%	10%	8%	--
Single[b]	31%	38%	39%	32%	11%	9%	8%	--
Anti-PD1/L1, n(%)[c]	0	0	0	2(0)	123(10)	230(17)	394(29)	191(30)
Still on 1L	--	--	--	--	6%	11%	19%	--
Rec'd 2L	--	--	--	--	37%	31%	25%	--
Single	--	--	--	--	37%	35%	24%	--
PBC	--	--	--	--	15%	18%	38%	--
Anti-PD1/L1	--	--	--	--	15%	22%	24%	--
Single, n(%)	44(9)	107(14)	95(10)	104(10)	98(8)	41(3)	41(3)	21(3)
Other, n(%)	23(5)	33(4)	34(4)	45(4)	43(4)	80(6)	69(5)	28(5)
EGFR/ALK, n(%)	13(3)	20(3)	25(3)	26(3)	18(2)	16(1)	9(1)	1(0)
PBC+(EGF, n(%)	10(3)	15(2)	14(2)	16(2)	19(2)	21(2)	13(1)	4(1)

[a]Patients still on 1L or prescribed 2L represent percentages of patients initially prescribed 1L.
[b]Percentages for 2L SACT regimens represent percentages of patients prescribed 2L.
[c]Anti-PD1/L1 regimens included anti-PD1/L1 monotherapy and combination therapy with PBC.

Conclusion: PBC remain the most common 1L SACT prescribed through mid-2018 for patients with squamous aNSCLC at US community oncology practices. Prescribing of PD1/PD-L1 inhibitors as 1L has gradually increased since regulatory approval starting in 2015. Approximately one-half of patients with squamous aNSCLC prescribed 1L PBC are treated with 2L therapy.

Keywords: squamous NSCLC, real-world therapy trends, Immunotherapy

P1.16-43 PREVALENCE OF CLINICAL AND SUB-CLINICAL MALNUTRITION IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS AND ASSOCIATION WITH OUTCOME

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Background: While weight loss and lean body mass wasting are common hallmarks of non-small-cell lung cancer (NSCLC), their early detection and management are usually overlooked in clinical routine. The present study aimed to explore the prevalence of malnutrition and its correlation with outcome in advance (A)-NSCLC pts. **Method:** A-NSCLC pts treated at AOUI of Verona (2016-2018) received nutritional counseling by a qualified dietitian. Prevalence of malnutrition was assessed by nutritional screening score (NRS). Bilateral psoas major muscles were measured at L3 vertebrae level with routine staging-computed tomography (CT). Changes in psoas muscles observed in subsequent scans were evaluated using Wilcoxon signed-rank test. Clinical, pathological and nutritional data were correlated to progression-free/overall survival (PFS/OS) and response rate (ORR) using a Cox and logistic regression model. Kaplan-Meier curves were compared with Log-Rank. **Result:** Data from 38 pts (20 males [52.6%], 18 females [47.4%]) were gathered (median age 59 years [range 42-82], with a median follow-up of 21 months (range 1-197). At baseline, 18.4% were underweight, 18.4% normal weight, 34.2% overweight and 31.6% obese. The majority (65.8%) were at risk of malnutrition (NRS≥3). At multivariate analysis, stage (HR 4.99, 95% CI 1.05-27.74, *p = 0.04*), performance status (HR 4.99, 95% CI 1.55-16.03, *p = 0.007*) and NRS (HR 7.61, 95% CI 1.52-38.11, *p = 0.01*), were significant independent predictors for PFS. Pts with baseline NRS≤3 had significantly longer 1-year PFS (58.6% vs 16.7%, *p = 0.04*) and 2-year OS (90.6% vs 68.3%, *p = 0.03*) and a better ORR than those with NRS > 3 (66.7% vs 21.4%). Conversely, BMI did not affect PFS/OS. A significant loss in psoas muscle mass was detected in pts treated with both immunotherapy and other therapies (*p = 0.01* and *p=0.002,* respectively). Of interest, in immunotherapy-treated pts (n = 16) loss in psoas muscle mass correlated with worse ORR, PFS and OS, although differences did not reach a statistical significance due to the limited sample. **Conclusion:** Our analysis suggests that malnutrition has a detrimental impact on ORR, PFS and OS in A-NSCLC. Particularly, in pts treated with immunotherapy, muscle mass wasting seems to impact on efficacy outcome, suggesting a potential interaction between immunological and nutritional parameters. Therefore, the introduction in the clinical routine of a comprehensive nutritional profiling and monitoring, beyond body weight and BMI, is highly recommended in A-NSCLC. A comparison between NSCLC pts who underwent a personalized nutritional intervention during therapy and who did not is ongoing, together with a series of biomolecular analysis.

Keyword: lung cancer; nutritional screening; survival.

P1.16-44 MULTIPLE PRIMARY CANCERS (MPC) IN A COHORT OF LUNG CANCER (LC) PATIENTS (P): INCIDENCE AND CLINICAL FEATURES

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Background: The prognosis of p with LC has drastically changed during the last decade due to the improvement in prevention, diagnosis and treatment. Therefore, the number of LC survivor ps has significantly increased and subsequently the incidence of MPC is also rising. This study investigates the co-occurrence of MPC among p diagnosed with LC. **Method:** We reviewed of clinical data of patients with histologically confirmed LC visited at our institution between February 2016 and December 2018. **Result:** A total of 492 p out of 777 p, (63.3%) had adenocarcinoma and 223 p (28.7%) had squamous LC. The most frequently related comorbidities were hypertension (42.5%), dyslipidemia (36.2%), COPD (21%), cardiovascular disease (15.7%) and diabetes mellitus (14.5%). Molecular analysis was perform in 402 p (51.7%). EGFR mutation was detected in 77 p (exon 19 in 14% and exon 21 in 5% of p). ALK and ROS1 translocation were diagnosed in 27 and 7 p, respectively. Two primary cancers occurred in 111 cases (14%), including 15 p (1.9%) with three or more primary cancers. Patients with MPC were predominantly males (76.8%), smokers (85%) and 34% had prior family history of MPC. Median age at the first tumor diagnosis was 64 years (57-71). LC occurred as first neoplasm in 8.1% of the cases, 92 p (83%) developed metachronic MPC and 19 p (17%) synchronous MPC. Most common secondary primary cancer were head and neck in 19%, non-melanoma skin cancer in 19%, prostate in 12.6%, bladder and upper urinary tract cancer in 10%, colorectal in 6.3% and breast in 5.4%. First-line treatment for advanced or locally advance LC included chemotherapy in 65.6%, concomitant chemoradiotherapy in 14%, targeted therapy in 4% and immunotherapy in 4%. Overall response rate (ORR) to first-line treatment was 43.7%. Second-line treatment included chemotherapy in 47.6% and immunotherapy in 30.4%, with and ORR of 30%. **Conclusion:** In our series, the frequency of the co-occurrence of MPC among LC p is 14%, suggesting that surveillance strategies are recommended in this population. Most frequent MPC in LC patients are related to smoking. ORR in first and second-line are consistent with the literature.

Keywords: Lung cancer, multiple primary cancers, Real-world data

P1.16-45 CHANGING ATTITUDES REGARDING LUNG CANCER: SHAME, EMBARRASSMENT, AND HOPE

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Background: Sriram and colleagues (2015) showed that implicit attitudes (IA) and explicit attitudes (EA) related to shame, embarrassment and hope are more negative toward lung cancer (LC) than breast cancer (BC). The current study used the same measurement procedures as in 2012 to test whether stigma related to LC has decreased in the intervening years. **Method:** To assess EAs, participants (people with cancer [*n*=223], caregivers [*n*=590], healthcare providers [HCPs, *n*=160], and the general public [*n*=637]) were asked to rate their agreement on a six-point scale, with statements about how people with LC and BC "do feel" (descriptive

attitudes). IAs were measured with 3 Implicit Association Tests (IAT) using LC or BC images and categories of good/bad; hope/despair; or suitable/shameful. An IAT *D*-score indicated the strength of bias of LC relative to BC where >0.15 = bias against LC; between -0.15 and +0.15 = no bias, and < -0.15 = bias against BC. **Result:** IAs and EAs were consistently more negative towards LC compared to BC, with the exception of the EA related to embarrassment. When compared to the 2012 data, all IAs and EAs indicate a significant reduction in negativity and stigma of IA and EA toward LC relative to BC, with the exception of IA related to Shame (p=.079). These trends were consistent across caregivers, patients, HCPs, and the public.

	Strain et al., 2015 (Data collected in 2012)	Current data (2019)	p
Explicit			
Ashamed	Mean* = 3.69 40%, 47%, 13%	Mean* = 0.16 28%, 55%, 18%	<.0001
Embarrassed	Mean* = 3.47 32%, 54%, 14%	Mean* = 0.903 19%, 61%, 20%	<.0001
Hopeful	Mean* = 1.08 4%, 41%, 55%	Mean* = -0.67 5%, 56%, 40%	<.0001
Implicit			
Good/Bad	D = 0.42 75%, 17%, 8%	D = 0.32 68%, 24%, 10%	<.0001
Shame/Suitable	D = 0.35 61%, 17%, 18%	D = 0.30 68%, 21%, 13%	.070
Hope/Despair	D = 0.42 74%, 16%, 10%	D = 0.34 78%, 16%, 11%	.003

Percentage order: LC bias%, no bias%, BC bias%; D=mean IAT score; *Means for explicit are difference between scores where positive numbers indicate higher scores for LC than BC.

Conclusion: Compared to data collected in 2012, five of six implicit and explicit attitudes showed a significant reduction in negativity toward lung cancer relative to breast cancer. These findings are especially notable given that current evidence indicates little support for longitudinal shifts in IA at the group level (e.g., Lai et al., 2016; Schmidt & Axt, 2016).

Keywords: Lung cancer, implicit attitudes

P1.16-46 GENETIC TESTING PATTERNS, TREATMENT CHARACTERISTICS, AND OVERALL SURVIVAL IN ALK-POSITIVE METASTATIC NSCLC PATIENTS TREATED WITH CERITINIB

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Background: In patients with ALK-positive metastatic non-small cell lung cancer (mNSCLC), the majority of data on ALK inhibitor (ALKi) use and related survival outcomes are from clinical trials; information from community practice is sparse. This study therefore sought to assess ALK testing patterns, treatment characteristics, and overall survival (OS) in patients with mNSCLC treated with ceritinib in routine practice. **Method:** In this retrospective cohort study, medical records for patients with ALK-positive mNSCLC (diagnosed during 2008-2016; aged ≥18 years) were selected from sites in Canada and Europe. Patients were treated with ceritinib in any line for mNSCLC and had at least 8 months of follow-up after ceritinib initiation, except for patients who died sooner than 8 months. Baseline patient characteristics, treatment patterns, and timing of ALK testing relative to start of therapy lines were descriptively assessed. OS was assessed using Kaplan-Meier methods. **Result:** 87 patients were selected (median age: 53 years). Nearly 56% of patients had been tested for ALK mutation before initiating the first-line therapy (1L); 72% were tested before 2L and 77% before 3L. The most common regimens were cisplatin/pemetrexed (25%) in 1L, crizotinib (28%) in 2L, and ceritinib (35%) in 3L. Over two-thirds (68%) received treatment with at least 2 ALKis. The most commonly observed ALKi sequences were crizotinib followed by ceritinib (52%), ceritinib only (23%), and crizotinib followed by ceritinib followed by alectinib (12%). Median OS (95% CI) from mNSCLC diagnosis was 39 (33.1-50.1) months. Median OS (95% CI) from treatment initiation was 36 (28.2-48.9) months for 1L, 29 (22.1-42.8) months for 2L, and 23 (14.0-40.5) months for 3L. **Conclusion:** Only slightly more than half of patients with ALK-positive mNSCLC were tested for ALK mutation before initiating the first-line therapy during the study period. ALKis were the preferred therapies in the second and third lines. Median OS following the first-line therapy initiation was nearly 3 years among the selected study patients.

Keywords: Ceritinib, ALK, metastatic NSCLC

P1.16-47 EMBEDDING RESEARCH (AND EVIDENCE) IN CANCER HEALTHCARE - ENRICH

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Background: In Australia, as in other regions, lung cancer persists as the most common cause of cancer related death and is the leading cause of morbidity and burden of disease. Improvements in lung cancer survival rates are not comparable with improvements for other cancers. The Sydney Catalyst flagship program 'Embedding Research (and evidence) in Cancer Healthcare – EnRICH', is building a program of translational research in lung cancer to develop and extend evidence of effective treatments and to increase the use of clinical care based on existing evidence. Specifically, this prospective clinical cohort of patients with lung cancer (non-small cell and small cell, any histological type, any clinical/pathological stage) will establish a comprehensive data platform, including biological samples (FFPE diagnostic tumour tissue, and serial pre- and post-treatment blood samples) with matched demographic, clinical, biomarker, molecular profile, and outcome data (including quality of care and patient-reported outcomes) to support a range of interconnected research from across the T1 – T3 translational research spectrum, from bench to bedside (and bedside to bench) through to policy and practice. A linked implementation science program will identify methods to promote better integration of research findings and evidence. EnRICH will build on existing collaborations within Sydney Catalyst, across NSW, Australia, and internationally to establish a multidisciplinary program of research in scientific discovery, diagnostic and therapeutic development, clinical trials and implementation science. **Method:** Aim To assemble a patient cohort to: describe the natural history of and patterns of care for lung cancer; identify current gaps in evidence and practice for clinical quality improvement; create a platform for researchers across the T1-T3 translational research spectrum to develop and initiate clinical research and intervention studies to address gaps. Initially lung cancer will be an exemplar. Design Prospective clinical cohort of lung cancer patients including matched demographic, clinical, biomarker, molecular profile, and outcome data (including quality of care and patient-reported outcomes) for current and future research projects. Planned sample size At least 1000 patients. 505 patients enrolled at 31 Jan 2019. Inclusion criteria All patients with lung cancer presenting to defined clinical sites for diagnosis or treatment, including: Patients with a new diagnosis of primary lung cancer (any histological type, any pathological/clinical stage including metastatic) undergoing primary treatment; curative or palliative Patients with first progressive disease, local recurrence or new metastasis after completing previous treatment for non-metastatic disease at the time of initial diagnosis Aged over 18 years Data and biospecimen collection Matched clinical and demographic data will be collected from patient medical records and hospital administrative data sets Archival tissue, for research, will be obtained from routine biopsy specimens. Serial blood samples for research, on average 3 per patient (e.g. prior to commencement of treatment [baseline], and post-treatment [6 and 12 month follow-up]) Patient reported outcomes will be measured through questionnaires Statistical considerations The cohort will enable reliable estimates of outcomes both overall and within histologic and genetic sub-types. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Translational research, Clinical cohort, Clinical quality improvement

P1.16-48 EXPERIENCES OF PTS ON 1ST LINE CARE (EP1C): SYMPTOMS AND IMPACTS OF EGFR TKI THERAPY ON REAL-WORLD DAILY LIVES OF NSCLC PTS

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Background: Approximately one third of patients with NSCLC have tumours harbouring actionable EGFR mutations (Zhang et al. Oncotarget 2016). These patients are routinely treated with EGFR-tyrosine kinase inhibitors (TKIs) that are approved based on their efficacy and safety in clinical trials. Clinical trials do not fully reflect patient experiences as felt and perceived by patients, and in the real world, symptoms related to EGFR-TKIs and impact on patients' daily lives are not well documented or understood. EP1C assessed patients' experience with EGFR-TKIs and their impact on patients' daily lives. Patient insights gained from EP1C can help guide symptom management strategies and improve communication with patients, helping to improve outcomes and quality of life. **Method:** This pilot, non-interventional, US-based, real-world study involved individual interviews with adult patients. Eligible patients were those diagnosed with EGFR-mutated metastatic NSCLC, taking one of three US-approved EGFR-TKIs (erlotinib/afatinib/osimertinib) as first-line treatment. Exclusion criteria included: major surgery or radiation therapy three months before treatment, chemotherapy or other therapy as first-line treatment, a second active cancer, or a cognition or sensory issue. Trained qualitative interviewers used a semi-structured interview guide, and conducted all interviews by telephone. Rating questions were included for the severity and degree of bother caused by their symptoms (0–10 point response scale: 0=not at all severe, 10=extremely severe). All interviews were audio recorded, transcribed and coded (ATLAS.ti software) for analysis of similar themes. **Result:** A total of 19 patients participated in the interviews. The average age was 54.0 years (range 37–76). The sample was 73.7% female (n=14), and 89.5% (n=17) had an education level of college or above. The most frequently reported symptoms were respiratory and gastrointestinal symptoms (n=18; 94.7% each), skin-related sympoms (n=18; 94.7%), discomfort and pain (n=17; 89.5%), hair and nail-related symptoms (n=17; 89.5% each), fatigue and other energy-related symptoms (n=15; 78.9%). Ratings of severity and bothersomeness trended toward the mid-range of the scale (4.0 to 6.0) for most of the more commonly reported symptoms. The higher ratings were seen for very specific symptoms reported by only one or two patients, including constipation (8.0 severity/8.0 bother), armpit rash (7.0/8.0), tightness in throat (8.0/8.0), mouth soreness (8.0/9.0) and stinging/burning in the genital area (10.0/10.0). All 19 patients reported impacts on their daily performance and emotional health. Sleep difficulties were reported by 12 patients (63.2%), and 9 patients (47.4%) reported limitations with inter-personal relationships and social functioning. The impacts on patients' daily activities (work, chores, daily routine; 7.8) and emotions (anxiety, worry, fear and depression; 7.2) were found to be the most difficult to cope with. Several specific impacts, reported by fewer patients, included decreased independence (n=2; 7.0), economic burden (n=6; 7.7), and childcare difficulties (n=2; 8.5). **Conclusion:** In EP1C, real-world interviews allowed patients to express a broader range of symptoms and impacts compared with clinical trials, which mostly focus on symptoms. Some of the traditionally less commonly reported symptoms had a greater impact on patients' daily lives. Clinicians should also consider these when assisting patients in managing their symptoms.

Keywords: EGFR, Quality of life, patient experience

P1.17 TREATMENT OF EARLY STAGE/ LOCALIZED DISEASE
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.17-01 SURGICAL OUTCOME OF EARLY STAGE LUNG CANCER RELATED VS UNRELATED TO HONEYCOMB LESIONS WITH INTERSTITIAL PNEUMONIA

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Background: Lung cancer complicated with idiopathic interstitial pneumonia (IIPs) is known to lead to worse prognosis. Recently, it has been reported that the pathological characteristics differ between the lung cancer arising the honeycomb lesion of interstitial pneumonia (H-IIP group) and arising in other lesions (NH-IIP group). In this study, we aimed to assess the clinicopathologic outcome of resected lung cancer in each group. **Method:** From a single center database of 1065 consecutive patients with clinical stage IA non-small cell lung cancer who had undergone preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/ computed tomography, 112 patients with a radiologically determined IIP (H-IIPs; n=33, NH-IIP; n=79) were included in this study. Examination of clinicopathological outcomes were performed comparing each group. **Result:** Median solid tumor size of each group were similar (18.4mm vs 18.6mm p=0.928), but median ground gloss opacity rate is significantly higher in NH-IIP group (6.7% vs 21.4% p=0.042). In the histopathological types, H-IIP group had significantly high rate of squamous cell carcinoma (45.5% vs 27.9%) and NH-IIP group had adenocarcinoma (27.3% vs 57.0%). As in previous reports, the proportion of EGFR mutation in adenocarcinomas tended to be high in NH-IIPs and also the high proportion of lepidic predominant. The disease-free survival (DFS) and overall survival (OS) were worse in patients of H-IIP group compared to NH-IIP group (DFS p=0.028, OS p=0.035). In a multivariate analysis, the H-IIP group and lower diffusing capacity for carbon of preoperative pulmonary functional test were significant worse predictors of OS and RFS (P < 0.001, respectively). **Conclusion:** Lung cancer arising the honeycomb lesion of IIP had a great unfavorable impact on the prognosis of NSCLC, because of the worse pathological features.

Keywords: interstitial pneumonia, surgery, Early Stage Lung Cancer

P1.17-02 THE INVESTIGATION OF INTRAOPERATIVE MARKING BY TRANSBRONCHIAL LOW POWER LASER IRRADIATION IN HUMAN LUNG

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Background: Small lung nodules which appear to be ground glass opacity in peripheral lung are difficult to identify during surgery. In order to identify the site of such lesions, various types of preoperative or intraoperative marking methods have been reported. However, there is no definitive way. Therefore, we have reported a new safe and reliable intraoperative marking method using low power laser light. By irradiating low power laser close to the lesion from a bronchus, the site of the lesion can be identified from the lung surface by looking at the laser light. We conducted an animal experiment and were able to observe the laser light irradiated in bronchus from the lung surface. In this study, we performed laser irradiation to the resected human lung to confirm whether the laser light can actually be observed safely from lung surface. **Method:** The patient was 70-year-old male (40 pack-years ex-smoker). The adenocarcinoma (55×40mm) was located at right S2 area. Immediately after right upper lobectomy, a plastic cylindrical-type laser probe was inserted into peripheral bronchus of the resected lung. The probe was very thin (0.8mm diameter) and flexible. Therefore, it can be inserted into the peripheral lung. It was developed jointly with Keio University. The probe was induced just below the pleura and 70mW low power laser irradiation was performed. We examined whether laser light could be confirmed from lung surface. The effect of laser irradiation to the lung tissue was evaluated pathologically. **Result:** When the probe was guided to just below the pleura, laser light could be clearly observed from the lung surface. After that, the probe was gradually

withdrawn. The laser light could be observed until the depth of 10mm from the pleura. No damage was obtained around the laser irradiated area in pathological findings. The observable depth of laser light was slightly shallow at10mm. The reasons of this were guessed that lung expansion was not sufficiently because harvested lung was used, so the density of lung tissue was increase and pleural thickening and anthracosis were observed in the lung because of his smoking history. **Conclusion:** It might be possible to confirm the localization of small nodules in peripheral lung using low power laser light during surgery.

Keywords: Lung cancer, small nodule, surgical marking

P1.17-03 INTER-FRACTION VARIABILITY OF 18-FDG PET DURING LUNG SBRT AND THE EFFECT OF SYSTEMIC AND IMMUNOTHERAPY: RESULTS OF A PROSPECTIVE PILOT STUDY

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Background: 18-FDG PET/CT has been used to inform prognosis, response to treatment, adaptive planning, and target volume delineation in NSCLC. Changes in PET characteristics, such as inter-fraction variation of 18-FDG uptake during a course of ablative radiation, and how PET metrics respond to systemic agents during SBRT, are unknown. This study prospectively characterized key metabolic parameters during lung SBRT, an important factor for biology-guided radiotherapy (BgRT). **Method:** Patients treated with lung SBRT of 50Gy in 5 fractions for early-stage NSCLC or lung metastases were eligible. Three PET/CTs were acquired per protocol: within 2 weeks of treatment start (PET1), between fractions 1 and 2 (PET2), and fractions 4 and 5 (PET3). The primary endpoint was inter-fraction variability. FDG-PET parameters including maximum and mean standardized uptake value (SUVmax, SUVmean), metabolic tumor volume (MTV), and derived metrics were extracted and compared longitudinally; where change between PET1 and PET2 is denoted as PET1-2. PET parameters were extracted using a MIMVISTA (v6.8.3) work station. Lesions were segmented with individualized location-based window settings. The effect of co-variates on each static (PET1, PET2, PET3) and change metric (PET1-2, PET2-3, PET1-3) were determined for each PET parameter. Continuous and categorical variables were compared by non-parametric methods with Spearman and Kruskal-Wallis tests. Clinical trial NCT03493789. **Result:** 14 patients who completed treatment as prescribed, with 17 total target lesions, were included. Treatment indications were: 5 (35.7%) medically-inoperable, 2 (14.3%) medically operable, 1 (7.1%) recurrent, 2 (14.3%) metastatic consolidation, 4 (28.6%) metastatic progression. 7 (50%) received prior systemic therapy, 4 (28.6%) received immunotherapy with 2 (14.3%) given concurrently. In aggregate, SUVmax did not significantly change over the SBRT course. Average SUVmax change from PET1 to PET2 (PET1-2) was -8.2% (p=0.51), -7.0% for PET1-3 (p=0.52), and 1.3% for PET2-3 (p=0.92). SUVmean, [SUVmax/SUVmean], and normalized parameters of [SUVmax/liver SUVmean] and [SUVmean/liver SUVmean] were similarly stable over the treatment course. Multiple PET2, PET1-2, and PET2-3 parameters were significantly related to systemic therapy, immunotherapy, and timing of administration. There were no significant interactions between age, sex, number of target lesions, target location, lesions centrality, smoking status, and static and change metrics for each PET parameter.

Table 1. Correlation between treatment variables and median SUVmax for each PET/CT study and each inter-fraction SUVmax change between PET/CTs.

	PET1		PET2		PET3		PET1-2		PET1-3		PET2-3	
Co-variates	Median SUVmax	p-value	Median SUVmax	p-value	Median SUVmax	p-value	SUVmax change	p-value	SUVmax change	p-value	SUVmax change	p-value
Systemic therapy (no vs yes)	7.52 vs 5.76	0.336	8.24 vs 4.91	0.021	6.12 vs 7.26	0.700	0.79 vs -1.46	0.034	0.13 vs -0.40	0.700	-2.46 vs 1.98	0.005
Immunotherapy (no vs yes)	7.46 vs 5.99	0.752	7.92 vs 4.82	0.058	7.26 vs 3.50	0.461	0.65 vs -3.11	0.027	0.14 vs -1.40	0.598	-1.14 vs 0.58	0.073
Concurrent administration (no vs yes)	5.99 vs 10.67	0.365	7.44 vs 6.30	0.821	6.12 vs 10.91	0.308	0.58 vs -4.37	0.024	0.10 vs -1.48	0.428	-0.40 vs 4.38	0.113

Conclusion: Serial 18-FDG PET imaging during lung SBRT demonstrated minimal variability of key parameters. FDG uptake at PET2, change from baseline, and between fractions, were related to systemic therapy, immunotherapy, and timing of administration. Mechanism of PET parameter variability, and its impact of on oncologic outcomes require investigation; prospective evaluation of BgRT is ongoing.

Keywords: PET/CT, SBRT

P1.17-04 MULTICENTER OBSERVATIONAL STUDY OF NODE-NEGATIVE NON-SMALL CELL LUNG CANCER PATIENTS WHO ARE EXCLUDED FROM A CLINICAL TRIAL

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Background: The Japan Clinical Oncology Group (JCOG) conducted a randomized phase III trial (JCOG0707), which compared the survival benefit of tegafur/uracil (UFT) and tegafur/gimeracil/oteracil (S-1) for completely resected pathological stage I (T1>2 cm and T2 in the 6th TNM classification) non-small cell lung cancer (NSCLC). A total of 963 patients were enrolled. Recently, there is a growing concern that those who participated in clinical trials are highly selected and do not represent the "real-world" population. Hereby, we conducted a multicenter observational study of patients excluded from JCOG0707 trial during the study period. **Method:** Patients with completely resected pathological stage I NSCLC, eligible for, but excluded from the JCOG0707 trial during the enrollment period (Nov. 2008– Dec. 2013) were eligible for this study. Physicians from institutions that participated in the JCOG0707 retrospectively assessed the medical records of each patient. The final survival data were collected as of Dec. 2018. **Result:** Of the 48 institutions participating in JCOG0707, 34 participated in this observational study. They had enrolled 917 ("JCOG" cohort) to JCOG0707. To this study, 5004 patients ("All"

cohort), or 85% of those initially considered for JCOG0707 at the 34 institutions, were enrolled. Among them, 2388 (47.7%) were ineligible for the trial and 2616 (52.3%) had not been enrolled to JCOG0707 despite being eligible ("Eligible" cohort). Of the 5004 patients, 1659 (33.2%) received adjuvant chemotherapy, mainly UFT (1550 of 1659, or 93.4% of those received any adjuvant chemotherapy). The 5-year survival rates (5yOS) for All and Eligible cohorts were 83.9% and 89.1%, respectively, versus 89.2% in the JCOG cohort. The 5yOS with UFT adjuvant were 89.4% in Eligible and 88.9% in JCOG cohorts, respectively. UFT administration was a significant prognostic factor in All (adjusted HR=0.66, p<0.0001), but not in Eligible cohort (adjusted HR=0.88, p=0.28). The patients were classified into 3 subgroups, those with tumors without GGA (ground-glass area, non-invasive component; GGA-), with GGA (GGA+) and tumor size < 3 cm, and GGA+ with tumor size > 3cm. 5yOS of 744 patients in the Eligible cohort with GGA+ and tumor size < 3cm were excellent, 96.9%/96.4% with/without UFT. For 416 patients with GGA+ tumor sized > 3cm in Eligible cohort, invasive tumor size in the pathological specimen was prognostic but not predictive for UFT effect. When the invasive tumor size was >3 cm, 5yOS with/without UFT were 90.0/87.8%, whereas when it was <3 cm, 5yOS with/without UFT were 96.2/96.2%. UFT tended to be associated with better prognosis in 1389 patients with GGA- tumor when the tumor size was >3 cm, (5yOS 83.8% vs 77.4%, adjusted HR=0.82, p=0.27), but not when it was <3 cm (5yOS 88.1% vs 88.1%, adjusted HR=0.97, p=0.87). **Conclusion:** Our "real-world" data reproduced the survival outcome of JCOG0707, especially in Eligible cohort. Invasive tumor size was a prognostic factor in GGA+ tumors, suggesting validity of the 8th IASLC TNM classification. GGA+ tumor with invasive tumor size of <3 cm would not require any adjuvant therapy. UFT effect appears to be limited to large GGA- tumor.

Keywords: Lung cancer, Surgery, adjuvant chemotherapy

P1.17-05 WHAT IS THE OPTIMAL NUMBER OF EXAMINED LYMPH NODE IN STAGE IA NON-SMALL CELL LUNG CANCER?

L. Huang[1], V. Chummun[2], W. Zhang[1], Q. Chu[1], Y. Chen[1]

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Background: 1.*To find out the optimal number of examined lymph nodes (ELNs) in stage IA non-small cell lung cancer (NSCLC).* 2.To figure out whether there was a turning point beyond which ELNs might have adverse effects on survival. **Method:** Using the Surveillance, Epidemiology, and End Results registry (SEER) database, we selected all NSCLC patients diagnosed with stage IA (T1N0M0) from 1995 to 2015. Cases from 1995 to 2005 were as analytical data set (group 1) and those from 2006-2015 as validation data set (group 2).The overall survival (OS) of patients with different ELNs was compared statistically by SPSS. The optimal cut point of ELNs was calculated by X-Tile and verified by univariable and multivariable analyses. Propensity score matching (PSM) was done by R software 3.5.2. **Result:** In total, we extracted 57481 stage IA NSCLC patients (group 1, n = 20814; group 2, n = 36667). The PSM of Group 1 and Group 2 were balanced based on sex, age and race. In both groups, we divided patients into 3 subgroups, recorded as ELN = 0, 1≤ ELNs < n and ELNs≥ n. ELN = 0 had the highest risk of death in each subgroup (all p < 0.001). From n = 6 to n = 16, OS was significantly different between 1 ≤ ELNs < n, and ELNs ≥ n. But from n = 17 to n = 30, OS was the same between 1 ≤ ELNs < n and ELNs ≥ n. When dividing patients into ELNs = 0, 1-2, 3-5, 6-9, 10-29, ≥ 30,serial improvement in OS was seen with increasing ELNs, up to ELNs = 6-9, and beyond which there was little further incremental survival benefit. The survival curve of ELNs ≥ 30 even had an obvious trend to drop down. **Conclusion:** For stage IA NSCLC, we suggested resecting 6-9 LNs was enough, and no more than 16 LNs. More than 16 ELNs did not improve survival and more than 30 ELNs might have a detrimental effect on survival.

Keywords: Non-Small Cell Lung Cancer, Lymph nodes, stage IA

P1.17-06 LONG-TERM ONCOLOGICAL OUTCOME AFTER THORACOSCOPIC LOBECTOMY FOR NON-SMALL CELL LUNG CANCER PATIENTS

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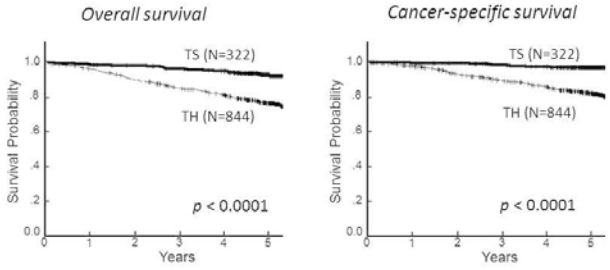
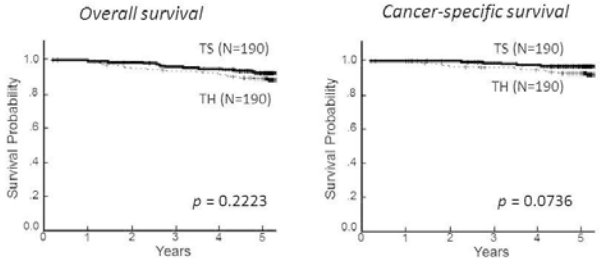
Background: Thoracoscopic surgery (TS) has been used more commonly as a less invasive procedure for early-stage non-small cell lung cancer (NSCLC) than conventional thoracotomy (TH) in Japan. However, limited evidential data are available to compare the treatment efficacy of TS and TH. The purpose of this study was to retrospectively investigate the difference in the long-term outcome and invasiveness of TS and TH. **Method:** Total 1,166 NSCLC patients who underwent surgery between 2005 and 2013 were enrolled. Of these, 844 patients underwent surgery via TH and 322 via TS. We compared several clinicopathological factors and the long-term outcome between the two groups. We performed propensity score matching analysis to minimize differences in the patient background and tumor states. Median follow-up period was 62 months. **Result:** The TS group included more women, non-smokers or light smokers, and healthy patients. In the TS group, the disease states were significantly less aggressive. The TS group had a much better 5-year overall survival (OS) rate and cancer specific survival (CSS) rate than the TH group (p <0.0001, p <0.0001). Using propensity score matching, we extracted 190 patients each from the two groups. No statistical differences were present in the OS and CSS rates of the two matched groups (p =0.2223, p=0.0736), indicating the achievement of adequate balance. For a balanced cohort, intraoperative blood loss was significantly less (44 ± 40ml vs. 100 ± 78ml, p <0.0001), and the duration of postoperative drainage was shorter (2.1 ± 1.7 days vs. 3.5 ± 2.9 days, p <0.0001) in the TS group.

Long-term outcome after thoracoscopic surgery and thoracotomy for non-small cell lung cancer patients; before propensity score matching



Long-term outcome after thoracoscopic surgery and thoracotomy for non-small cell lung cancer patients; after propensity score matching



Conclusion: We reported the excellent long-term oncological outcomes in patients with early-stage NSCLC after TS lobectomy. Although this is a single institutional, retrospective study, we successfully avoided selection bias in the patients and showed comparable treatment outcomes with lower invasiveness of TS as compared to that of TH.

Keywords: Non-Small Cell Lung Cancer, long-term outcome, thoracoscopic surgery;

POSTERS

P1.17-07 NEOADJUVANT GEFITINIB IN RESECTABLE EARLY STAGE EGFR MUTANT NON-SMALL CELL LUNG CANCER (NSCLC): A WINDOW-OF-OPPORTUNITY STUDY

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Background: EGFR TKI therapy is standard of care in metastatic EGFR mutant NSCLC, however its role in resectable NSCLC remains unclear. Furthermore, although EGFR TKIs elicit tumor shrinkage in 60% of patients, determinants of response are poorly understood. This was a window-of-opportunity study of neoadjuvant gefitinib prior to surgery for resectable NSCLC with serial plasma and tissue sequencing. **Method:** From Feb 2015 to Nov 2018, stage IA-IIIA EGFRmt NSCLC pts received minimum 4 weeks oral gefitinib 250mg daily before surgery. Biomarkers for TKI sensitivity were correlated with RECIST response, pharmacodynamic changes with serial PET-CT scans and pathologic response. Safety and feasibility were determined. Translational studies included multiregion whole exome sequencing (WES, n=44 sectors total) and RNAseq (n=39 sectors). **Result:** 14 pts were treated, 1 pt withdrew consent prior to surgery without toxicity or progression. Gefitinib (median exposure 1.4 mths) was well tolerated, 1 (8%) pt had ≥G3 AE, with G3 AST/ALT elevation leading to gefitinib cessation. ORR was 62% and DCR was 100%. 13/13 pts underwent resection, 6 (46%) pts had pathological downstaging, 4 (31%) pts had nodal pathCR and 1 (8%) pt had a major pathological response (<10% residual viable tumor cells). There was no correlation between CT response or residual FDG uptake post TKI with % residual viable tumor. WES (up to 370x) showed low tumor purities (median 0.17, range 0.1-0.37) across sectors. Purity correlated with number of coding mutations (r^2=0.29, p<0.01) but not ploidy (r^2=0.04, p=0.2). Compared to a matched treatment naïve cohort (n=18), phylogenetic analysis showed higher proportions of private driver mutations (p=0.04) and sub-clonal copy number variations. The presence of co-occurring truncal drivers did not account for the 5 pts with SD. On RNAseq, all pts had upregulation of immune regulatory and inflammatory response related genes, with significantly higher GEP score (median score; -0.17 vs -1.06, p=0.01) compared to the treatment naive cohort, although with heterogeneity across sectors. EPIC and xCell de-convolution showed high residual FDG uptake may be due to CAFs or infiltrating T-cells. After median 23 mths follow-up, 7/13 pts recurred, median RFS was 20.2 mths. Of 4 evaluable pts re-treated with palliative EGFR TKI, 3 had PR, 1 had PD (leptomeningeal only recurrence). **Conclusion:** Neoadjuvant gefitinib is safe, feasible and effective. Post EGFR TKI treatment samples had low tumor purities influencing genomic and transcriptomic analyses. Percentage residual disease did not correlate with residual FDG uptake or tumor response. There was pervasive upregulation of immune regulatory and inflammatory response genes, indicating infiltration of fibroblasts and T cells, providing unique insight into adaptive response and for the development of rational combination approaches in EGFR mutant NSCLC.

Keywords: Neoadjuvant therapy, Early stage NSCLC, EGFR mutant NSCLC

P1.17-08 MRNA EXPRESSION LEVEL OF RECEPTOR TYROSINE KINASES AND NON-RECEPTOR TYROSINE KINASES AS A RECURRENCE RISK IN RESECTED ADENOCARCINOMA OF THE LUNG

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Background: The profile of receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (non-RTK) is crucial for tumor genesis and therapeutic strategy in several types of cancer. We previously reported that elevated mRNA expression level of some RTKs/non-RTKs (AXL, CDCP1, STAT3, YAP1) were related to poorer prognosis in lung adenocarcinoma patients receiving EGFR-TKI. The prognostic impact of RTKs/non-RTKs is unclear in early-stage lung cancer. This study aims to explore the usefulness of RTK and non-RTK to detect the risk of recurrence in resected NSCLC, especially in EGFR mutant adenocarcinoma. **Method:** We retrospectively collected pathologic N0-2 adenocarcinoma cases resected in Japanese and Spanish institutions. mRNA expression levels of RTK or non-RTK (STAT3, YAP1, AXL, CDCP1, MET, SHP2, and EGFR) in surgical specimens were evaluated and the impact of expression level on recurrence-free survival (RFS) was compared. The oncological significance on RTK or non-RTK was validated *in vitro*. **Result:** Among enrolled 268 cases, 100 cases (37.3%) harbored EGFR mutation. Forty-five EGFR mutation positive cases recurred and cases with higher mRNA expression level of EGFR showed worse RFS. In addition, higher expression of CDCP1 or SHP2 indicated poorer RFS in EGFR mutation positive cases. *In vitro*, combination of SHP099 (SHP2 inhibitor) and osimertinib showed synergism in EGFR mutation positive cell line (Combination index was 0.62). **Conclusion:** Higher expression of SHP2 and CDCP1 is potential risk of recurrence in EGFR mutant lung adenocarcinoma. The synergism of SHP2 inhibitor plus EGFR-TKI suggests that the expression level of SHP2 is involved in tumorigenesis and is a promising predictor for recurrence in EGFR mutant lung adenocarcinoma.

Keywords: Early stage, Seurgery, mRNA

P1.17-09 SURGICAL OUTCOMES OF COMPLEX VERSUS SIMPLE SEGMENTECTOMY FOR STAGE I NON-SMALL CELL LUNG CANCER

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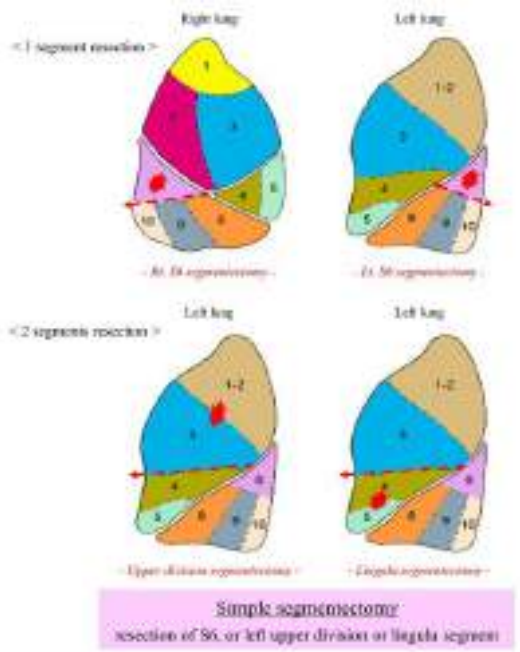
Background: As segmentectomy becomes widely used for lung cancer treatment, "complex segmentectomy," which makes several, intricate intersegmental planes, remains controversial because of procedural complexity and risk of increased complications and incurability. Questions remain regarding mortality, morbidity, surgical margin, lymph nodes dissection, and postoperative pulmonary function. We evaluated operative and postoperative outcomes of complex compared to simple segmentectomy. **Method:** We retrospectively reviewed clinical stage I lung cancer patients who could tolerate lobectomy and underwent complex or simple segmentectomy between April 2007 and March 2017. Clinicopathologic, operative, and postoperative results of the complex (*n* = 117) and simple (*n* = 92) segmentectomy groups were compared.



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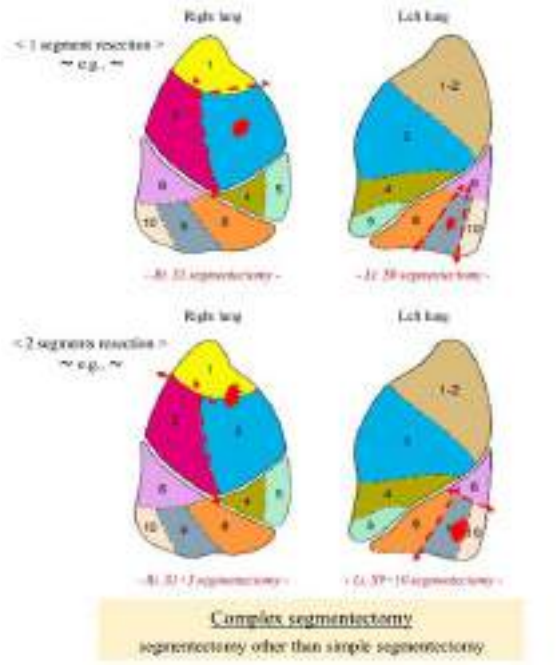

Result: No significant differences were detected in age, sex, comorbidities, preoperative pulmonary function, tumor histology, and size. Although only median operative time (180 vs. 143.5 minutes; $P < 0.0001$) was significantly longer in the complex group, 30-day mortality (0% vs. 0%), overall complications (24.8% vs. 22.8%), and prolonged air leakage (11.9% vs. 10.9%) were nearly equivalent between the two groups, respectively. The complex group showed comparable results in median surgical margin distance (16.0 vs. 17.5 mm) and number of dissected lymph nodes (6.0 vs. 7.0 nodes). Margin relapse occurred in two patients in the simple group but none occurred in the complex group. Both groups also showed similar postoperative pulmonary functions. **Conclusion:** Complex segmentectomy is a safe option in the treatment of lung cancers with adequate operative outcomes.

Keywords: Operative outcome, Postoperative complication, segmentectomy

P1.17-10 PREDICTION OF VISCERAL PLEURAL INVASION IN C-N0 NON-SMALL CELL LUNG CANCER

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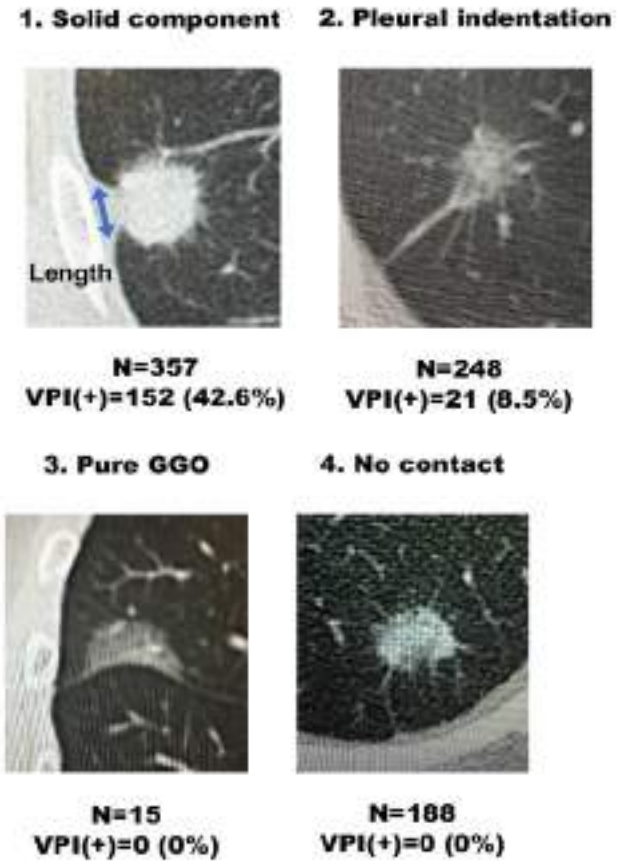
Background: Visceral pleural invasion (VPI) is a tumor invasion pattern and a poor prognostic factor. However, accurate preoperative diagnosis of VPI remains difficult. This study aimed to clarify the clinical and radiological predictors of VPI in patients with c-N0 non-small cell lung cancer (NSCLC). **Method:** A retrospective review was conducted in 808 patients with c-N0 NSCLC who underwent complete resection between 2009 and 2014. VPI included pathological pl1 and pl2. Patients with pl3 were excluded. Radiological findings were evaluated based on thin-section CT and PET. The patients were divided into 4 categories according to the following patterns of pleural contact with tumor: a solid component, pleural indentation, a ground glass opacity (GGO) component, and no pleural contact.

Pattern of pleural contact with tumor



Result: VPI occurred in 173 patients (21.4%), with a significantly higher incidence of pathological nodal involvement than those without VPI (32.9% vs 10.6%, $p<0.001$). Of the 357 patients with pleural contact by a solid component, 248 patients with pleural indentation, and 203 patients with pleural contact by a GGO component/no pleural contact, 152 (42.6%), 21 (8.5%), and none (0%) had VPI, respectively. The length of pleural contact by a solid component was positively correlated to VPI ($p<0.001$). Receiver-operating characteristic curve analysis revealed a cutoff length of 1 mm, indicating the importance of the presence of pleural contact by a solid component. Multivariate logistic regression analysis revealed that pleural contact pattern, pure-solid tumor, SUVmax, and CEA were independent significant predictors of VPI. Adjusted ORs (95%CI) of pleural contact by a solid component and pleural indentation were 181 (11.8–NA) and 40.1 (2.55–633), respectively (in reference to a GGO component/no pleural contact). **Conclusion:** Pleural contact by a solid component was the most relevant predictor of VPI. VPI was reflected by malignant clinical (high CEA) and radiological features (high SUVmax, pure-solid tumor) and a pleural contact pattern (solid component, indentation).

Keywords: Lung cancer, visceral pleural invasion, Prediction

P1.17-11 NOMOGRAM PREDICTING OVERALL SURVIVAL BENEFIT OF STEREOTACTIC ABLATIVE RADIOTHERAPY FOR EARLY STAGE NON-SMALL CELL LUNG CANCER

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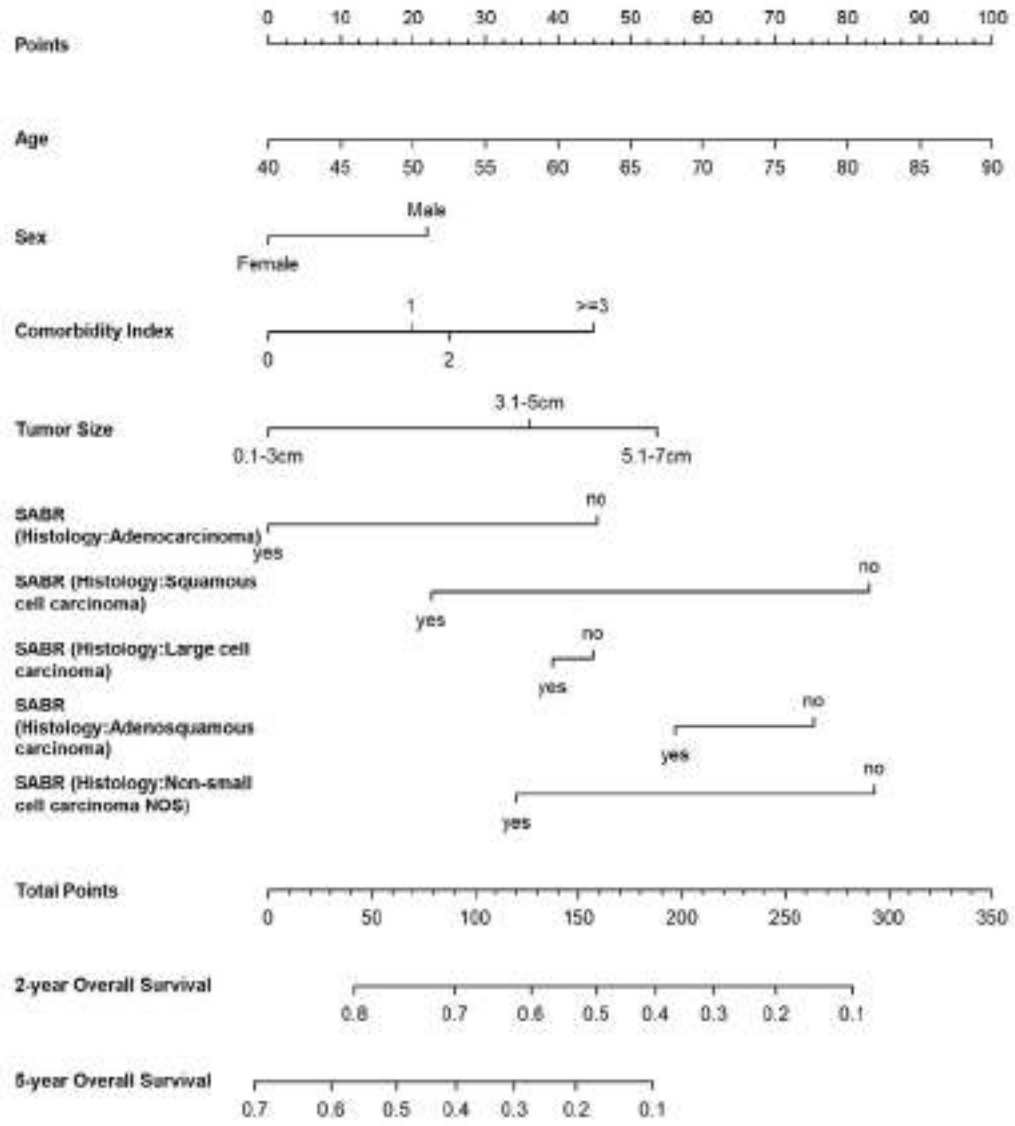
Background: Stereotactic ablative radiotherapy (SABR) is the preferred treatment for medically inoperable T1-T2N0M0 non-small cell lung cancer (NSCLC). This population is at high risk of mortality from comorbidities precluding surgery. A nomogram to better identify patients most likely to benefit from SABR would be clinically meaningful. **Method:** Adults with T1-T2N0M0 NCSLC (AJCC 7th edition) treated with SABR (30-70 Gy in 1-10 fractions with biologically effective dose ≥100 Gy_{10}) or observation between 2004-2015 in the National Cancer Database were identified. Exclusion criteria included prior malignancy, surgery to the primary tumor, chemotherapy, and no pathologic diagnosis. Propensity score was used to match

SABR and observation cohorts on prognostic demographic and clinicopathologic factors identified by logistic regression. Using backward selection, a multivariable Cox proportional hazards model with Frailty term was identified predicting 2- and 5-year overall survival (OS) via a nomogram. The model prediction accuracy was assessed by the concordance between observed and predicted OS. **Result:** 4,440 matched pairs (total n=8,880) were identified with median age 75, 53% female, 54% Charlson-Deyo comorbidity index of zero, 62% tumor size ≤3 cm, and 50% adenocarcinoma. Factors associated with improved OS on multivariable analysis included younger age (HR 0.824 by decade, p<0.001), female sex (HR 0.809, p<0.001), lower comorbidity index (HR 0.647 for 0 versus ≥3, p<0.001), smaller tumor size (HR 0.595 for ≤3cm versus 5.1-7cm, p<0.001), adenocarcinoma histology (p<0.001), and SABR (p<0.001). Interaction between SABR and histology was significantly associated with OS (p=0.017). Uno's concordance index, evaluating the nomogram's accuracy for predicting OS, was 0.623 (95%CI 0.615–0.631) based on 100 perturbations.



Conclusion: This nomogram predicts the impact of SABR versus observation on 2- and 5-year OS, and may help identify patients with medically inoperable T1-T2N0M0 NSCLC who would benefit most from SABR. Inclusion of other variables, such as performance status, may improve the model prediction accuracy.

Keywords: Nomogram, Early stage non-small cell lung cancer, Stereotactic ablative radiotherapy

P1.17-12 OSTEOGENIC AND BRAIN METASTASES AFTER RESECTION OF NSCLC: IMPLICATIONS FOR THE USE OF FDG-PET AND BRAIN MRI IN POSTOPERATIVE SURVEILLANCE

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Background: In several guidelines for lung cancer treatment, routine use of FDG-PET and brain MRI have not been recommend due to their insufficient evidence of survival benefits for resected NSCLC. In clinical practice, not a small portion of patients experience metastases in osteogenic and/or brain at the initial recurrence after surgery, which routine chest CT hardly diagnose them. In this retrospective study, we aimed to propose the candidates for surveillance using FDG-PET and brain MRI to diagnose OM/BM. **Method:** We retrospectively enrolled 1099 patients who underwent pulmonary resections of lobectomy or more for NSCLC between 2002 and 2013. From medical records, clinicopathological data were collected and reviewed. Surveillance by using FDG-PET and brain MRI were basically performed at patients' complaint of symptoms and/or detection of other metastatic disease. Clinicopathological factors associated with osteogenic metastases (OM) and/ or brain metastases (BM) were investigated by univariate and multivariate analyses. **Result:** We included 1055 patients with lobectomies and 44 patients with pneumonectomies. Nine hundred thirty-three patients (88.4%) received mediastinal and hilar lymphnodes dissection. Seven hundred twenty-one patients had adenocarcinoma histology, 274 had squamous cell carcinoma histology. The prevalence of pStage was as following; pIA: 265 (25.1%), pIB: 348(33.0%), pIIA: 185(17.5%), pIIB: 105 (10.0%), pIIIA: 193 (18.3%), pIIIB: 3 (0.3%) (TNM 7th edition). Postoperative recurrence were identified in 344 patients (32.6%), OM or/and BM were observed in 115 patients (10.9%) as the initial recurrence. OM were diagnosed in 56 patients (5.6%). In the initial year after resection, 41.1% of OM were diagnosed, and 82% in the 2 years. BM were identified as the initial recurrence in 72 patients (6.6%). In the initial year, 44.1% of BM were diagnosed, and 78.9% in the 2 years. Multivariate analyses following univariate analyses revealed higher preoperative serum CEA level than 5ng/ml and presence of pathological nodal metastases were significantly associated with both postoperative OM and BM (p=0.011,<0.001 in OM, p=0.044, <0.001 in BM). Prevalence of OM and/or BM was 24.6% in patients with high serum CEA and nodal metastases. Postrecurrence survival of asymptomatic patients were better than those of symptomatic patients in both OM and BM groups (p=0.009 and 0.29, respectively) **Conclusion:** Preoperative high serum CEA level and pathological nodal spread were closely associated with OM and BM after resection of NSCLC. Most of those events developed in 2 years after resections. Under the patient selections, efficacies of the use of FDG-PET and brain MRI are worthy to be evaluate in respect to earlier detections, maintenance of QOL and survival outcomes.

Keywords: osteogenic metastasis, brain metastasis, postoperative surveillance

P1.17-13 NEXT GENERATION SEQUENCING OF THE CIRCULATING SMALL RNA FROM SERUM IDENTIFIES SMALL RNA-BASED BIOMARKER PANEL FOR STAGE I-II LUNG ADENOCARCINOMA

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Background: Circulating small RNAs have been reported as biomarkers for cancer diagnosis, including lung cancer. The purpose of this study is to identify the small RNA for the early detection of lung adenocarcinoma. In this study, we used next generation sequencing (NGS) in order to screen and validate expressions of the small RNAs between persons with and without adenocarcinoma and built the RNA-based biomarker panel. **Method:** We used next generation sequencing in all phases (screening set, validation set, and the panel evaluation set) and researched micro RNAs(miR) and transfer RNA fragments(tRF) as small RNAs. We analyzed the RNAs from serum of 21 patients with adenocarcinoma and 20 healthy control for screening and assessed small RNAs from 22 patients with adenocarcinoma and 20 healthy control for validation. Regarding significantly upregulated and downregulated small RNAs, we built RNA-based biomarker panel and evaluated the panel with a different dataset (33 patients with adenocarcinoma and 27 healthy control). **Result:** Based on screening and validation set, four miR and one tRF were upregulated. Tow miR and nine tRF were downregulated. An area under the curve value of each small RNA was 0.65 to 0.85. Among them, nine small RNA were adopted to the biomarker panel by using multiple regression analysis. In the cohort of screening and validation set, the panel showed a sensitivity of 93.0% and specificity of 88.0%, with an area under the curve value of 0.983, which was much larger than that of a single RNA. The panel was evaluated with a different dataset and showed a sensitivity of 90% and specificity of 74.1% when the threshold was 1.8. **Conclusion:** In conclusion, we built the small RNA-based biomarker panel which included nine small RNA and our results showed the diagnostic efficacy of the panel. Further investigation is required to understand the cause for the expression change of each small RNA.

Keywords: diagnosis of lung cancer, Next generation sequencing, small RNA

P1.17-14 PROGNOSTIC VALUE OF IMMUNE CELL BIOMARKERS IN SURGICALLY RESECTABLE NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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Background: Immune cells within the tumor microenvironment (TME) play an important role in the development, progression and outcomes of non-small cell lung cancer (NSCLC). We conducted the first meta-analysis of studies assessing the role of individual immune cells in surgically resected stage I-III NSCLC to evaluate the prognostic value of immune cell biomarkers. **Method:** PubMed was searched to identify eligible studies assessing clinical outcomes of surgically resected stage I-III NSCLC patients according to immune cell subsets: CD3+ T cells, CD4+ T Helper cells, CD8+ T cytotoxic cells, CD20+ B cells, FoxP3+T Regulatory cells, Natural Killer cells (CD56/CD57+), macrophages (CD68+), and Mast Cells. Meta-analysis was performed using a linear mixed-effects model to determine overall survival (OS) and disease free survival (DFS), and was reported according to whether or not the study adjusted for clinical covariates. I^2 was used to assess heterogeneity across studies. **Result:** 42 articles (7,906 patients) were included in this analysis. Higher levels of CD20+ B cells were associated with better OS, while increased FoxP3+ T regulatory cells and Mast Cells were associated with worse OS in unadjusted studies. However, in studies adjusting for clinical variables, CD8+ T cytotoxic cells and Natural Killer cells were also found to be associated with improved OS, while mast cells no longer were significantly detrimental. CD20+ B cells were associated with better DFS in unadjusted studies; in adjusted studies, CD8+ T cytotoxic cells were associated with better survival and FoxP3+ T Regulatory cells were associated with worse survival, with CD20+ B cells no longer significantly associated survival. I2 did not show substantial heterogeneity between studies. Table 1: Meta-Analysis Survival Estimates

	OS				DFS			
Biomarker	**Unadjusted HR (95% CI)**	**N, Hetero-geneity (%)**	**Adjusted HR (95% CI)**	**N, Hetero-geneity (%)**	**Unadjusted HR (95% CI)**	**N, Hetero-geneity (%)**	**Adjusted HR (95% CI)**	**N, Hetero-geneity (%)**
CD3+ T cells	0.98 (0.87-1.12)	6 articles I2= 0.00	0.71 (0.37-1.37)	3 articles I2= 0.00	0.98 (0.86-1.12)	5 articles I2= 0.00%	-------	-------
CD4+ T Helper cells	0.64 (0.37-1.10)	4 articles I2= 13.65	0.80 (0.50-1.28)	4 articles I2= 0.00	0.72 (0.39-1.32)	3 articles I2= 0.00%	0.59 (0.11-3.12)	1 article
CD8+ T Cytotoxic cells	0.99 (0.95-1.04)	14 articles I2= 0.00	**0.71 (0.52-0.96)**	12 articles I2= 20.95	0.94 (0.77-1.16)	8 articles I2= 16.65%	**0.60 (0.41,-0.87)**	9 articles I2= 20.43%
CD20+ B cells	**0.45 (0.22-0.93)**	5 articles I2= 52.29	**0.16 (0.04-0.64)**	1 article	**0.57 (0.33,-1.00)**	4 articles I2= 0.00%	0.51 (0.20-1.32)	1 article
FoxP3+ T Regulatory cells	**1.78 (1.20-2.64)**	9 articles I2= 14.93	**2.38 (1.56-3.65)**	6 articles I2= 0.00	1.45 (0.81-2.59)	3 articles I2= 0.00%	**2.07 (1.10-3.90)**	3 articles I2= 0.00%
Natural Killer cells	0.66 (0.35-1.25)	3 articles I2= 13.63	**0.50 (0.26-0.95)**	4 articles I2= 0.00	1.35 (0.39-4.66)	1 article	0.59 (0.27-1.28)	2 articles I2= 0.00%
Macro-phages	1.11 (0.65-1.90)	5 articles I2= 18.11	1.04 (0.69-1.55)	6 articles I2= 0.00	-------	-------	1.88 (0.87-4.08)	4 articles I2= 43.97%
Mast Cells	**1.81 (1.01-3.15)**	3 articles I2=0.00	2.01 (0.88-3.92)	3 articles I2=43.99	2.30 (1.20-4.70)	1 article	1.50 (0.60-3.60)	1article

HR= Hazard Ratio, CI = Confidence Interval

Conclusion: Immune cell subsets are able to provide prognostic information in early-stage NSCLC undergoing surgical resection. When evaluating these immune biomarkers, adjustment for clinical covariates can have a profound impact on survival estimates.

Keywords: Biomarker, Immune Cell

P1.17-15 RISK, PATTERN AND OUTCOME OF BRAIN METASTASES IN COMPLETELY RESECTED STAGE I (AJCC 8TH EDITION) NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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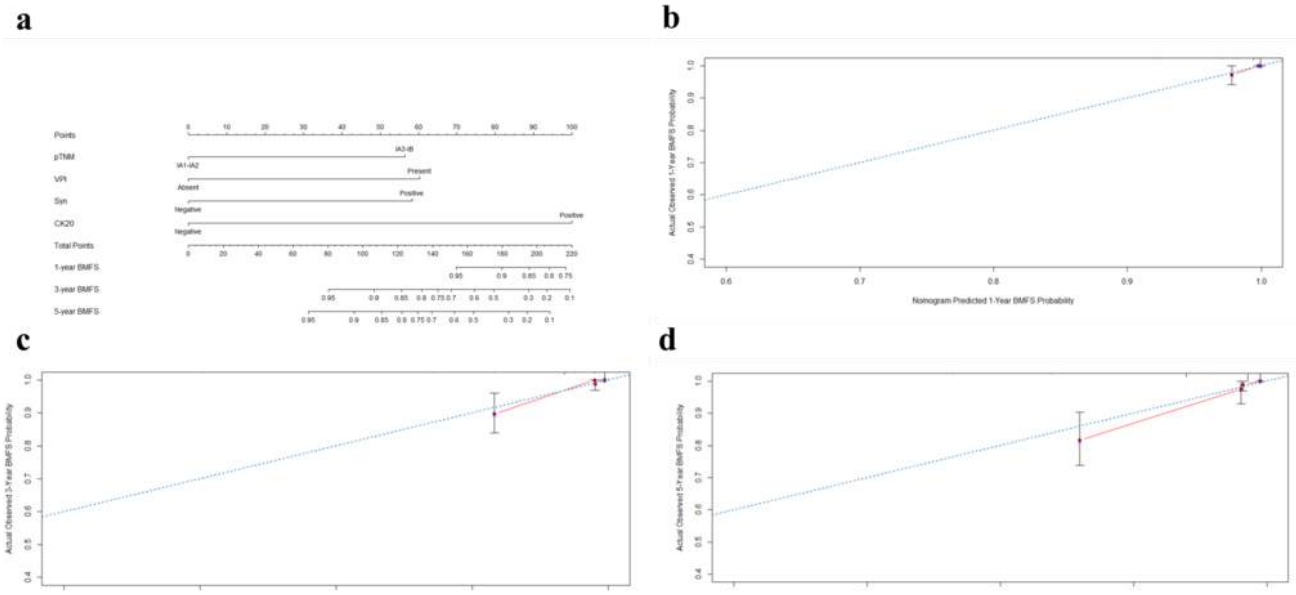
Background: Brain as the first site of recurrence after complete resection in stage I non-squamous non-small cell lung cancer (NSCLC) is occasionally encountered. However, the risk factors and clinical outcomes of this uncommon situation are not fully understood. **Method:** The records of patients who underwent curative surgery at Fudan University Shanghai Cancer Center were reviewed and two cohorts with stage I non-squamous NSCLC were identified. The training cohort consisted of randomly selected patients from January 2013 to December 2017. The validation cohort included consecutive patients from January 2011 to December 2012. Brain metastasis free survival (BMFS) were calculated from the time of surgery to the documentation of brain metastasis (BM). Overall survival (OS) was measured from the documentation of BM to the time of any cause of death. A nomogram was developed based on variables selected in multivariate analysis. **Result:** With a median follow-up of 28 (range, 10-69) months, 16 of the 596 patients in the training cohort had its initial relapse in the brain. The 1-year, 2-year, and 3-year cumulative incidence of BM were 0.7%, 1.9% and 4.2%, respectively. Tumor size≥2cm (HR=5.09, p=0.024), visceral pleural invasion (HR=2.79, p=0.007), expression of Syn (HR=4.24, p=0.007) and expression of CK20 (HR=14.01, p<0.001) were independent risk factors of BM. Afterwards, a nomogram predicting BMFS was developed based on these four factors. Of note, EGFR mutation was not associated with BMFS. Additionally, with a median follow-up of 75 (range, 7-98) months, 18 of the 478 patients in the validation cohort had its initial recurrence in the brain. The nomogram was validated with a concordance index of 0.93 (95%CI, 0.88-0.98) and the calibration curves displayed good agreement between the predicted BMFS and the actual observation. Among the 34 patients with BM, 10 also had extracranial recurrence, 7 were symptomatic and 24 had oligo-metastases in the brain. By the time of data cut-off, 14 patients died with a 5-year OS rate of 24.8%. Positive expression of Syn or CK20 was significantly associated with reduced OS, while upfront local therapy (surgery and/or radiotherapy) after detection of BM tended to prolong OS (p=0.068).



Conclusion: Positive expression of Syn and CK20, but not EGFR mutation, were independent risk factors of BM and reduced survival in curative resected stage I non-squamous NSCLC. The majority of patients developing BM were asymptomatic and initially having oligo-metastases, highlighting the importance of regular brain imaging for patients with high risks.

Keywords: stage I, brain metastasis, Risk Factors

P1.17-16 NEO-ADJUVANT TARGETED THERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS: A 10-YEAR EXPERIENCE IN A TERTIARY MEDICAL CENTER

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Background: Epidermal growth factor receptor (EGFR) Tyrosine kinase inhibitor (TKI) or anaplastic lymphoma kinase (ALK) inhibitor had can provide dramatic response in lung adenocarcinoma patients, and have been the first line treatment for stage IV patients with corresponding genes mutations. Recent clinical trials had demonstrated both safety and tolerability in neo-adjuvant settings. However, there are still limited clinical data regarding long-term outcome and additional adjuvant treatment options. Our purpose was to investigate the treatment response and image change of neoadjuvant target therapy in non-small cell lung (NSCLC) cancer patient patients. **Method:** Taipei Veterans General Hospital Lung Cancer Database was used to search for stage I to stage III NSCL patients, who's first line treatment was TKI. Their medical records and chest CT and PET images were reviewed. **Result:** We identified 20 patients in a 10 year period (January 2007 - December 2017) receive neoadjuvant TKI. 2 failed to receive further surgery treatment. One of them was due to disease progression while the other remained non-operable despite tumor sized down. The overall response rate for neoadjuvant TKI was 86%. 17 patients were clinical stage IIIA(AJCC 8th edition), 1 was IIIB, 2B and 1b. One of them received ALK inhibitor while the others received EGFR TKI. The mean duration of neo-adjuvant therapy was 73 days. For 18 patients receiving surgical treatment, 12 experienced down-staging (one got pathological complete response). 13 patients received adjuvant therapy with great variety. 7 patients did not have recurrent disease after surgery, and they all had pathological down staging. The median recurrence-free survival and overall survival was 13.7 months and 6 years, respectively. **Conclusion:** As long-term survival was potentially achievable in such patient group, and with the diverse treatment options, results from randomized clinical trials are needed to give solid conclusion.

Keywords: EGFR, tyrosine kinase inhibitor, Neo-adjuvant

P1.17-17 OUTCOMES FOLLOWING STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR BIOPSY-CONFIRMED VS. RADIOLOGICALLY-DIAGNOSED PRIMARY LUNG CANCER

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Background: Stereotactic body radiotherapy (SBRT) is increasingly used to treat inoperable non-small cell lung cancer (NSCLC). Obtaining tissue confirmation prior SBRT is not always feasible. We aim to evaluate clinical outcomes in biopsy-confirmed vs. radiologically-diagnosed NSCLC treated with SBRT. **Method:** This is a single-institutional retrospective cohort of NSCLC patients treated with SBRT between February 2014 and October 2018. Differences in baseline characteristics between biopsy-confirmed vs. radiologically-diagnosed NSCLC were compared using chi-squared test for categorical variables and student's t-test for continuous variables. The oncological outcomes of interest were: local failure (LF), distant failure (DF), and overall survival (OS). Probability of LF, DF and OS were estimated using the Kaplan-Meier method. The difference in outcomes between those who had biopsy confirmation vs. no biopsy was evaluated using the log-rank test. **Result:** 63 lesions in 60 patients were treated with SBRT, comprising 35 (58%) men and 25 (42%) women. Mean age was 76.8 years (SD=8.1). 34 (57%) patients were ECOG 0-1 and 26 (43%) were ECOG 2-3. 22 (37%) patients had biopsy-confirmation while 38 (63%) were radiologically-diagnosed. No significant differences in baseline characteristic between the 2 groups. Of the 63 treated lesions, 9 (14%) received 54Gy/3 fractions, 44 (70%) had 48Gy/4 fractions, 7 (11%) had 50Gy/5 fractions, 2 (3%) had 40Gy/5 fractions, and 1 (1%) had 20Gy/1 fraction. The patients were followed-up for a median of 10.6 months (IQR=5.7-14.9). There were 5 cases of LF (4 in biopsy-confirmed, 1 in non-biopsy) observed at a median of 12.8 months post-SBRT. The actuarial 12-month LF-free survival was 95%, with no significant differences between lesions that was biopsied vs. not biopsied (P=0.07). Of the 60 treated patients, 11 developed DF (8 biopsy-confirmed, 3 non-biopsy) at a median of 6.5 months post-SBRT. The 12-month actuarial DF-free survival was 87%, with no difference between patients who had biopsy vs. no biopsy (P=0.3). There were 11 deaths of which only 1 was cancer-specific, reported at a median of 9.6 months post-SBRT. The 12-month OS was 83%. No differences between patients who had biopsy vs. no biopsy (P=0.1). No grade 3 toxicities were observed. **Conclusion:** The LF, DF, and OS did not appear to be affected by

biopsy confirmation in this cohort of NSCLC patients. In situations where biopsy confirmation is not feasible, it is not unreasonable to offer SBRT to patients with presumed NSCLC based on radiological suspicion following multidisciplinary discussions.

Keywords: SBRT, NSCLC

P1.17-18 SURGERY ALONE OR PLUS ADJUVANT RADIOTHERAPY FOR PATIENTS WITH N0 NON-SMALL-CELL LUNG CANCER >5 CM: A POPULATION-BASED STUDY

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Background: According to the eighth edition of the TNM classification for Lung Cancer, T2b (5–7 cm) and T3 (>7 cm) non-small cell lung cancers (NSCLC) should be reclassified as T3 and T4. Here, we evaluated the effect of surgery alone or surgery plus adjuvant radiation (SART) on survival in node-negative patients with NSCLC >5 cm. **Method:** We identified 4557 N0 patients with NSCLC >5 cm from the Surveillance, Epidemiology, and End Results database between 2004 and 2014. Overall survival (OS) and lung cancer-specific survival (LCSS) were compared between patients who underwent surgery alone and those receiving SART. The proportional hazards model was used to evaluate multiple prognostic factors. **Result:** After propensity-score matching, 1042 and 525 patients were included in the surgery alone and SART groups, respectively. OS and LCSS favored surgery alone over SART. In the multivariate analysis, dissection of ≥6 lymph nodes was associated with better OS and LCSS in patients with NSCLC >5 cm, especially in patients treated with surgery alone. Lobectomy was associated with better OS and LCSS in NSCLC 5–7 cm, whereas it was not significantly superior over sublobectomy in NSCLC >7 cm.

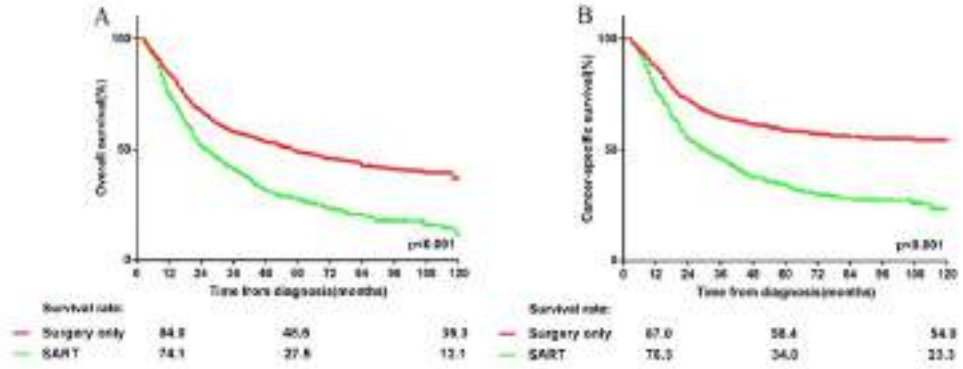

Figure 1 Overall and lung cancer-specific survivals in patients with non-small cell lung cancer (NSCLC) >5 cm who underwent surgery alone or surgery plus adjuvant radiotherapy. SART, surgery plus adjuvant radiotherapy.

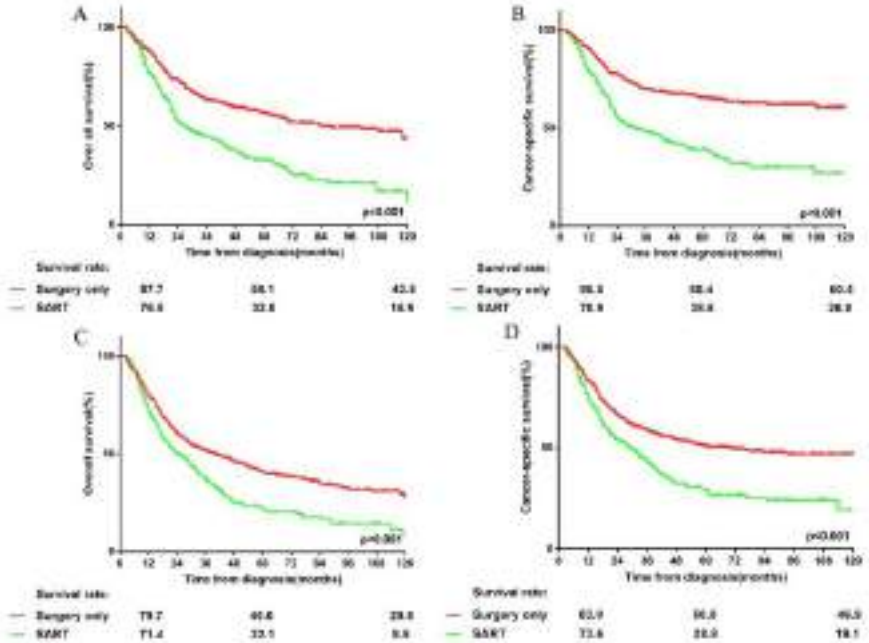

Figure 2 Stratification of overall survival and lung cancer-specific survival in patients with node-negative NSCLC > 5 cm at the cut point of the number of harvested lymph nodes who underwent surgery or surgery plus adjuvant radiotherapy. A and B, overall survival and lung cancer-specific survival in patients with node-negative NSCLC > 5 cm who had more than six lymph nodes dissected.C and D, overall survival and lung cancer-specific survival in patients with node-negative NSCLC > 5 cm who had less than six lymph nodes examined.

Conclusion: Surgery alone with a number of examined lymph nodes greater than six should be recommended as the first choice for patients with NSCLC >5 cm. Lobectomy should be recommended for patients with NSCLC 5-7 cm. For patients with NSCLC >7 cm who do not tolerate lobectomy, sublobectomy might be an alternative surgical procedure.

Keywords: Non-Small Cell Lung Cancer, postoperative radiotherapy, T-staging

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P1.17-19 LOBE-SPECIFIC LYMPH NODE DISSECTION FOR CLINICAL EARLY-STAGE (CIA) PERIPHERAL NON-SMALL CELL LUNG CANCER PATIENTS: FEASIBLE AND HOW?

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Background: Currently, the extent of lobe-specific lymph node (LN) dissection (L-SLND) for early-stage non-small cell lung cancer (NSCLC) in previous literatures remains controversial without well-recognized agreement on exact definition of L-SLND. We aimed to investigate the possible lobe-specific LN metastasis pattern of clinical T1N0M0 peripheral NSCLC and define the extent of L-SLND for them. **Method:** We retrospectively collected clinical data of patients undergoing lobectomy or segmentectomy with systematic lymphadenectomy for early-stage NSCLC from January 2015 to December 2018. The LN metastasis pattern of them was analyzed by tumor lobe location. **Result:** A total of 590 patients were included for analysis. The rate of mediastinal LN metastasis was 9.5% (table 1). For cases in the upper lobes and these in the lower lobes, 8.8% and 6.0% of them respectively metastasized to the upper LN zone (P=0.274). However, cases in the upper lobes hardly metastasized to the subcarinal (0.3%) and lower (0.3%) LN zones while it was 10.2% and 5.4% for cases in the lower lobes, respectively (both P<0.001). When stratified by tumor size, all these cases (100%) metastasizing from lower lobes had a tumor size of 2-3 cm while cases with a tumor size ≤2 cm had no metastasis to upper LN zone. For cases in right middle lobe, none of them metastasized to the lower LN zone. Table 1. Lymph node metastasis pattern among non-small cell lung cancers in different lobes.

Conclusion: A lobe-specific LN metastasis pattern of early-stage peripheral NSCLC was observed and for cases in the upper lobes (≤3cm), there is no need to dissect lower mediastinal LNs and for cases in the lower lobes (≤2cm), there is no need for dissecting upper mediastinal LNs. Otherwise, systematic LN dissection or sampling instead of L-SLND should be recommended.

Keywords: Non-Small Cell Lung Cancer, lobe-specific lymph node dissection, early-stage

Characteristics	Total (N=590)	Right upper lobe (N=220)	Right middle lobe (N=48)	Right lower lobe (N=84)	Left upper lobe (N=156)	Left lower lobe (N=82)	P value
Total dissected LN number (Mean±SD)	12.3±5.8	13.0±4.5	11.3±5.1	13.3±6.0	11.1±5.3	12.1±5.1	0.008
Total dissected mediastinal LN number (Mean±SD)	8.2±4.1	9.1±4.5	8.7±3.9	9.2±4.8	6.8±3.2	7.1±3.2	<0.001
LN metastasis rate	83 (14.1%)	29 (13.2%)	8 (16.7%)	13 (15.5%)	20 (12.8%)	13 (15.9%)	0.915
Upper zone metastasis rate	47 (8.0%)	16 (7.3%)	4 (8.3%)	5 (6.0%)	17 (10.9%)	5 (6.1%)	0.586
Subcarinal zone metastasis rate	22 (3.7%)	1 (0.5%)	4 (8.3%)	11 (13.1%)	0 (0%)	6 (7.3%)	<0.001
Lower zone metastasis rate	10 (1.7%)	1 (0.5%)	0 (0%)	4 (4.8%)	0 (0%)	5 (6.1%)	0.001
Note: LN=lymph node; SD=standard deviation.							

P1.17-20 EVALUATION OF EFFICACY AND SAFETY OF UNIPORTAL SEGMENTECTOMY IN THE TREATMENT OF LUNG CANCER

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Background: Uniportal segmentectomy is a therapeutic option for early stage lung cancer, but the debate over uniportal segmentectomy still remains. The aim of this study is to evaluate of efficacy and safety of uniportal segmentectomy in the treatment of lung cancer. **Method:** A total of 137 patients who underwent uniportal segmentectomy or subsegmentectomy between January 2017 and April 2019 in Liaoning Cancer Hospital. The clinical data of these patients were retrospectively analyzed, including operation time, number of lymph nodes dissected and postoperative mortality, postoperative complications, postoperative intubation time, and postoperative hospital stay. **Result:** The surgery procedure was anatomical pulmonary segmentectomy or subsegmentectomy. Uniportal segmentectomy was in 133 cases, and subsegmentectomy was in 4 cases. The median operation time was 243 minutes (range, 60-405 minutes), median number of lymph nodes dissected was 14 (range, 0-31), median drainage time was 5 days (range, 1-9 days), median postoperative hospital stay was 8 days (range, 3-19 days). The postoperative complications were pneumonia 2 case (1.5%), fever 12 cases (8.8%), hemoptysis 1 case (0.7%), air leak 2 case (1.5%), atrial fibrillation 1 case (0.7%), and subcutaneous hydrops 2 cases (1.5%). There was no severe postoperative complications, including death, bleeding, reoperation, and bronchopleural fistula. **Conclusion:** Uniportal segmentectomy is a safe and feasible technique for treating early stage lung cancer, with acceptable postoperative complications and mortality.

Keywords: uniportal segmentectomy, subsegmentectomy, Lung cancer

P1.17-21 SAFETY AND EFFECTIVENESS OF STEREOTACTIC ABLATIVE RADIOTHERAPY FOR ULTRA-CENTRAL LUNG LESIONS: A SYSTEMATIC REVIEW

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Background: The safety and effectiveness of stereotactic ablative radiotherapy (SABR) for patients with ultra-central lung tumours is currently unclear. We performed a systematic review to summarize existing data and identify trends in treatment-related toxicity and local control following SABR in patients with ultra-central lung lesions. **Method:** We performed a systematic review using the PRISMA guidelines. The PubMed and Embase databases were queried from dates of inception until September 2018. Studies

in the English language that reported treatment-related toxicity and local control outcomes post-SABR for patients with ultra-central lung lesions were included. Ultra-central lung lesions were defined as lesion whose gross tumour volume (GTV) or planning target volume (PTV) abutted or invaded the proximal tracheo-bronchial tree (PBT) or other mediastinal structures such as the great vessels or esophagus. Guidelines, reviews, non-peer reviewed correspondences, studies focused on re-irradiation and studies with fewer than 5 patients were excluded. **Result:** A total of 446 studies were identified, with 10 meeting all criteria for inclusion. The total sample size from the identified studies was 250 patients with ultra-central lung lesions and all studies were retrospective in design. Six out of the 10 studies included a majority (>50%) of primary lung cancers. Radiotherapy dose and fractionation ranged from 30 to 60 Gy in 3 to 12 fractions, with biologically-effective doses (BED_{10}) ranging from 48 to 138 Gy_{10} (median 78-103 Gy_{10}). Median treatment-related grade ≥3 toxicity was 10% (range: 0-50%). Median treatment-related mortality was 5% (range: 0-22%), most commonly from pulmonary hemorrhage (55%). High-risk indicators for SABR-related mortality included gross endobronchial disease, maximum dose to the proximal bronchial tree (PBT) ≥180 Gy_3 (BED_3, corresponding to 45 Gy in 5 fractions or 55 Gy in 8 fractions), peri-SABR bevacizumab use, and antiplatelet/anticoagulant use. Median 1-year local control rate was 96% (range: 63-100%) and 2-year local control rate was 92% (range: 57-100%). **Conclusion:** SABR for ultra-central lung lesions appears feasible and local control levels are comparable to those found in SABR for central lung lesions. There is a potential for severe toxicity in delivering SABR to ultra-central lung lesions especially in patients receiving high doses to the PBT, patients with endobronchial disease, and patients receiving bevacizumab or anticoagulants around the time of SABR. Prospective studies are required to establish the optimal doses, volumes and normal tissue tolerances for SABR in this patient population.

Keywords: Stereotactic ablative radiotherapy, ultra-central, systematic review

P1.17-22 DO STATINS IMPROVE OUTCOMES AFTER RADICAL RADIOTHERAPY FOR LUNG CANCER? AN IN-DEPTH ANALYSIS OF OVER 1100 PATIENTS

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Background: Statins exhibit anti-cancer activity *in vitro* in addition to cardiovascular protection effects. Trials using statins in lung cancer have shown mixed results. This study investigates statins' impact on patients treated with curative radiotherapy for lung cancer. **Method:** All patients who received radical radiotherapy for lung cancer from 01/01/2010-31/12/2016 at a large cancer centre were included. Individual patient information, including drug history at diagnosis, has been retrieved from hospital electronic database. Pre-existing cardiac conditions, Charlson Co-mobidity index and Qrisk[3] scores were calculated. **Result:** 1181 patients were identified. Patient and treatment demographics are summarised in table 1. Patients in the statin group were older, had more co-morbidities and higher Qrisk[3] scores. For the whole patient population, being on stains at the time of diagnosis was not significantly associated with better Overall Survival (OS) or Progression Free Survival (PFS). A 'High Risk Cohort'(HRC) was identified, which consists of patients with a history of cardiac disease or Qrisk[3] score >40. In HRC, statins significantly improved OS and PFS (p=0.016 and p=0.031 respectively), Graph 1. Table 1

		Total N = 1181	Patients NOT on Statins N = 652	Patients ON statins N = 529
Sex	Male	603	298	305
	Female	578	354	224
Age at RT treatment		Median = 73 Range 24 - 97	Median = 71 Range 24 - 92	Median = 74 Range 48 - 97
PS	0	94	67	27
	1	578	347	231
	2	438	212	226
	3	71	26	45
	Unknown	16	7	9
Smoking Status	Never smoked	43	28	15
	Ex-Smoker <10 PY	14	9	5
	Ex-smoker <20 PY	158	76	82
	Ex-Smoker 20-40PY	276	132	144
	Ex-Smoker >40 PY	259	140	119
	Current Smoker(at time of seeing on-cologist)	415	260	155
Charlson Score (2 points for having lung cancer)		Median = 6 (2% estimated 10 year survival)	Median = 5	Median = 6
Qrisk3 Score (For those without history of MI/IHD/ CVA and < 84)		Median = 21% (%risk of stroke/MI in next 10 years)	Median = 18.7	Median = 25.7
Known pre-existing cardiac condition	= 349	101 had previous MI 113 had no MI but IHD/Angina	105 -15 previous MI -33 IHD/Angina	244 -86 previous MI -78 IHD/Angina
RT indication	Adjuvant RT	70	46	24
	SBRT	478	240	238
	Concurrent ChemoRT	202	135	67
	Sequential ChemoRT	122	84	38
	Radical RT	278	112	166
	Consolidation RT after chemo for stage 4	31	10	21

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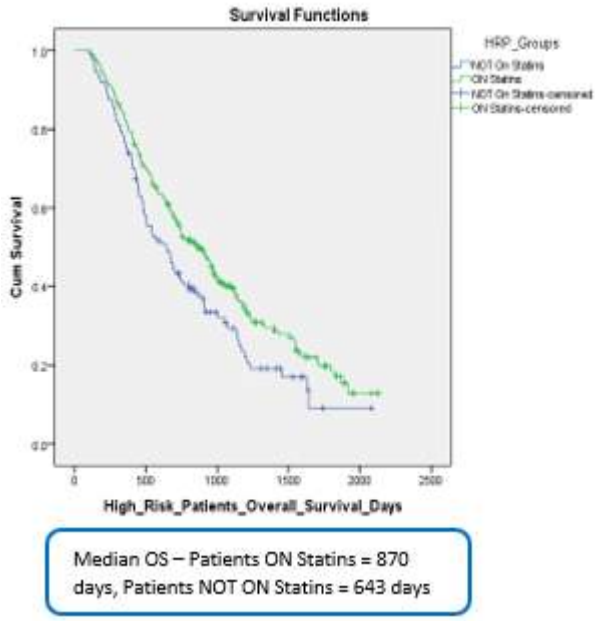
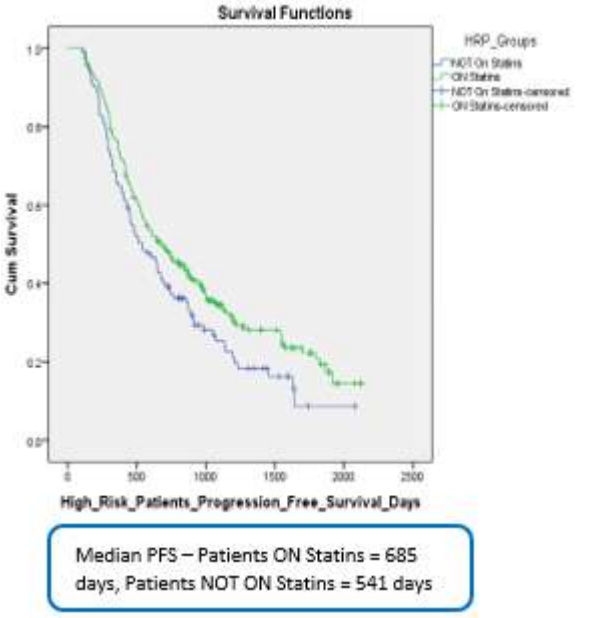
Graph 1





Conclusion: In this retrospective analysis, patients who were on statins in the HRC had better survival outcomes, despite being older and have more comobidities. Mechanism of action of statins in lung cancer remains unclear and may be different in the post radiotherapy setting. Prospective studies would be useful to evaluate statins in this setting.

Keywords: radiotherapy, Cardiotoxicity, Statins

P1.17-23 OUTCOME AFTER SURGICAL RESECTION FOR CLINICAL STAGE I NON-SMALL CELL LUNG CANCER ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

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Background: It has been reported that interstitial lung disease is associated with an increased risk of lung cancer. Several studies have reported surgical results for lung cancer with interstitial lung disease showed poor prognosis. To improve the outcome of surgical treatment for non-small lung cancer with interstitial lung disease, we need to examine the oncological characteristics. **Method:** All of the patients who underwent surgical treatment for clinical stage I non-small cell lung cancer with interstitial lung disease at our institution from January 2004 to December 2016 were reviewed. We retrospectively analyzed the following data; surgical procedure (lobectomy or sublobar resection), clinical and pathological stage, pathological findings, outcomes. **Result:** The 54 patients with interstitial lung disease comprised 52 men and 2 women, with a median age of 73 years (range 55-84 years). 22 patients had UIP and 32 patients had non-UIP. Of the 54 patients, 43 patients had clinical stage IA and 11 had clinical stage IB. The surgical procedures were lobectomy in 25, segmentectomy in 3, wedge resection in 25 and exploratory thoracotomy in 1. Histologically, 30 squamous cell carcinomas, 20 adenocarcinomas, 4 others were noted. Pathological stage (IA/IB/IIA/IIB/IIIA/IV) was as follow; 17/23/2/1/8/3. Pathological upstaging was confirmed in 33 out of 54 after surgical resection. The reasons for pathological upstaging were pleural invasion in 18 patients, nodal metastasis in 9, malignant pleurisy in 3, tumor size in 2 and pulmonary metastasis in 1. Pleural invasion and malignant pleurisy were observed in 21 out of 33 patients. One patient died from acute exacerbation. The median follow-up period was 21.6 months (1.0-103.6 months). The 3-years overall survival rate was 48.8%. Death occurred in 30 (25 from lung cancer, 3 from respiratory failure, 2 from pneumonia). **Conclusion:** Non-small cell lung cancer with interstitial lung disease has a high rate of pleural invasion and pathological upstaging revealing after surgical resection. Regarding the selection of surgical procedure, we should take into consideration the possibility of pleural invasion.

Keywords: Non-Small Cell Lung Cancer, interstitial lung disease, clinical stage I

P1.17-24 TREATMENT OF ULTRACENTRAL LUNG TUMORS WITH HYPOFRACTIONATED RADIATION THERAPY

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Background: The optimal dose schedule for ultracentral (UC) lung lesions remains poorly defined. The aim of this study is to report the efficacy and toxicity of hypofractionated radiation therapy (HFRT) in a single institution experience. **Method:** An IRB approved retrospective review of patients with UC lung lesions treated with HFRT between 2008 and 2015 was performed. UC was defined as gross tumor volume (GTV) abutting the trachea, proximal bronchial tree (PBT), or esophagus. Both primary lung lesions and lung metastases were included. 4D simulation was typically employed, and respiratory management was utilized if appropriate (e.g. tumor motion exceeding 1 cm). Patient characteristics, treatment planning and delivery parameters, patient outcomes, and toxicity were collected. Toxicity was graded using CTCAE 4.03 and statistical analyses were performed using SPSS (Version 25). **Result:** A total of 37 patients, 32 with primary lung tumors and 5 with metastases, were included. Primary lung tumors were stage T1, T2, T3, and T4, in 48%, 42%, 6% and 6% of patients, respectively. 39% had N1 disease and 16% were M1. Median age was 70 (range: 49-89) and 73% were male. The predominant histologies were adenocarcinoma (41%) and squamous cell carcinoma (43%). UC status was due to abutment of PBT in 78% of patients. 32% were treated with three dimensional conformal radiation therapy, and 68% with intensity modulated radiation therapy. 78% (29) of patients were treated in 20 fractions to 60 or 70 Gy, of which, 17 received concurrent weekly carboplatin and paclitaxel. A minority received regimens approximating stereotactic body radiotherapy (SBRT) dosing (60 Gy in 8 fractions in 10% and 50 Gy in 10 fractions in 6%). With a median follow up of 17 months, the crude local failure rate was 8%. Median overall survival was 33 months (range: 0-73 months). There were three grade 3 toxicities consisting of tracheal stenosis, hypoxia, and dysphagia, and no late grade 4/5 events. Notably, two patients receiving 60 and 70 Gy in 20 fractions died during the final week of treatment, after 51 and 60 Gy, respectively. One from sudden massive hemoptysis (hemoptysis to some extent dated back prior to HFRT), and one from complications of lung cancer, with additional details unclear. The GTV abutted/involved multiple critical structures in both cases, and attributability to treatment is uncertain. **Conclusion:** Local tumor control appears promising following treatment with HFRT for UC lung lesions. As with any regimen utilized in this anatomic location, caution is warranted. Additional prospective studies are required to further elucidate optimal dose and fractionation, and how it might compare with the therapeutic index of SBRT.

Keywords: ultracentral, hypofractionated radiation therapy

P1.17-25 OUTCOMES OF PRIMARY LUNG CANCER SBRT IN PATIENTS WITH COMPROMISED LUNG FUNCTION

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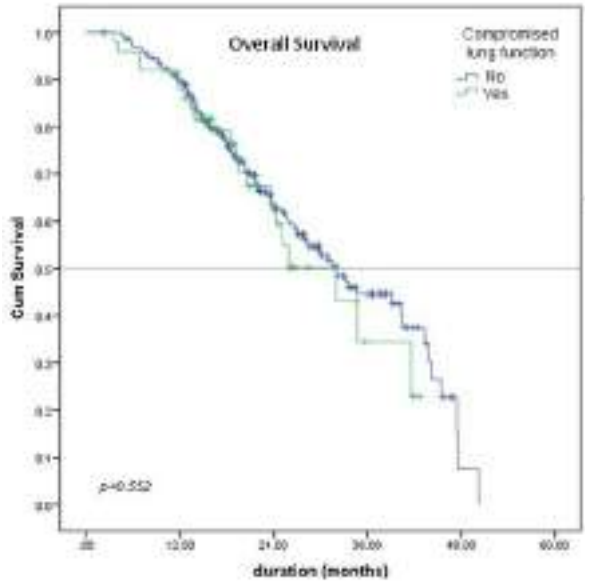
Background: Stereotactic Ablative Body Radiotherapy (SABR) is a standard treatment option for early lung cancer, especially in patients who are not medically fit to undergo surgery. The tolerability and efficacy of this treatment has lead to more comorbid patients being referred for SABR treatment. The objective of this study was to assess outcomes of SABR lung patients treated over a 4 year time frame, with a focus on patients with pre-existing lung fibrosis and/or lung function compromise. This patient group is known to have a poorer survival outcome with conventional radiotherapy due to worsening of their pre existing lung condition.This study was aimed at generating real world data of SABR outomes in this population. **Method:** Data about staging, pathology, lung function, treatment response and follow up in primary early stage lung cancer patients treated with SABR at a tertiary cancer center over a 4 year time frame was gathered retrospectively and analysed for outcomes in survival differences between patients with compromised and non compromised lung function. For the purpose of this abstract compromised lung function was defined as clinical/radiological diagnosis of pulmonary fibrosis and /or a transfer factor for carbon monoxide (TLCO) < 40% predicted. **Result:** The records of 274 patients with a median age of 78 years were analysed. 50(18.2%) patients were found to have compromised lung function as defined. 53% had MRC dypsnoea scores of ≥3 and 75% were current or ex smokers. 80% of the patients had moderate to severe comorbidity. Median overall survival estimate by Kaplan Meir method for patients with compromised lung function undergoing SBRT was 31.9 months(95% CI 22.3 - 41.5) was not significantly different from patients without compromised lung function 32.0 months (95% CI 27.1- 37.0) p=0.552.



Compromised lung function	Median Overall Survival (months)			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No	32.033	2.515	27.104	36.963
Yes	31.933	4.892	22.346	41.521
Overall	31.933	2.345	27.336	36.530

Conclusion: SBRT for primary lung cancer appears to be as safe in patients with compromised lung function as those without.

Keyword: SBRT, lung fibrosis, NSCLC

P1.17-26 DELIVERY OF STEREOTACTIC MR-GUIDED ADAPTIVE RADIATION THERAPY FOR PERIPHERAL LUNG TUMORS

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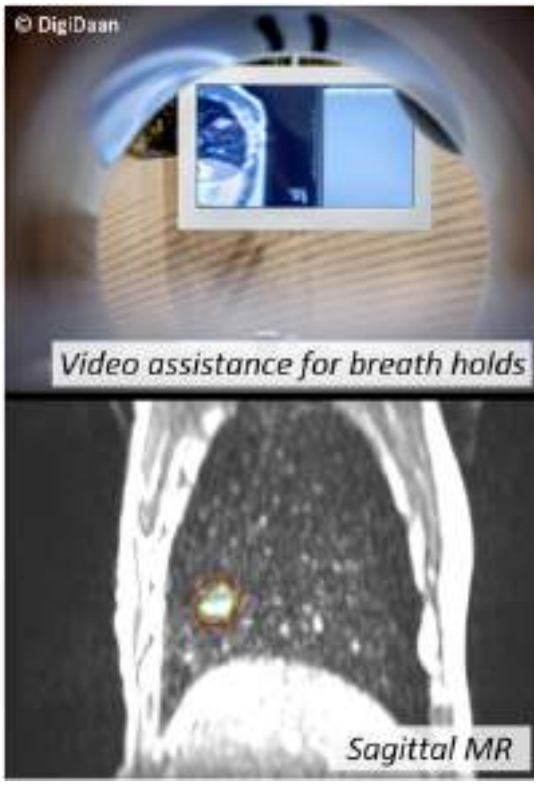
Background: Stereotactic MR-guided adaptive radiation therapy (SMART) allows delivery of stereotactic ablative radiotherapy (SABR) with high precision (van Sörnsen de Koste JR, 2018). For central lung tumors, SMART with on-table plan adaptation improves target coverage and avoids excessive normal organ doses (Finazzi T, 2019). The benefits of SMART for peripherally located lung tumors are unknown. **Method:** Between 2016-2019, 23 patients (25 peripheral lung tumors) underwent SMART delivered in 3-8 fractions on an MR-Cobalt-60 system or MR-Linac. Before each fraction, a 17-second breath-hold MR scan was acquired, followed by on-table plan adaptation based on the anatomy-of-the-day, using a planning target volume (PTV) margin of 3 or 5 mm. Breath-hold gated delivery was performed under continuous MR-guidance using an in-room monitor (Fig. 1). For 14 patients, a motion-encompassing internal target volume (ITV) was created from a free-breathing 4DCT scan. Benefits of on-table adaptation were studied by comparing 112 «predicted» plans, which are the baseline plans recalculated on the anatomy-of-the-day, with on-table reoptimized plans.



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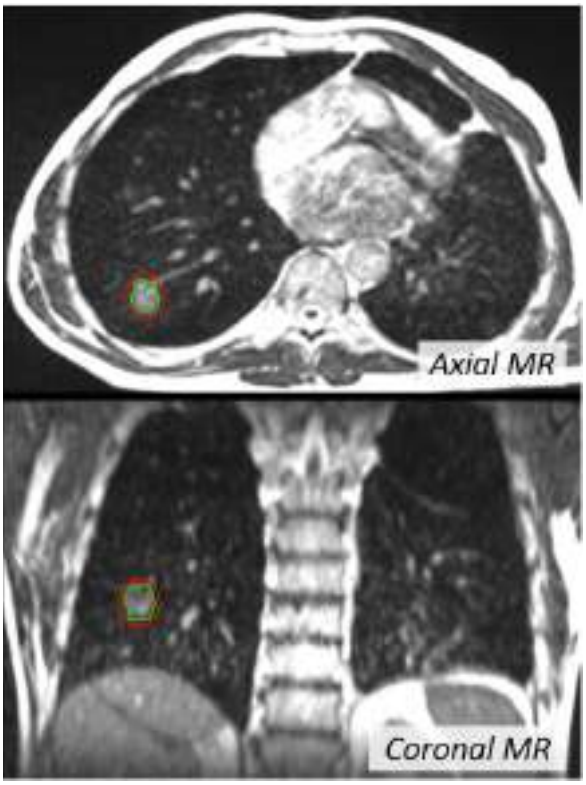

Result: The SMART procedure took a median of 62 minutes on the MR-Cobalt-60 system, and 48 minutes on MR-Linac. Average SMART-PTVs were 15.4 cc (range, [3.1-55.6]). In 14 patients with a 4DCT, SMART-PTVs measured only 53.7% (range, [31.9-75.0]) of PTVs generated from the corresponding 4DCT scans (ITV+5mm). Clinicians chose the reoptimized plan for 91% of fractions. Per fraction, on-table plan adaptation improved prescription dose coverage (V100%) of the PTV from a median of 92.2% in predicted plans, to 95.0% in reoptimized ones, thereby increasing the proportion of fractions delivering a BED_{10Gy} ≥100Gy to 95% of PTV from 90.2% to 100.0%. **Conclusion:** Using SMART for peripheral lung tumors resulted in smaller target volumes, and on-table plan adaptation ensured delivery of ablative doses to the PTV. Despite longer SABR delivery times, our findings suggest that SMART can be beneficial for some peripheral lung tumors.

Keywords: SABR, stereotactic radiotherapy, MR-guided radiotherapy

P1.17-27 STEREOTACTIC RADIOTHERAPY FOR PRIMARY LUNG TUMORS: THE INFLUENCE OF SIZE

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Background: Stereotactic radiotherapy (SBRT) is the main treatment modality for inoperable early-stage lung cancer. Tumor size is commonly associated with higher local and distant relapse rates, but recent studies demonstrate promising results also in larger tumors. **Method:** We retrospectively analysed all patients treated with SBRT for primary lung cancers in our department between 2012 and 2017 and evaluated the influence of size. Survival analysis was carried using the Kaplan-Meier method. **Result:** SBRT was performed in 218 patients (with 233 tumors) with primary lung tumors. Median follow-up was 22 months. Most were males (78.9%), with a median age of 73 (from 51-91). Median maximum diameter was 2.3cm (0.5 to 7.5cm) – 76.4% were T1(≤3cm) and 21.9% were T2(>3 and ≤5cm). A complete local response was observed in 19.3% lesions, a partial response in 22.3% and stable disease in 45.9%. Disease progression was observed locally in 11.5% patients, in the lung in 8.4%, in hilar/mediastinal nodes in 10.7% and a distal progression in 12.1%. In T1 and T2 tumors, overall survival (OS) at 18 months was 74.5%, disease-specific survival (DSS) was 88.8% and local progression-free survival (L-PFS) was 91.3%. At 18 months, a larger tumor size was significantly associated with lower L-PFS (T1-93.6 Vs T2-87.2%, p=0.03) and DSS (T1-91.6 Vs T2-80.8%, p=0.013), but had no impact in OS (p=0.342). There was no significant relationship between size and time of local relapse. **Conclusion:** Lower L-PFS and DSS rates were observed for tumors >3cm, with no impact in OS. Still, the results for T2 lesions are within literature-reported outcomes, with a favourable toxicity profile.

Keywords: SBRT, stereotactic radiotherapy, Early-stage lung cancer

P1.17-28 REFUSAL OF SURGERY FOR EARLY STAGE LUNG CANCER: RISK FACTORS AND SURVIVAL

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Background: The standard of care for treatment of early stage non-small cell lung cancer (NSCLC) is surgical resection. However, suitable patients refuse surgery for various reasons. We characterize the clinical and sociodemographic predictors of those who refuse recommended surgery for early stage NSCLC cancers and explore the influence of surgical compliance on survival. **Method:** Primary Stage I and II NSCLC cases diagnosed between 2007 and 2014 were selected from the Surveillance, Epidemiology and End Results (SEER) database (n = 36,926). All cases were recommended surgery for treatment. Predictors of surgery refusal were examined using multivariate logistic regression. The likelihood of mortality after refusing surgery and any chemotherapy/radiation and refusing surgery but receiving alternative forms of treatment was performed using a cox proportional hazards model. Propensity-matched survival analysis was then performed between those who received surgery and those who refused surgery. SAS v9.4 was used for statistical analyses. **Result:** The majority of the sample was non-Hispanic White (79%), female (52%), married (57%) and Stage I (83%). Most were between 50-64 years old (31%) or 65-79 years old (55%) and had tumor sizes of 11-20 mm (32%), 21-40 mm (42%), or > 40 mm (20%); 909 cases (2.5%) refused surgical intervention. Of these, 634 (69.7%) cases underwent radiation therapy and 87 (9.6%) received chemotherapeutic treatment. At multivariable analysis, non-Hispanic blacks (OR_{adj} 2.14, 95% CI: 1.76-2.61), increasing age (65-79 years old: OR_{adj} 4.29, 95% CI: 2.02-9.11), increasing tumor size (21-40 mm: OR_{adj} 2.79, 95% CI: 1.73-4.50), and single marital status (OR_{adj} 2.14, 95% CI: 1.85-2.48) were associated with increased odds of surgical refusal. Stage II lung cancer was inversely associated (OR_{adj} 0.75, 95% CI: 0.62-0.92) with surgical refusal. Refusing surgery and having no chemotherapy/radiation (HR_{adj} 4.16, 95% CI: 3.48-4.96) as well as refusing surgery but undergoing alternative forms of treatment (HR_{adj} 2.90, 95% CI: 2.55-3.29) were associated with increased mortality compared to those who received recommended surgery. After propensity matching (n = 1790), refusing surgery was associated with increased likelihood of mortality (HR_{adj} 2.77, 95% CI: 2.22-3.46). **Conclusion:** Identifiable risk factors exist for refusing recommended surgery for Stage I/II NSCLC, and refusal is associated with an increased likelihood of mortality. Recognizing that certain subgroups are more likely to refuse surgery is vital when providing treatment choices and reducing disparities in survival for early stage lung cancer.

Keywords: mortality, Risk Factors, surgery refusal

P1.17-29 8-YEAR EXPERIENCE OF NAVIGATIONAL BRONCHOSCOPY FOR PREOPERATIVE LOCALIZATION OF SUBCENTIMETER LUNG NODULES IN A SMALL COMMUNITY HOSPITAL

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Background: With the advent of lung cancer screening, CT imaging has led to the identification of sub-centimeter nodules that are challenging to localize for both diagnosis and resection. The traditional approaches are problematic because biopsies often have poor diagnostic yield, resulting in repeat attempts at tissue collection, delay in time to treatment, and increased cost. Electromagnetic navigation bronchoscopy (ENB) is a newer technology that allows greater precision in preoperative localization of nodules to obtain tissue for diagnosis and fiducial marker placement. Our institution has adopted a practice that combines simultaneous ENB for nodule localization and video-assisted thoracoscopic surgery (VATS) for resection with single anesthetic administration and operating

room team. We aimed to evaluate changes in time to treatment, time to surgery, and length of stay. **Method:** Retrospective review of all patients who underwent nodule localization and VATS or robotic-assisted VATS (RATS) between (May 2011- March 2019). ENB localization was performed with transbronchial injection of ICG and/or placement of gold fiducial markers. **Result:** A total of 72 patients underwent VATS or RATS. During the first two years of the study period, ENB was performed with portable C-arm fluoroscopic guidance with diagnostic yield of 48%. Surgery was performed on average 29.7 days (4-190 days) after ENB (3 patients had non-diagnostic bronchoscopy and were followed with serial CT scans that resulted in >100 days until surgery). In August 2017 utilization of Cone Beam CT scan began during ENB, which resulted in reduction in time to surgery to average of 20.1 days (1-39 days). After persistent low diagnostic yield with bronchoscopy and demand for expedient diagnosis, in February 2018, ENB and surgical resection were performed simultaneously with single anesthetic administration and OR team. Furthermore, in December 2018 utilization of daVinci Xi robot began for RATS with ICG injection during ENB for intraoperative localization of nodules. The hospital length of stay (LOS) and time to treatment (from the initial identification of a lung nodule to surgery) for Super D bronchoscopy group (SDB) (n=36) is 5.7/63.8 days, SDB-with cone beam technology (n=8) is 4.5/62.8 days, respectively. Transition to simultaneous resection (n=28) resulted in 100% diagnostic yield, further decrease of both hospital LOS and time to treatment, to 3.6 days and 43.7 days, respectively. **Conclusion:** Our data demonstrates that intraoperative ENB lung lesion localization with simultaneous VATS/RATS resection results in decreased hospital length of stay, reduced time to treatment, and 100% diagnostic yield. Both metrics significantly impact patient satisfaction and healthcare costs.

Keywords: ENB, VATS, lung cancer screening

P1.17-30 SEX AND AGE-ASSOCIATED SURVIVAL FOLLOWING RESECTED EARLY STAGE NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) is the most common malignant tumour, and a leading cause of mortality worldwide. Rising rates of NSCLC have been observed among females, but nonetheless females also are often observed to possess better prognosis across all stages of disease. We aimed to assess the impact of biological sex along with age at diagnosis on the outcome of NSCLC patients with resected early-stage disease. **Method:** A 15-year population-based retrospective analysis was conducted on *de novo* early stage (AJCC 7th edition, Stage I or II) patients between 1999-2014, whose primary tumor was surgically resected. Demographic, clinical characteristics, treatment modalities and outcome data were extracted from the institutional Glans-Look Lung Cancer Database, and univariate analysis, including Kaplan-Meier survival, alongside multivariate Cox regression was performed to compare outcomes by sex and determine prognostic factors associated with survival. **Result:** 872 early-stage resected NSCLC patients were identified. Median age at diagnosis 65.9 years (IQR: 59.1-72.6), 56% female, 76% 'ever' smokers, 68% Stage I, 91% oncologic resection (9% wedge resection). Median overall survival (mOS) for all early-stage resected cases was 93 months (95% CI: 81.9 – 105.4) with a 5-year survival rate of 62.5%. Females exhibited superior survival outcomes to males (105.4 months vs. 77.5 months, log-rank p=0.002), as did those < 75 years at diagnosis compared to those ≥ 75 years (103.9 vs. 76.2 months, log-rank p <0.001). Best and worst survival outcome was observed in females under age 75, and males over age 75, respectively (mOS 114.3 vs. 64.5 months; 5-year survival: 67.9% vs. 50.5%). No difference in rate of recurrence (overall) or rate of metastatic recurrence between males and females was identified (39% vs. 36%, p=0.214; 19% vs. 16%, p=0.591). After controlling for confounding variables, a reduced risk of mortality was found for females (HR: 0.8, p=0.016), age under 75 years at diagnosis (HR: 0.6, p < 0.001) and stage I presentation (HR: 0.6, p< 0.001). **Conclusion:** Females experience significantly longer mOS, in particularly females under the age of 75 years at diagnosis. After adjusting for confounding factors, we found significantly reduced mortality risk for females aged under 75 years at diagnosis, and Stage I disease. Despite possessing the poorest outcomes among this cohort, males ≥ 75 years still possessed a 5-year survival rate of 50%, suggesting that surgical resection is a highly effective treatment option for suitable NSCLC patients, regardless of age.

Keywords: resected early stage NSCLC, age-based differences in survival, sex-based differences in survival

P1.17-31 VATS SEGMENTECTOMIES ARE AT LEAST AS SAFE AS VATS LOBECTOMIES

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Background: Video-assisted thoracic surgery (VATS) segmentectomy is a feasible and effective treatment of not only benign lung tumors but also non-small cell lung cancer (NSCLC). Expanding the indications for surgical treatment of early NSCLC in high-risk patients may result in an increased number of complications in the postoperative period. **Method:** Between January 2018 and December 2018 22 VATS segmentectomies were performed in a single center. The postoperative period was recorded and these data were compared to postoperative results of 31 patients who underwent VATS wedge excisions in the relevant period and 438 VATS lobectomies during the VATS program in the department. In order to assess the influence of the type of resection on the number of postoperative complications, multivariable analysis was performed. The selection biases were reduced by the use of propensity-score matched analysis (PSMA; using the nearest neighbor matching method by age, gender, Charlson Comorbidity Index [CCI] and 6-minute walking distance). **Result:** In the multivariable analysis, CCI was the only independent risk factor of increased complications rate (HR 1.321 95%CI 1.009-1.730 p=0.042). Type of resection, gender, and 6-minute walking distance did not influence the risk of complications. The rate of complications in patients who underwent VATS wedge excision was 12.9%, VATS segmentectomies 27.2% and VATS lobectomies 51.5% (OR 2.846 95%CI 1.021-8.298 p=0.026 segmentectomies vs. lobectomies). However, in PSMA analysis, there was a trend towards lower complications rate in patients who underwent VATS segmentectomy comparing to VATS lobectomies (30% vs. 60% OR 0.286 95%CI 0.061-1.263 p=0.057). Postoperative hospital stay did not differ between the study groups 4 vs. 5 days (p=0.170). **Conclusion:** VATS segmentectomy is characterized by similar complications rate and postoperative hospital stay if compared with VATS lobectomy.

Keywords: VATS, lobectomy, segmentectomy

P1.17-32 THE 8TH EDITIONS OF THE AJCC STAGING SYSTEM IN TERMS OF PREDICTING RECURRENCE AND SURVIVAL IN RESECTED NSCLC LONG-TERM SURVIVORS

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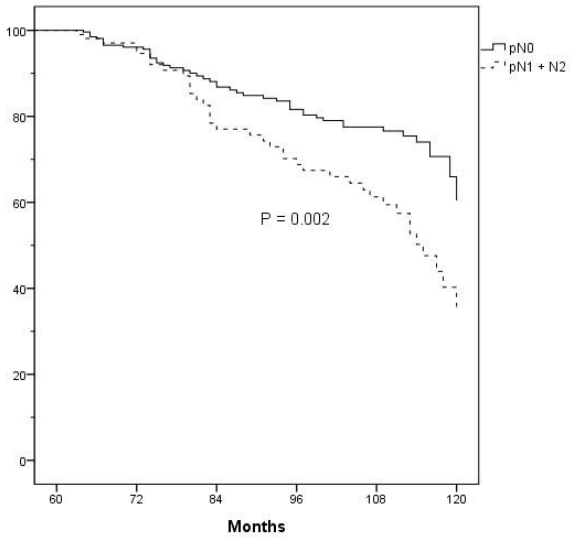
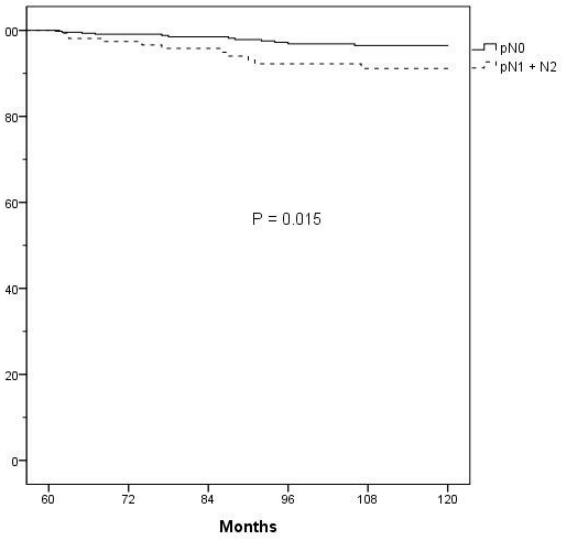
Background: Lung cancer has a poor prognosis, and the number of long-term survivors (LTSs) is small compared with that of other cancers. There are few studies focusing on late recurrence in long-term survivors with lung cancer. The purpose of this study was to analyze the risk factors for survival and late recurrence in long-term survivors after a disease-free period of 5 years. **Method:** A retrospective analysis of patients with a disease-free survival of at least 5 years after surgical resection for non-small cell lung cancer between January 1998 and December 2009 was conducted. Patients who received neo-adjuvant therapy, had incomplete resection, were of advanced stages according to the AJCC (American Joint Committee on Cancer) 7th edition (stage IIIb and IV), or missing data were excluded. **Result:** A total of 648 (41.7 %) of 1,555 patients were enrolled. The median age was 62.6 (range, 21.3–82.2) years. Pathologic N0 (485 patients, 74.8 %) and stage I (394 patients, 60.8 % in 7th and 363 patients, 56.0 % in 8th edition) were the dominant stage. According to the 7th edition, node-positive (N1+N2) status was an independent risk factor only for disease-free survival (HR, hazard ratio, 2.575; *p*=0.028; CI, confidence interval, 1.107-5.990) on multivariable analysis. By contrast, node-positive was an

independent risk factor for both overall survival (HR, hazard ratio, 1.608; *p*=0.031; CI, confidence interval, 1.043-2.477), and disease-free survival (HR, 2.662; *p*=0.019; CI, 1.175-6.034) in the 8th edition.





Conclusion: Compared to the 7th edition, nodal stage of the 8th edition seems more appropriate as a risk factor for both overall survival and disease-free survival 5 years after surgical treatment in patients with completely resected non-small cell lung cancer.

Keywords: Non-Small Cell Lung Cancer, 5-year disease-free survival, AJCC 8th edition

P1.17-33 SURGICAL TREATMENT STRATEGY FOR LUNG CANCER PATIENTS WITH INTERSTITIAL PNEUMONIA

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Background: In conducting surgical treatment for lung cancer patients with interstitial pneumonia (IP), it is important to conduct oncological radical surgery in consideration of the risk of acute exacerbation. Sato et al. reported risk factors and scores of acute exacerbations of IP in lung cancer (General Thorac Cardiovasc Surg 63; 164-172, 2015), and are being used in daily practice. **Method:** We retrospectively analyzed data from patients with non-small cell lung cancer with a clinical diagnosis of IP who underwent pulmonary resection between 2013 and 2018 at our hospital. **Result:** We analyzed 79 cases, 11.2% of the 701 lung cancer cases in the subject period. 70 men, 9 women, average age 72 years (53-85 years old), average of smoking index of 74 cases excluding 5 cases of never smokers averages 1400 (400-2950). Histological types were adenocarcinoma 29, squamous cell carcinoma 41, large cell carcinoma 4, and 6 others. Surgery was performed with 60 lobectomies, 2 segementectomies, 17 wide wedge resections. The average of acute exacerbation risk scores was 12.3 (5-22), and the incidence rate of acute exacerbations was predicted to be 25% or more in 13 cases. In 13 cases, 6 lobectomy resections, 1 segmentectomy was performed, WWR were 6 cases. There was no case of acute exacerbation in 13 cases, and 3 cases of pirfenidone (lobectomy 1, segmentectomy 1, partial resection 1), nintedanib 1 case (lobectomy), predonine 4 cases (lobectomy 1, partial resections 3). Acute exacerbation onset occurred in 2 cases (2.8%), both risk scores were 11. **Conclusion:** Although there was no correlation between the onset of acute exacerbations and the risk score, it was suggested that oral administration drugs such as pirfenidone was effective.

Keywords: Interstitial pneumonia (IP), acute exacerbation, Lung cancer

P1.17-34 PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE CT-DETERMINED SARCOPENIA AND RADIODENSITY IN RESECTED NON-SMALL CELL LUNG CANCER

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Background: Sarcopenia, reduced skeletal muscle mass, is associated with poor prognosis in advanced non-small cell lung cancer (NSCLC) patients. The purpose of this study was to evaluate predictive value of CT–determined skeletal muscle area on prognosis after curative resection of NSCLC. **Method:** For a total 272 NSCLC patients (male=164, mean age=63±10 years) that underwent surgery between 2011 and 2016, skeletal muscle (CT Hounsfield unit: −29 to 150 HU) at the level of the third lumbar vertebra (L3) was assessed using preoperative CT images. Sarcopenia was defined as L3 muscle index of <55 cm^2/m^2 for men and of <39 cm^2/m^2 for women. Moreover, skeletal muscle was subsequently classified as abnormal muscle (-29 to <30HU) and normal muscle (30 to 150 HU) by radiodensity. Data on clinical characteristics, disease-free survival (DFS), and overall survival (OS) were retrospectively collected. **Result:** The prevalence of sarcopenia was 22.4% for all study subjects, 32.9% for men, and 6.5% for women. Using a maximal chi-squared method determined optimal cut-off to determine unhealthy muscle (proportion of abnormal muscle >24.5%), the prevalence of patient with unhealthy muscle was 84.2% (78.7% for male and 92.6% for female). There was no significant difference in the prevalence of unhealthy muscle between sarcopenia and non-sarcopenia patients (86.9% vs. 83.4%, p = 0.690). No significant difference was observed between the 3-year DFS rate (77.0% vs 67.0%, *p* = 0.142) or 3-year OS rate (84.8% vs 87.9%, *p* = 0.576) between patients with and without sarcopenia. However, patients with unhealthy muscle tends to have shorter 3-year DFS rate (67.2% vs 79.4%, *p* = 0.094) and 3-year OS rate (86.1% vs 92.6%, *p* = 0.176). In the multivariable analysis, unhealthy muscle was one of independent indicator to predict a 3-year DFS rate (HR, 2.072, p=0.044), along with pathologic T stage (HR, 3.348, p<0.001), pathologic N stage (HR, 3.401, p<0.001), and R1 resection (HR, 3.804, p=0.033). **Conclusion:** Radiodensity based muscle quantification is associated with shorter DFS in resected lung cancer. Further research is warranted to establish whether muscle measures should be integrated into routine practice to improve prognostic accuracy.

Keywords: sarcopenia, Computed tomography, Non-Small Cell Lung Cancer

P1.17-35 SOLID PREDOMINANT SUBTYPE IS AN INDEPENDENT RISK FACTOR FOR RECURRENCE IN PATIENTS WITH PATHOLOGIC STAGE I ADENOCARCINOMA

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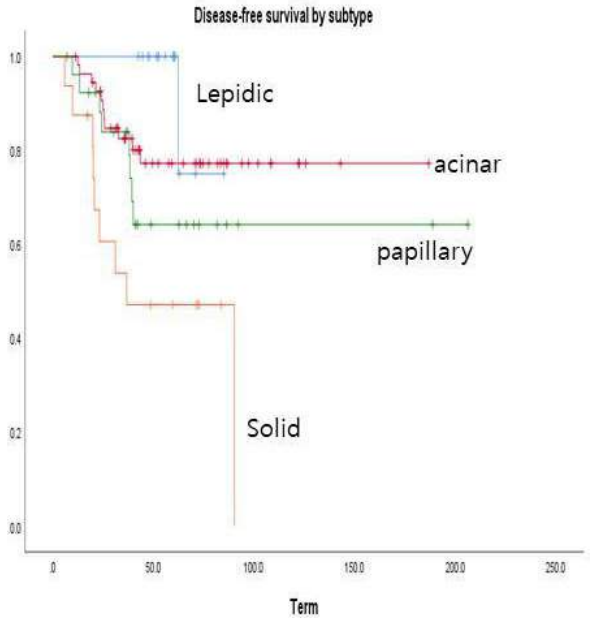
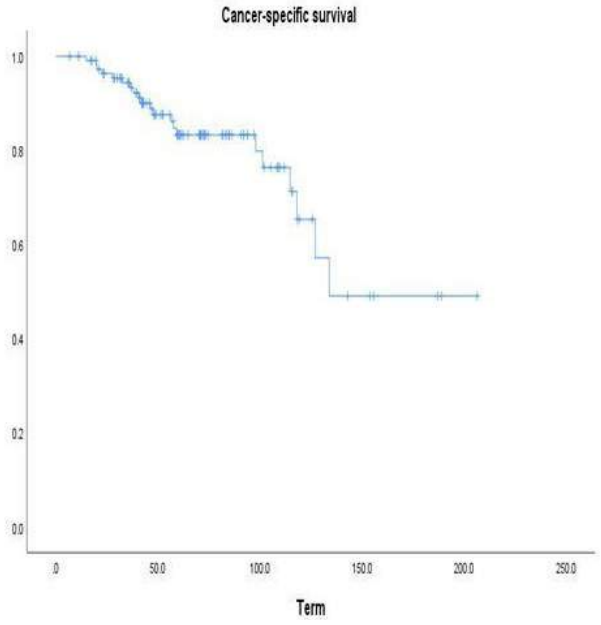
Background: Lobectomy and mediastinal lymph node dissection(MLND) is the standard treatment in patient with stage I non-small cell lung cancer (NSCLC). We expect the high 5-year survival and freedom from recurrence rate in early staged cancer through curative intent. But even in stage I NSCLC, recurrence may occur, which does not fit the expected therapeutic outcome. Therefore, we investigated the risk factors of recurrence and survival outcome in stage I adenocarcinoma. **Method:** We retrospectively

reviewed a total of 114 patients diagnosed with pathologic stage I adenocarcinoma who underwent lobectomy and MLND from June 2001 to July 2017. The risk factors were statistically analyzed using Cox proportional hazard model and the Kaplan meier method for survival. **Result:** The median follow-up period was 59.5months (range 7.0-206.3). Recurrence occurred in 29 of patients (25.4%). Median survival time was 133.9 months. The 5-year cancer specific survival and freedom from recurrence rate were 83.3% and 73.8%, respectively. In univariate analysis, the significant variables for recurrence were ever smoker at the time of surgery, pathologic tumor size, SUVmax in PET-CT, central located tumor, solid predominant histologic subtype. In multivariate analysis, solid predominant subtype(p=0.035, HR=9.70, CI 1.18-79.88) was the independent risk factor for higher probability of recurrence. **Conclusion:** In pathologic stage I NSCLC, the risk factor with higher probability of recurrence was solid pathological subtype. This may be a useful parameter in considering whether adjuvant therapy is needed to reduce recurrence in pathologic stage I adenocarcinoma.





Keywords: adenocarcinoma, solid, Subtype

P1.17-36 ANALYSES OF SEGMENTAL AND INTRAPULMONARY LYMPH NODE METASTASES OF SMALL-SIZED PERIPHERAL SOLID PREDOMINANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Currently, randomized clinical trials to evaluate segmentectomy compared with lobectomy for peripheral small size non-small cell lung cancer (NSCLC) are ongoing, and the results are expected. The extent of lymph node dissection in intentional segmentectomy has not been clarified. The purpose of this study was to retrospectively investigate the pattern of segmental and intrapulmonary metastasis in intentional segmentectomy. **Method:** We reviewed the records of patients who underwent lobectomies and systematic lymph node dissections for small(≦2cm) peripheral solid-predominant and clinical/surgical N0 NSCLC from 2002 to 2018. Among them, a total of 239 patients whose primary nodules was located in the outer third peripheral lung field and consolidation-tumor ratio (CTR) >0.5 on thin-section computed tomography (TSCT); who could be candidates for intentional segmentectomy were enrolled in this study. We analyzed the clinical and radiological factors, which may predict nodal metastases, and the distribution patterns of lymph node metastases. **Result:** Of all patients, 33 (14%) had lymph node metastases (pN1:15, pN2:18). Segmental lymph node metastases (# 13) were observed in 4 cases(1.7%), and there were no metastasis of #13 in adjacent segment. #12 lymph node metastases were in 18 cases (7.5%), and # 11 lymph node metastases in 12 cases (5.0%), respectively. Skip N2 metastases were in 7 cases (2.9%), and all were in the range of regional lymphatic resection. **Conclusion:** Solid-predominant NSCLC may have 14% lymph node metastasisa even with clinical and surgical N0. It may not be necessary to examined outside tumor-bearing segmental lymph nodes. However, there should be adequate lymph node sampling and intraoperative frozen section. In particular, intraoperative sampling of # 11 and # 12 is useful for selection of lobectomy convert cases.

Keywords: Lung cancer, intentional segmentectomy, Lymph node metastasis

P1.17-37 MINIMALLY INVASIVE OPEN SURGERY (MIOS) FOR CLINICAL STAGE I LUNG CANCER: PERIOPERATIVE OUTCOMES IN RECENT 5 YEARS

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Background: Many thoracic surgeons have tried to make lung cancer surgery less invasive. Although several minimally invasive procedures for lung cancer surgery have been proposed, it has been controversial which procedure is the most optimal. Since around 2010, minimally invasive open surgery (MIOS) has been adopted for lung cancer surgery at our institute. MIOS was performed with direct vision and thoracoscopic vision through a 2-cm port and a muscle-sparing mini-thoracotomy (incision, 6-8 cm in the fourth or fifth intercostal space at the anterior or posterior axillary line). The objective of this study was to evaluate MIOS in terms of perioperative outcomes in recent 5 years. **Method:** Between 2013 and 2017, 2404 patients underwent pulmonary resection for lung cancer at National Cancer Center Hospital, Tokyo, Japan. Among them, 1930 patients with clinical stage I lung cancer were included in this study. We investigated several perioperative factors according to the type of pulmonary resection: lobectomy, segmentectomy and wedge resection. **Result:** The patients consisted of 993 men (51.5%) and 937 women (48.5%) with a median age of 69 years (range: 32-90 years). Lobectomy was performed in 1288 patients (66.7%), segmentectomy in 397 (20.6%), and wide wedge resection in 245 (12.7%). Median blood loss was 32 ml (range: 1-1489 ml) for lobectomy, 20 ml (range: 1-435 ml) for segmentectomy, and 4 ml (range: 1-177 ml) for wedge resection. Median operative time was 122 min (range: 45-293 min) for lobectomy, 115 min (range: 69-211 min) for segmentectomy, and 66 min (range: 29-177 min) for wedge resection. Median length of post-operative hospital stay was 4 days (range: 1-57 days) for lobectomy, 4 days (range: 2-20 days) for segmentectomy, and 3 days (range: 2-24 days) for wedge resection. There were no operative deaths. The morbidity rate was 11.8% for lobectomy, 7.3% for segmentectomy, and 4.1% for wedge resection. The 30-day mortality rate was 0.16% for lobectomy, 0.25% for segmentectomy, and 0% for wedge

resection. **Conclusion:** MIOS for clinical stage I lung cancer is a technically safe and feasible procedure with a low complication rate and a shorter hospital stay. The oncological outcomes with a longer follow-up need to be investigated.

Keywords: minimally invasive surgery, clinical stage I, Lung cancer

P1.17-38 DOES USE OF EPIDURAL ANESTHESIA AFFECTS SURVIVAL OF RESECTABLE NSCLC? ANALYSIS FROM A JAPANESE NATIONWIDE DATABASE

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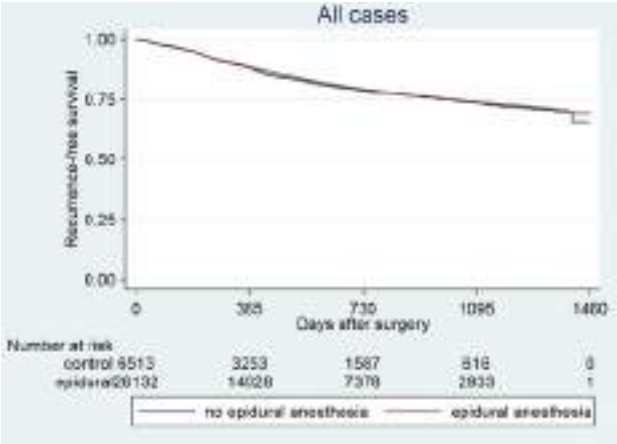
Background: Several studies have suggested that epidural anesthesia may increase postoperative survival by reducing the cancer recurrence rate. The rationale for this phenomenon is that epidural anesthesia decreases the surgical stress response by suppressing circulating glucocorticoids, catecholamines and inflammatory mediators, and thus reduces transient immunosuppression during cancer surgery. Moreover, epidural anesthesia can reduce the use of opioids, which are generally thought to be immunosuppressive (suppresion of NK cell cytotoxicity, promotion of VEGF-dependent angiogenesis, and activation of EGF pathway). The topic is still controversial, and there are no previous studies related to lung cancer and thoracic epidural anesthesia. Our study aim is to reveal the probable impact of epidural anesthesia during radical lung cancer surgery on long-term postoperative survival and cancer recurrence. **Method:** We used Japanese Diagnosis Procedure Combination database, the national databese which covers 55% of all acute-care hospitalizations in Japan. We retrospectively reviewed the medical records of 34,694 patients who received lobectomy or pneumonectomy for curative intent for non-small cell lung cancer, between July 2010 and March 2016. Propensity score matching and stabilized inverse probability of treatment weighting (IPTW) was used to adjust the patient background. Recurrence-free survival was assessed using Kaplan-Meier curves. **Result:** Among the patients, 27,810 received epidural anesthesia during lung cancer surgery and 6,884 underwent the surgery without epidural anesthesia. Video assisted thoracoscopic surgery (VATS) was performed in about 23,682 (81.2%) in epidural anesthesia patients, and 6,180 (85.5%) in non-epidural anesthesia patients (<0.001). According to the Kaplan-Meier curve after baseline adjusting by using propensity score matching and inverse weighting, there was no stastically significant difference in recurrence-free survival between the groups (p=0.89). Stratification according to the cancer stage revealed no significant difference in recurrence-free survival depending on the type of anesthesia administered at each stage.



Conclusion: Oncological outcome after lung cancer surgery was not affected by the use of epidural anesthesia.

Keywords: surgical outcome, national database, epidural anesthesia

P1.17-39 PREOPERATIVE PREDICTION OF INCOMPLETE RESECTION IN NON-SMALL CELL LUNG CANCER: AN EXTERNALLY VALIDATED CLINICAL NOMOGRAM

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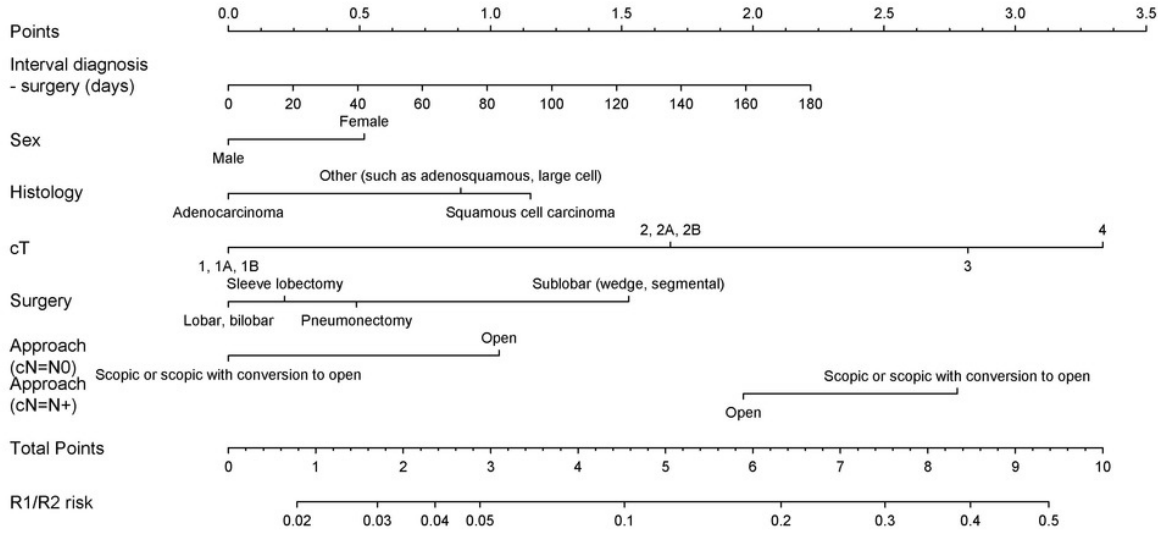
Background: Patients who are surgically treated for stage I-III non-small cell lung cancer have a worse prognosis after incomplete (R1-R2) resection. Predictive factors for completeness of resection have not satisfactorily been established. Our study aimed to develop, and internally and externally validate a prediction model to estimate the risk of incomplete resection, based on preoperative patient-, tumor-, and treatment-related factors. **Method:** From a Dutch national database (NKR) all consecutive NSCLC patients diagnosed from 2011 to 2014 who had surgery without neoadjuvant therapy were selected. Fifteen possible predictors were analyzed. Multivariable logistic regression analysis with stepwise backward elimination was used to create a prediction model. Discriminatory ability and calibration of the model was determined after internal validation. External validation was applied in an American dataset from the NCDB, whereupon the model was adjusted. The prediction model was presented as a nomogram. **Result:** In the development set of 7,124 patients an incomplete resection was reached in 496 patients (7.0%). Remaining predictors were gender, histology, cT-stage, cN-stage, extent of surgical resection, time interval from diagnosis to surgery, open versus thoracoscopic procedure, and the interaction between procedure and cN-stage. After internal validation, the corrected c-statistic of the resulting nomogram was 0.73. Application of the nomogram to the external dataset of 85,235 patients with R1-R2 resections in 2,485 patients (2.9%) resulted in a c-statistic of 0.70. Calibration revealed good overall fit of the nomogram in both cohorts.

Image 1. Nomogram of prediction model for risk of incomplete resection, for development set. The numbers listed at the upper line of the figure indicate the points to be assigned per variable. By counting up all points, the predicted risk of incomplete resection can be read out by drawing a straight vertical line from the 'Total points' line to the bottom line of the figure.



Conclusion: An internationally validated nomogram is presented providing the ability to predict the individual risk of an incomplete resection in patients with stage I-III NSCLC planned for surgery. In case of a relevant probability of incomplete resection, alternative treatment strategies could be considered, such as a larger extent of surgery, neoadjuvant or definitive chemoradiotherapy. In contrast, with a small predicted probability of incomplete resection, the use of surgery is further supported.

Keywords: NSCLC, incomplete resection, prediction model

P1.17-40 CLINICAL IMPLICATIONS OF USING CIRCULATING TUMOR DNA TO ASSESS MINIMAL RESIDUAL DISEASE (MRD) IN PATIENTS WITH NSCLC AFTER DEFINITIVE TREATMENT

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Background: Circulating tumor DNA (ctDNA) has been used to identify driver genomic alterations during treatment of metastatic nonsmall cell lung cancer (NSCLC). Recent studies have also demonstrated the role of ctDNA to monitor response to therapy. Here we performed an analysis on a cohort of NSCLC patients (pts) with localized disease who underwent ctDNA testing after definitive treatments to determine whether ctDNA can be used as a marker of MRD. **Method:** Between 2015-2019, 70 pts with localized NSCLC received ctDNA testing. ctDNA testing was done using the next generation sequencing (NGS) panel of 73 genes via digital sequencing technology (Guardant360). Statistical analysis was performed to determine which factors were associated with ctDNA levels and recurrence free survival (RFS). **Result:** Of the 70 pts analyzed, 26 pts had ctDNA testing performed after definitive treatment. Median duration of follow up was 22 months (range: 3 to 36). 26% (n = 7) had stage I disease, 30% (n = 8) had stage II disease, and 42% (n = 11) had stage III disease. 81% (n = 21) were adenocarcinoma while 19% (n = 5) were squamous cell carcinoma. 42% (n = 11) had no recurrence during our observation time, while 58% (n = 15) experienced progression. For definitive treatments, 38% (n = 10) underwent surgery alone, 35% (n = 9) underwent surgery with adjuvant chemotherapy, 15% (n = 4) underwent chemoradiation therapy, 8% (n=2) underwent surgery followed by radiation, and 4% (n=1) under went surgery with adjuvant chemoradiation prior to their ctDNA levels [variant allele frequency (VAF)] being drawn. Of these, 15% (n = 4) tested negative for any ctDNA, while 85% (n = 22) were positive. Only one of the pts with undetectable levels of ctDNA experienced recurrence of cancer 34 months after definitive treatment with surgery followed by chemotherapy. 13 among 22 pts with detectable ctDNA had recurrence (median time to recurrence = 6.3 months). Kaplan-Meir survival analysis revealed a trend toward significant association between the presence of detectable ctDNA and RFS (p = 0.10). **Conclusion:** Our analysis demonstrates that ctDNA could potentially be used as a marker to assess MRD following definitive treatment for localized NSCLC.

Keywords: ctDNA, minimal residual disease, circulating tumor DNA

P1.17-41 PREOPERATIVE PROGNOSTIC NUTRITIONAL INDEX (PNI) AS A PROGNOSTIC FACTOR IN PATIENTS WITH CLINICAL STAGE I NON-SMALL-CELL LUNG CANCER

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Background: The prognostic nutritional index (PNI) is one of immune nutritional markers. The PNI has reported to predict the risk of postoperative complication or recurrence in various digestive malignancies. In this study, we investigated whether or not PNI be a prognostic factor in clinical stage I non-small-cell lung cancer patients. **Method:** We analyzed 429 patients of clinical stage I lung cancer retrospectively and evaluated the relationship between the preoperative PNI and postoperative outcomes. The PNI was calculated as 10 × preoperative the serum albumin level (g/dL) + 0.005 ×the total lymphocyte count (cells/mm3). We used the cutoff value 48 of PNI referred from K.Migita et al. Ann Surg Oncol (2013) 20:2647-2654. The Prognostic Nutritional Index Predicts Long-term Outcomes of Gastric Cancer Patients Independent of Tumor Stage. Low PNI was less than 48, and high PNI was more than 48. **Result:** In the univariate analysis, the results for low PNI (N=153) and high PNI

(N=276), respectively, were as follows: Age, 72.8±8.6 and 67.5±10.1 years (p<0.001); Sex (Male / Female), 108/45 and 170/106 (p=0.043); FEV1.0, 2102±507 and 2309±596ml (p<0.001); tumor size, 23.0±10.2 and 20.6±8.9 mm (p=0.010); FDG-PET SUV, 5.5±5.3 and 3.5±4.1 (p<0.001); postoperative complication, 56 and 73cases (p=0.030); pathological stage (IA/IB/IIA&IIB/IIIA&IIIB&IV), 87/33/18/15 and 200/32/20/24 (p=0.006); histology (adenocarcinoma/ squamous cell carcinoma/ others), 98/45/10 and 226/36/14cases (p<0.001); pleural invasion (0/1/2/3), 114/23/11/4 and 238/25/8/3cases (p=0.014); intra-tumoral lymphatic vessel invasion (0/1), 94/58 and 184/88cases (p=0.228); intra-tumoral blood vessel invasion (0/1/2), 103/49/1 and 201/71/0cases (p=0.124); 5-year overall survival, 77.4% and 90.2% (log-rank p<0.001) ; disease free survival, 64.8% and 84.2% (log-rank p<0.001); and recurrence free survival, 80.9% and 86.9% (p=0.182). In multivariate analysis, PNI (RR:2.447; 95% CI: 1.113-5.349; p=0.026), FDG-PET SUV (RR:1.067; 95% CI: 1.008-1.128; p=0.025) were independent prognostic factors. **Conclusion:** The low PNI showed inferior outcomes compared to high PNI for clinical stage I lung cancer. Patients with low PNI tended to have more progressive lung cancer stages and higher SUV of FDG-PET than them with high PNI. The preoperative PNI is a useful predictor of all-over survival.

Keyword: PNI lung nutrition

P1.17-42 THE IMPORTANCE OF LYMPHATIC AND VASCULAR INVASION IN STAGE 1 NON-SMALL CELL LUNG CANCER AND DEFINITION OF A TOTALLY CURABLE TUMORS

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Background: A number of non-anatomic prognostic factors have been reported for resected non-small cell lung carcinoma. Certain histopathologic properties of the tumor such as lymphatic and vascular invasion could help to predict the patients with excellent survival. **Method:** A retrospective study was conducted on 550 surgically resected stage 1 non-small cell lung carcinomas, and the following prognostic factors were evaluated in univariate analysis: age, gender, size of tumor, histologic type of tumor, grade of differentiation, lymphatic invasion, vascular invasion, and perineural invasion. The mean follow-up time was 69 months(range;10 to 181 months). **Result:** Lymphatic vessel invasion, perineural invasion, blood vessel invasion, size of tumor(i.e.,T1a, T1b, T1c) of the tumor were found to be significant prognostic factors (p=0.001, p=0.006, p<0.001 and p=0.029 respectively). According to multivariate analyses, two factors were selected as prognostic indicators: (1) lymphatic invasion (p=0.027;OR:2.27;95%confidence interval:1.097-4.7), (2) vessel invasion (p =0.013;OR:2.021;95%confidence interval:1.16-3.53). By combining these factors we identified a poor and excellent prognostic subgroups of patients with stage I disease. The patients with 1A1 disease without lymphatic or blood vessel invasion had 100% of 5-year survival **Conclusion:** Our study showed that lymphatic vessel and blood vessel invasion of the tumor could be prognostic factors, along with anatomical determinants. The patients with stage 1A1 tumors who had no lymphatic or blood vessel invasion seem to be totally cured by surgical resection.

Keywords: stage 1, lymphatic invasion, blood vessel invasion

P.1.17-43 SUBLOBER RESECTION FOR ADENOCARCINOMA IN SITU DIAGNOSED BY INTRAOPERATIVE FROZEN SECTIONS

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Background: The establishment of sublobar resection procedures for non-small cell lung cancer is expected. Many groups have suggested adenocarcinoma in situ (AIS) to be a potential indication for sublobar resection. **Method:** From 2012 to 2016, 80 patients (23 men and 57 women; median age, 70 years; range 40-86) diagnosed with adenocarcinoma in situ from intraoperative frozen sections, and underwent sublobar resection or lobectomy at our institution. Of these, 74 patients received sublobar resection and 6 patients underwent lobectomy.for adenocarcinoma in situ. We evaluate the predictive value of the intraoperative pathologic examination for AIS diagnosis, and overall survival, disease-free survival, and cancer-specific survival. **Result:** Permanent pathologic examination revealed 61patients had AIS, 17 patients had minimally invasive adnocarcinoma and 2 patients had invasive adnocarcinoma. The predictive value of intraoperative pathologic examination for AIS diagnosis was 79.3%. During a median 48-month follow-up, there were 1 cancer unrelated deaths. The 5-year overall survival rate was 98.8%. The disease-free survival rate and the 5-year cancer-specific survival rate were 100%. **Conclusion:** The results of our retrospective study indicate that an intraoperative pathologic diagnosis of AIS is strongly predictive and allows for an intraoperative decision to perform a sublobar resection in these patients.

Keywords: Limited resection, Adenocarcinoma in situ, Intraoperative frozen section

P1.18 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
SUNDAY, SEPTEMBER 8 09:45 – 18:00

P1.18-01 RELAY EU/US SUBSET: RAMUCIRUMAB PLUS ERLOTINIB IMPROVES PROGRESSION-FREE SURVIVAL IN FIRST-LINE EGFR MUTATION-POSITIVE NSCLC

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Background: Dual blockade of EGFR and VEGFR pathways in *EGFR* mutation-positive NSCLC augments anti-tumor efficacy versus EGFR inhibition alone. The RELAY (NCT02411448) phase 3 study demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for erlotinib plus ramucirumab versus erlotinib plus placebo in patients with previously untreated *EGFR* mutation-positive metastatic NSCLC (median PFS 19.4 vs 12.4mo, HR 0.591 (95% CI 0.461–0.760), p<0.0001). Here we report efficacy and safety data of the EU/US subset. **Method:** Eligible patients (untreated, metastatic NSCLC with an *EGFR* exon 19 deletion or exon 21 (L858R) substitution mutation and no CNS metastasis) were randomized (1:1) to receive 150 mg daily oral erlotinib plus 10 mg/kg intravenous ramucirumab (RAM+ERL) or placebo (PL+ERL) Q2W until progressive disease or unacceptable toxicity. Patients were stratified by geographic region (East Asia vs 'other', i.e. EU/US). Primary endpoint was investigator-assessed PFS. Other key objectives included safety, ORR, DoR, PFS2, and OS. **Result:** In the EU/US, 113 (25.2%) of 449 total patients (58 RAM+ERL, 55 PL+ERL) were randomized between Feb 2016-Feb 2018. Baseline characteristics were balanced between treatment arms: ~60% female, ~52% never-smokers and ~66% *Ex19del*. RAM+ERL improved PFS and had a longer DoR (Table). PFS2 and OS data were immature. Grade≥3 TEAEs occurring in >5% of patients included (RAM+ERL vs PL+ERL): hypertension (29.8% vs 7.3%), diarrhea (12.3% vs 1.8%), AST increased (7.0% vs 3.6%), ALT increased (7.0% vs 1.8%), dermatitis acneiform (5.3% vs 9.1%), fatigue (5.3% vs 0%), and rash (0% vs 5.5%).

Abbreviations: CI=confidence interval; DoR=duration of response; ERL=erlotinib; HR=hazard ratio; N=total population; n=total responders; NR=no response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PL=placebo; RAM=ramucirumab

	RAM + ERL (N=58)	PL + ERL (N=55)	Unstratified HR (95% CI)	p-value
PFS				
Median, months (95% CI)	20.6 (14.7-26.0)	10.9 (8.3-19.4)	0.605 (0.362-1.010)	0.0523
Censoring rate	52%	38%		
ORR, % (95% CI)	74.1 (62.9-85.4)	76.4 (65.1-87.6)	NA	0.8319
DoR, for responders only	n=43	n=42		
Median, months (95% CI)	18.0 (12.7-22.0)	10.0 (7.1-17.7)	0.527 (0.296-0.939)	0.0274
Censoring rate	54%	33%		
PFS2				
Median, months (95% CI)	NR	NR	0.632 (0.304-1.313)	0.2143
Censoring rate	79%	67%		
OS				
Median, months (95% CI)	NR	NR	1.096 (0.465-2.582)	0.8344
Censoring rate	81%	82%		

Conclusion: The EU/US subset analysis was consistent with the full ITT population where RAM+ERL demonstrated a statistically significant improvement in PFS over PL+ERL. Efficacy and tolerability were similar to that of the overall RELAY study population. Ramucirumab is an effective and safe addition to standard-of-care *EGFR*-TKI for treating *EGFR* mutation-positive metastatic NSCLC.

Keywords: EU/US subset, EGFR-mutation positive NSCLC, Ramucirumab

P1.18-02 THE AEGEAN PHASE 3 TRIAL OF NEOADJUVANT/ADJUVANT DURVALUMAB IN PATIENTS WITH RESECTABLE STAGE II/III NSCLC

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Background: For patients (pts) with early stage non-small cell lung cancer (NSCLC) (Stages I–IIIA) surgery is the primary treatment. Adjuvant and neo-adjuvant chemotherapy (CTx) are both accepted approaches for resectable NSCLC, and result in modest but clinically meaningful improvements in overall survival (OS) compared with surgery alone; nevertheless, recurrence rates remain high and improved therapies are needed. Checkpoint inhibitors that block programmed death 1 (PD-1)/PD ligand 1 (PD-L1) have shown benefit as monotherapy and in combination with CTx in NSCLC. Durvalumab (durva), a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, significantly improved progression-free survival and OS in pts with unresectable Stage III NSCLC who did not progress following chemoradiotherapy (Antonia et al, NEJM 2017; 2018). The AEGEAN study (NCT03800134) will assess the activity and long-term clinical outcomes of durva plus CTx prior to surgery, as well as further administration of durva post-surgery, in pts with resectable Stages II and III NSCLC. **Method:** The AEGEAN trial is a Phase 3, double-blind, placebo-controlled, multi-center study. Approximately 300 pts with resectable Stage II and III NSCLC will be randomized 1:1 to receive either durva (1500 mg intravenously) or placebo every 3 weeks (wks) alongside platinum-based CTx (4 cycles) prior to surgery, followed by either durva or placebo alone every 4 wks for an additional 12 cycles post-surgery. Pts will be stratified by disease stage and PD-L1 expression levels (<1% vs ≥1%); the number of pts with EGFR/ALK mutations will be capped at 20%. Tumor size (according to RECIST v1.1 criteria) will be evaluated at completion of neo-adjuvant CTx prior to surgery, every 12 wks for the first year; every 24 wks for 2–4 years; then yearly thereafter. The primary endpoint is major pathological response (≤10% residual viable tumor in the resected primary lung tumor after neoadjuvant treatment) in the full analysis set (FAS). Secondary endpoints include safety assessments, a range of efficacy measures including complete pathological response (FAS and PD-L1-TC ≥1%) and OS, pt-reported outcomes, durva pharmacokinetics and immunogenicity. This trial is currently recruiting. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: durvalumab, NSCLC, Chemotherapy

P1.18-03 HOW TO PREDICT HIGH GRADE RADIATION PNEUMONITIS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH THORACIC RADIOTHERAPY

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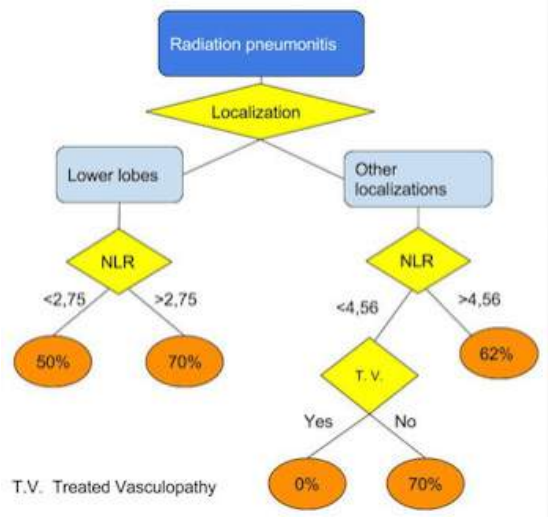
Background: Predictive factors of radiation pneumonitis (RP) have been studied without conclusive results. The aim of this retrospective study was to identify clinical, inflammatory or dosimetric factors that could predict the development of high grade RP (HGRP). **Method:** A retrospective analysis was conducted in patients with non-small cell lung cancer (NSCLC) treated with concurrent chemo- radiotherapy, secuential chemo-radiotherapy or radiotherapy (RT) alone at the Catalan Institute of Oncology from 2012 to 2016 who developed symptomatic RP. Collected variables were: anthropometric values, Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio, lung function, tumor features (histology, localization, staging) and treatment characteristics. RP was classified using RTOG scale. Patients were divided in 2 groups (low-grade [G1-G2], and HGRP [G3-G5]). Multivariate and regression tree analysis were performed. **Result:** Sixty-seven patients were identified: 61% had low-grade RP and 39% HGRP. Development of HGRP was only associated with RT total dose (p=0.045). The most relevant predictive factors of HGRP were tumor location in lower lobes, high NLR values and the presence of peripheral vasculopathy. Figure 1 shows, when tumor is located in lower lobes and NLR is > 2.75, the probability of HGRP was 70% vs 50% when NLR <2.75. In other locations with NLR >4.56 the probability to develop a HGRP was 62%. But, when NLR<4.56, the presence of peripheral vasculopathy and its treatment determine the development of HGRP. When vasculopathy was not treated the probability to develop HGRP was 36% vs 0% when it was treated.61% had low-grade RP and 39% HGRP. Development of HGRP was only associated with RT total dose (p=0.045). When cancer is localized in lower lobes and NLR is > 2.75 the probability to develop HGRP was 70% vs 50% when NLR <2.75. In other locations with NLR >4.56 the probability to develop a HGRP was 62%. But, when NLR<4.56, the presence of vasculopathy and its treatment determine the development of HGRP. When vasculopathy was not treated the probability to develop HGRP was 36% vs 0% when it was treated. Figure 1. Probability to develop HGRP (G3 –G5)



Conclusion: The probability of develop HGRP has been associated with RT dose and the association of cancer location, NLR, presence of vasculopathy and its treatment.

Keywords: radiotherapy, High grade radiation pneumonitis, Non-Small Cell Lung Cancer

P1.18-04 NEOADJUVANT CERITINIB FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER WITH ALK REARRANGEMENT: SAKULA TRIAL

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Background: Ceritinib is a highly selective ALK inhibitor that has been shown potent antitumor activity against ALK-positive non-small cell lung cancer (NSCLC). We conducted a multicenter single-arm phase II study to assess the efficacy and safety of neoadjuvant therapy with ceritinib followed by surgery in patients with ALK-positive resectable locally advanced (LA) NSCLC. **Method:** Three cycles of ceritinib were administered as induction therapy. The drug was administered orally at the dose 750 mg once daily for 28 days per cycle. The primary endpoint was the major pathological response rate (mpRR). This study required 19 patients, with mpRR of 15% considered non-promising and 45% promising (one-side alpha = 0.025; beta = 0.2). Biomarker analyses using pre- and post-ceritinib through next-generation sequencing (NGS) of plasma and tissue is also planned. (Trial Identifier, UMIN000017906). **Result:** A total of 395 patients with LA-NSCLC were screened from March 2015 to March 2018 and 15 patients (4%) were identified as ALK-positive. Only 7 patients were enrolled because of slow accrual. The median age of the patients was 50 years and 71% (n=5) were male. All patients had stage IIIA disease and adenocarcinoma. 6 out of 7 patients completed three cycles of neoadjuvant therapy with ceritinib as planned, 71% (n=5) of patients required dose adjustment. One patient was withdrawn from the study because of hepatitis. The objective clinical response rate was 100%. Surgical resection was performed in 6 patients, and complete (R0) resection was achieved in 5 patients. Among the 7 evaluable patients, the mpRR was 57% (95% CI, 18 to 90); 4 patients achieved mpR and 2 patients achieved pathologic complete response. With a median follow-up of 10 (range 8-33) months, 1 patient died of disease progression and 6 patients remain alive, including 4 patients who are recurrence-free. The most common toxicities were gastrointestinal toxicities. **Conclusion:** Our results showed that neoadjuvant ceritinib is safe and effective, with a high rate of pathologic response, in patients with ALK-positive resectable LA-NSCLC, although the limitation of the data interpretation due to small sample size.

Keywords: Neoadjuvant ceritinib, locally advanced non-small cell lung cancer, ALK rearrangement

P1.18-05 CHEMOXRT W/ CONSOLIDATION PEMBROLIZUMAB IN UNRESECTABLE STAGE III NSCLC: LONG-TERM SURVIVAL UPDATE AND ANALYSIS OF POST-PROGRESSION THERAPY

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Background: Consolidation PD-1/PD-L1 inhibition following chemoradiation is a new standard of care for patients with stage III NSCLC. 3-year survival rates in patients receiving consolidation PD-1/PD-L1 have not been previously reported. In addition, the response to subsequent chemotherapy or immunotherapy in patients who experienced disease progression following consolidation PD-1/PD-L1 has also not been previously reported. **Method:** This is a phase II, single-arm, multi-center trial of consolidation pembrolizumab 200mg IV every 3 weeks for up to a year following concurrent chemoradiation in patients with unresectable stage III NSCLC. This analysis provides the first-ever report of 3-year overall survival (OS) estimates with consolidation PD-1. In addition, treatment details for patients who experienced progression of disease on or after consolidation pembrolizumab are described. **Result:** Median follow is 31.1 months (range 1.2-42.4). Median OS is 35.8 months (95% CI, 24.2 -not estimable). One, two, and three-year OS estimates are 81.1%, 62%, and 49.5%. Of 37 patients reported to have progressive disease (PD), subsequent treatment data were available for 35. Twenty-four received additional systemic therapy, and 11 received no subsequent systemic treatment. Fifteen experienced PD during pembrolizumab, 18 after pembrolizumab (and 4 had missing data). The best response to any systemic therapy (n=24) was 3 partial responses (PR), 9 stable disease (SD), and 12 PD. Chemotherapy was given to 21 patients and 1 patient each received erlotinib, ponatinib, and an investigational agent. Best response to chemo was 2 PR, 6 SD, and 13 PD. 11 patients received pemetrexed with 2 SD and 9 PD; 6 patients received a single agent taxane with 1 SD and 5 PD. 5 patients received combination therapy with 1 PR, 3 SD, and 1 PD. 3 patients received gemcitabine with 1 PR and 2 PD. 6 of 24 patients received subsequent PD-1 or PD-L1 inhibitors; the best response to immunotherapy was 1 PR and 5 PD. The PR was a patient who had completed pembro consolidation 14 months prior to PD and subsequently was retreated with pembro at the time of biopsy-proven recurrence (PD-L1 TPS was 90%). He responded after 3 cycles of pembro and has maintained this response for 13+ cycles. **Conclusion:** The 3-year OS estimate indicates that nearly half of all patients treated with consolidation pembrolizumab may be long-term survivors. For patients with disease progression after consolidation pembrolizumab, response rates with chemotherapy are similar to what is expected in the 2nd line setting with 38% experiencing disease control for a period of time. Only 1 of 6 patients re-challenged with a checkpoint inhibitor responded, but this patient has maintained a durable response lasting 13+ cycles.

Keywords: Stage III, NSCLC, Pembrolizumab

P1.18-06 EFFICACY AND SAFETY OF NEOADJUVANT PD-1 BLOCKADE WITH SINTILIMAB IN RESECTABLE SQUAMOUS NON-SMALL CELL LUNG CANCER

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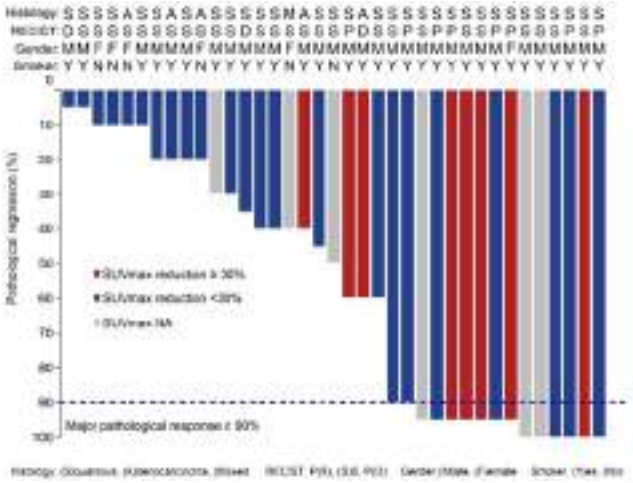
Background: Non-small cell lung cancer (NSCLC) patients with potentially resectable disease most would experience relapse after surgery. New strategy preventing recurrence is in urgent need. In the current study, we first evaluated the efficacy and safety of neoadjuvant sintilimab in Chinese patients with resectable NSCLC. **Method:** Patients with treatment-naïve resectable NSCLC (stage IB-IIIA) received two cycles of sintilimab (200 mg IV) on Day 1 and 22. Surgery was performed between Day 29-43. The tumor imaginations were obtained at baseline and within seven days prior to surgery. The efficacy endpoints include disease free survival, rate of major pathologic response (MPR, ≤10% viable tumor cells) and objective response rate (ORR). Safety and expression of programmed death ligand 1 (PD-L1) in baseline biopsy tissues and surgical samples were investigated. (Registration Number: ChiCTR-OIC-17013726). **Result:** A total of 40 patients with NSCLC were enrolled, among which 32 (80%) were male; 33 (82.5%) had squamous-cell carcinoma; 35 (87.5%) had stage IIA to IIIB disease; and 33 (82.5%) were former or current smokers. As of June 15th, 2019, all of the patients received 2 dose of sintilimab and 37 patients underwent radical resection. Among 37 patients, 8 patients achieved radiological partial response (PR), resulted in an ORR of 21.6% regarding RECIST 1.1. Fifteen (40.5%) patients achieved MPR, and 6 (16.2%) patients had complete pathologic response (cPR) (Figure 1). There's no correlation between baseline characteristics and MPR (Table 1). Maximum standardized uptake values (SUVmax) reduction of primary tumor after sintilimab treatment was significantly corelated with pathological response (correlation coefficient = 0.86, p <0.00001). However, there was no significant correlation between decrease in sum of lesion diameter (SLD) and pathological response (correlation coefficient = 0.21, p = 0.2104). Squamous cell carcinoma showed a better MPR (15/33, 45.5%) compared with adenocarcinoma (0/6 0%). In 18 patients with post-surgery pathologically positive lymph nodes, heterogeneity of response between primary tumor and lymph nodes were found by comparing MPR, change of SUVmax and SLD. Hyperporgression and pseudoprogression were both identified indicating the importance of biomarker selection for neo-adjuvant immunotherapy. Among 40 patients, 18 (45%) patients experienced neoadjuvant treatment-related adverse events (TRAEs). Two (5%) patient experienced grade 3-4 neoadjuvant TRAE. One treatment related surgery delay was reported because of grade 1 hyperthyroidism. None of the patients has confirmed recurrence to date. **Conclusion:** Neoadjuvant sintilimab for Chinese NSCLC patients was well tolerated and the 40.5% MRP rate is encouraging. A SUVmax reduction may be more predictive of pathologic response than decrease in SLD after neoadjuvant PD-1 therapy in NSCLC. Heterogeneity exists between primary tumor and lymph nodes.



Keyword: Sintilimab, neoadjuvant, squamous NSCLC

P1.18-07 POSTOPERATIVE COMPLICATIONS AND LONG-TERM SURVIVAL AMONG OCTOGENARIANS TREATED SURGICALLY FOR NON-SMALL CELL LUNG CANCER

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Background: Non-small-cell lung cancer (NSCLC) is a very common disease in the elderly population and its incidence in this particular population is expected to increase further. The purpose of this study is to evaluatesafety and outcome in octogenarians treated surgically for non-small cell lung cancer. **Method:** 225 patients with non-small cell lung cancer have undergone surgical treatment between January 2014 and June 2018. We reviewed 38 (16.9%) consecutive patients over 80 years old. We evaluate safety and postoperative complications of surgical treatment among octogenarians compared to patients under 79 years old. As for long-term survival, we reviewed 69 consecutive octogenarian treated surgically for non-small cell lung cancer (pathological stage IA: 32 cases, IB: 24 cases, over IIA: 12 cases) between January 2007 and June 2014. **Result:** 26 patients (68.4%) have undergone lobectomy and 15 of these patients have undergone mediastinal lymph node dissection. 20 patients (55.6%) were pathological stage IA. As for postoperative complications, 7 cases (18.4%) were prolonged air leak, 1 respiratory failure (emergent thoracotomy due to glottic edema), 1 exacerbation of interstitial pneumonia and 1 chylothorax. There was no significant difference between octogenarians and patients under 79 years old in complications. Five-year survival rate of overall octogenarians, pathological stage IA and stage IB were 55.1%, 67.7% and 43.0%, respectively. 22 cases died in the observation period, and 8 patients died postoperatively due to recurrence of lung cancer. 14 patients (63.6%) died from other diseases without recurrence of lung cancer. **Conclusion:** Surgical treatment for non-small cell lung cancer to octogenarians is a safe modality. assessment of the surgical indication and procedure is the most important because of high mortality due to other diseases.

Keywords: octogenarians, Lung cancer, surgery

P1.18-08 SURVIVAL OUTCOMES OF SALVAGE THERAPY FOR LOCOREGIONALLY RECURRENT NON-SMALL CELL LUNG CANCER

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Background: Treatment of locally recurrent non-small cell lung cancer (NSCLC) after initial curative therapy may be curative or palliative intent, with options influenced by patient and disease characteristics. We sought to perform a real-world analysis of therapeutic strategies used in locally recurrent NSCLC, and explore the impact of prognostic factors and treatment choice on outcomes. **Method:** A retrospective review was completed of all patients with stage I-III NSCLC who were referred to BC Cancer and received curative intent therapy between 2005 to 2012. Patients were followed to determine if they developed locoregional recurrence. Two cohorts were created: those receiving curative intent treatment at recurrence (surgery, radiotherapy >=50Gy, or stereotactic radiosurgery) and those receiving palliative treatment. Information was collected on known prognostic factors. The primary outcome was overall survival from the date of recurrence. **Result:** During the study period, 1571 patients received curative intent therapy for stage I-III NSCLC. Of these, 187 (12%) developed recurrence; 48% local only, 28% regional nodes, 25% both. 54 (29%) patients were treated with curative intent at recurrence (14 surgery, 40 radiotherapy), and 133 (71%) received palliative treatment due to comorbidities, poor PS, inadequate pulmonary reserve, overlapping radiotherapy fields, or disease distribution. Initial diagnosis characteristics: 30% stage I/24% stage II/47% stage III, 10% never smokers, 46% adenocarcinoma, up front 50% surgery/47% RT/4% both, curative intent chemotherapy 53%. Characteristics at recurrence: median DFS 15.2 m, median age 70, 49% female, 67% ECOG 0-1. Patients receiving curative intent therapy were more likely to have ECOG 0-1 (91% vs 58%), earlier stage at diagnosis (50% stage I vs 22%), no nodal disease at relapse (63% vs 41%), and receive more aggressive staging at recurrence with pathologic confirmation in 76% vs 27%, and PET scan in 72% vs 26%. Overall survival was significantly longer

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in the cohort receiving curative intent therapy. Median OS 33.1 m vs 9.7 m and 5 year OS 28.2% vs 3.3%. In a multivariate model incorporating stage at diagnosis, age, sex, histology, smoking status, and ECOG at recurrence, the impact of curative intent vs palliative therapy remained significant (HR for death 2.11 for palliative therapy, p<0.001). **Conclusion:** In this real world population, isolated locoregional recurrences occurred in 12% of patients after curative therapy for NSCLC. Patients who receive curative intent treatment at recurrence have a reasonable chance of achieving long term survival, making aggressive therapy of locoregional recurrences a viable treatment option in selected patients.

Keywords: salvage therapy, recurrent NSCLC, Outcomes

P1.18-09 TRIMODAL TREATMENT OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: MODEL-BASED COMPARISON WITH CHEMORADIATION ONLY

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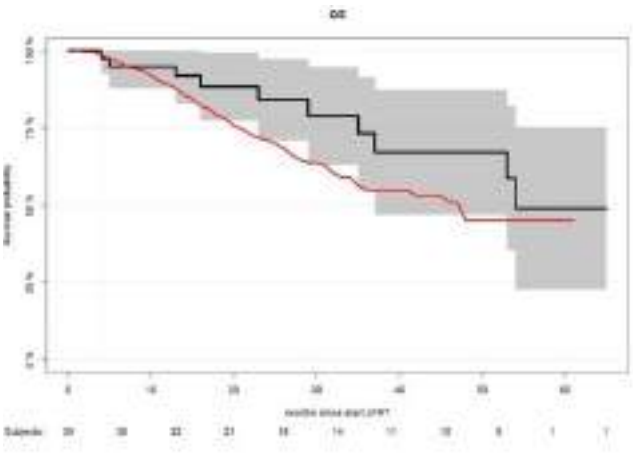
Background: Standard treatment for patients with locally advanced non-small cell lung cancer (LA-NSCLC) is chemoradiation (CRT). Some patients with minimal N2 disease are offered surgery after CRT (trimodal treatment) but evidence is sparse. In our institution patients were possible candidates for trimodal treatment if they were fit for surgery and had minimal N2 disease or poor local response to CRT. We evaluate the outcome of trimodal treatment compared to CRT alone using a model-based comparison. **Method:** Patients with LA-NSCLC treated with CRT with a radiation dose of 60-66 Gy from 2013-18 were eligible. We registered patient and disease characteristics, treatment outcome and survival. For the trimodal patients we registered complications and postoperative mortality[IRV1] [GP2] . A multivariable model was generated based on data from CRT treated patients to provide an expected survival given the covariables: Age, T- and N-stage, histology, performance status and Charlson Comorbidity Score. The model provided expected survival for trimodality patients and observed outcome was compared to CRT. **Result:** Two-hundred-sixty-six patients were included. Forty-one received trimodal treatment. Patient characteristics are shown in the table. Median time from CRT to surgery was 10 (5-113) weeks. Video assisted thoracic surgery was performed in 36.5% and open surgery in 63.4% of cases. Postoperative complication rate was 51.2%, most commonly infection (29.3%) and bleeding (12,2%). Reoperation rate was 17.1%. 30- and 90-day mortality was 7.3%. Complete pathological response after CRT was seen in 26.8% of cases. In univariate analysis, trimodality patients had improved survival (p=0.01) as compared to CRT. Adjusting for available covariables, the observed survival tended to remain superior to the expected survival if CRT was given (Figure). In the multivariate model thirty-six patients including two cases were excluded as comorbidity score was missing.

Characteristic	*CRT, n (%)*	*Trimodal, n (%)*
Total (n = 266)	225	41
Median Age at diagnosis, y (range)	69 (45-89)	66 (36-79)
Clinical Stage*		
IIA	2 (0.9)	0
IIB	15 (6.6)	5 (12.2)
IIIA	76 (33.8)	22 (53.7)
IIIB	101 (4.7)	11 (26.8)
IIIC	30 (13.3)	3 (7.3)
Tumor Stage		
TX	7 (3.1)	0
T1	26 (11.5)	4 (9.7)
T2	53 (23.4)	8 (19.5)
T3	44 (19.5)	14 (34.1)
T4	95 (42)	15 (36.6)
Nodal Stage		
N0	19 (8.4)	8 (19.5)
N1	28 (12.4)	11 (26.8)
N2	118 (52.4)	17 (41.5)
N3	59 (26.1)	5 (12.2)
Sex		
Male	116 (51.3)	25 (61)
Female	109 (48.4)	16 (39)
Median FEV at diagnosis % (range)	73 (31-115)	88 (44-134)
Histologic Type		
Adenocarcinoma	131 (58.2)	24 (58.5)
Squamous Cell Carcinoma	85 (37.6)	16 (39)
Other	9 (4.0)	1 (2.4)
WHO Performance Status		
0	133 (59.1)	31 (75.6)
1	84 (37.2)	9 (22)
2	7 (3.1)	1 (2.4)
Charlson comorbidity score		
0	73 (32.4)	21 (51.2)
1-2	102 (45.2)	17 (41,5)
3-5	16 (7.0)	3 (7.3)
Progression free survival (weeks)		
Mean	13.3	18.5
Median (range)	8.0 (0-72)	11.0 (3-60)
Survival (weeks)		
Mean	20.2	27.6
Median (range)	16.5 (0-67)	23 (4-65)
*restaged according to IARC 8		



Conclusion: Trimodal treatment appears to improve survival, but residual confounding from case selection is a limitation.

Keywords: Trimodal therapy, surgery effect, NSCLC

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P1.18-10 THE PROGNOSTIC IMPACT OF THE EXTENT OF NODAL INVOLVEMENT IN NSCLC TREATED WITH RADICAL CHEMORADIATION

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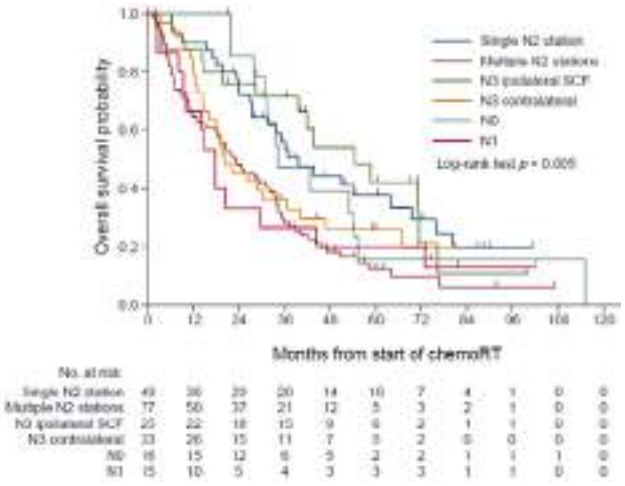
Background: There is inconclusive evidence that single station N2 disease has better prognosis compared to multi-level N2 or N3 involvement in NSCLC. We aimed to evaluate the prognostic impact of the extent and location of nodal involvement in NSCLC treated with radical chemoradiation (CRT). **Method:** We retrospectively evaluated patients treated with radical CRT between 2007-2015 in a single tertiary institution. Nodal staging was based on imaging (CT/PET) and/or endoscopic/surgical evaluation. Nodal involvement was categorised as N0, N1, single station N2 ($N2_{single}$), multi-level N2 ($N2_{multi}$), ipsilateral N3 SCF ($N3_{scf}$) and contralateral mediastinal/SCF N3 ($N3_{contra}$). Single station N2 was further divided into one or >1 nodal deposits. Overall survival (OS) and disease-free survival (DFS) were defined from the date of radiation commencement to the date of death and relapse, respectively. Cox regression and Kaplan-Meier methods were used for survival analysis. **Result:** A total of 207 patients were included, with 165 (80%) treated with concurrent and 42 (20%) with sequential CRT. Most tumours were adenocarcinomas (55%: EGFR+ 26%, EGFR- 49%, unknown 25%) followed by SCC (36%) and other subtypes (9%). Clinical nodal staging was as follows: N0=8%, N1=7%, $N2_{single}$=19%, $N2_{multi}$=37%, $N3_{scf}$=12% and $N3_{contra}$=16%. Conventional AJCC nodal staging was not prognostic of OS (p=0.4) or PFS (p=0.4). However, patients with $N2_{single}$ (median OS=40 months) and $N3_{scf}$ (median OS=55 months) had improved OS compared to $N2_{multi}$ (median OS=23 months) and $N3_{contra}$ (median=20 months) (p=0.005) (Figure 1). In the $N2_{single}$ subset, those with single nodal deposit had longer median OS (44 months) compared to >1 nodal deposits (27 months) but this was not statistically significant, likely due to the small number of patients (p=0.4). There was no significant difference in DFS between nodal groups, although $N2_{single}$ and $N3_{scf}$ showed a trend towards longer PFS compared to $N2_{multi}$ and $N3_{contra}$ (p=0.09). In multivariate analysis, $N2_{multi}$ (HR 1.71, 95% CI 1.08-2.71, p=0.02), T4 (HR 2.02, 95% CI 1.12-3.65, p=0.02) and older age (HR 1.03, 95% CI 1.01-1.05, p=0.003) were associated with inferior OS but not the use of sequential CRT (HR 1.31, 95% CI 0.86-1.99, p=0.2).



Conclusion: In this study, $N2_{single}$ and $N3_{scf}$ stage III NSCLC showed improved overall survival compared to $N2_{multi}$ and $N3_{contra}$ disease after CRT. These findings suggest that nodal distribution, rather than conventional AJCC nodal staging, may have a greater prognostic impact in NSCLC treated with CRT.

Keyword: nodal staging, chemoradiation, prognosis

P1.18-11 DOSE DENSE PACLITAXEL AND CARBOPLATIN AS NEOADJUVANT THERAPY FOR RESECTABLE/ BORDERLINE RESECTABLE NSCLC - A PHASE II TRIAL

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Background: Neoadjuvant chemotherapy in locally advanced NSCLC is controversial. Available data suggest modest benefit and ideal regimen is unknown. Dose dense approach has not yet been tested in neoadjuvant setting. **Method:** This phase II trial tested a novel approach of dose dense paclitaxel at 80mg/m^2on d1, d8, d15 with three weekly carboplatin at AUC-6 for 4 cycles. Only patients with ECOG PS 0-2 with non-bulky N2 (defined as single lymph node < 2cm or multiple LNs or conglomerate, all < 2cm) were included in the study. Response assessment was done after two and four cycles. Primary end point was objective response rate. Relative dose intensity was calculated to define safety and tolerability. Secondary end points included progression free survival (PFS) and recurrence free survival (RFS) for patients who underwent surgery. IEC approved the study and the trial was registered with CTRI (ref no-CTRI/2016/05/006916). **Result:** A total of 33 patients were included in the study. Male to female ratio was 1.75:1. The median age was 54 years (40-78) and majority were smokers (78.8%). Most common histology was squamous cell carcinoma (57.6%) followed by adenocarcinoma (36.4%). Sixteen patients (48.48%) had N2 disease by PET out of which only three were TBNA positive, all were non bulky (<2cm). Around 76% of patients were able to complete the planned 4 cycles of treatment with only one patient having CTCAE ver 5 grade ¾ toxicity. Objective response rate was 61.3%. Relative dose intensity of 80.25% was maintained in patients who completed 4 cycles. Around 58% patients required dose modification, most common reasons included peripheral neuropathy (47%), myalgia (16%), diarrohea (10.5%) and neutropenia (10.5%). A total of 138 grade ½ toxicity events were reported in the study over 12 courses of chemotherapy, with nausea (48.5%), myalgia (42.4%), neutropenia (30.3%), peripheral neuropathy (27.3%) and diarrhea (27.3%) being the most common. Thirteen patients underwent surgery with majority undergoing lobectomy (77%). After a median follow-up time of 19.3 months, median PFS was 11.1 months (95%CI 7.26-18.16) and median overall survival was 26.63 (95% CI 15.03-NR). TNM stage on CT/PET and PET response to NACT significantly correlated with progression free survival on univariate analysis. In patients who underwent surgery, median RFS was 17.36 months (95%CI 6.5-31.86) and 2 year RFS rates were 25%. **Conclusion:** Dose dense therapy with paclitaxel/ carboplatin is feasible, safe and efficacious and can be considered for N2 negative/ low node burden patients.

Keywords: dose dense chemotherapy, borderline resectable NSCLC, Neoadjuvant therapy

P1.18-12 PACIFIC-4/RTOG 3515: PHASE III STUDY OF DURVALUMAB FOLLOWING SBRT FOR UNRESECTED STAGE I/II, LYMPH-NODE NEGATIVE NSCLC

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Background: Approximately 20% of non-small-cell lung cancer (NSCLC) patients (pts) present with localized disease and this percentage is expected to increase with routine computerized tomography screening. While surgery remains standard of care (SoC) for operable pts, for unresected pts stereotactic body radiation therapy (SBRT) is now the standard. However, locoregional and distant failures occur in >30% of pts after SBRT, with higher failure rates associated with larger tumors. Durvalumab is a selective high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. In the Phase 3 PACIFIC trial of durvalumab vs placebo in patients with unresected, Stage III NSCLC without progression on concurrent chemoradiotherapy (cCRT), durvalumab significantly improved both primary endpoints of progression-free survival (PFS) and overall survival (OS) versus placebo and the two treatment arms had similar safety profiles (Antonia et al, NEJM 2017; 2018). Accordingly, the PACIFIC regimen is becoming the SoC for

Stage III NSCLC. Accumulating evidence suggests potential benefit with immunotherapy at early stage NSCLC. PACIFIC-4 will assess the efficacy and safety of durvalumab versus placebo following SBRT in pts with unresected Stage I/II lymph-node negative NSCLC. **Method:** PACIFIC-4 is a Phase 3, randomized, placebo-controlled, double-blind, international study of durvalumab in pts with clinical Stage I/II node-negative (T1 to T3N0M0) NSCLC following definitive SBRT. Approximately 630 pts will be randomized 1:1 to receive durvalumab (1500 mg intravenously) or placebo every 4 weeks for 24 months, or until discontinuation due to disease progression, toxicity or withdrawal of consent. Eligible pts are adults with unresected Stage I/II NSCLC, are node-negative, ECOG PS 0–2, and have completed SoC SBRT. The primary endpoint is PFS using BICR assessments and the key secondary endpoint is OS. Other endpoints include health-related quality of life, lung cancer mortality, pharmacokinetics, immunogenicity, and safety. Recruitment for this trial is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: durvalumab, NSCLC, SBRT

P1.18-13 PREDICTING FAILURE PATTERNS IN PATIENTS WITH INOPERABLE LOCAL ADVANCED NON-SMALL CELL LUNG CANCER RECEIVING DEFINITIVE CHEMORADIOTHERAPY

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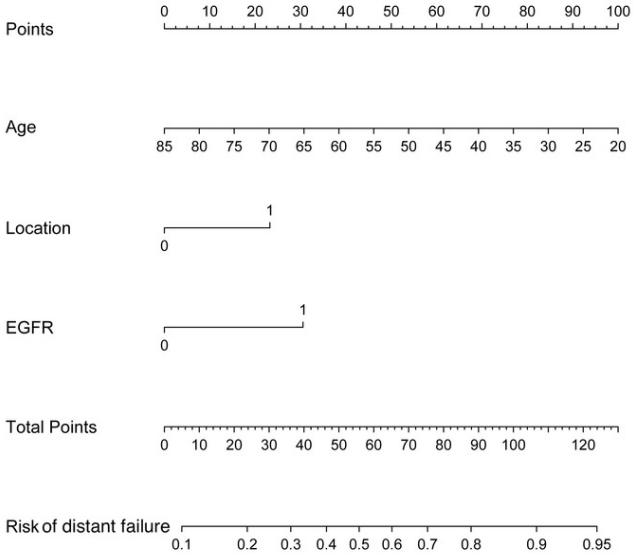
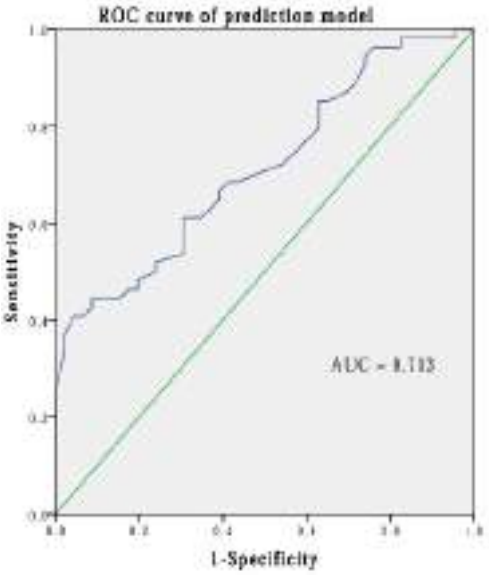
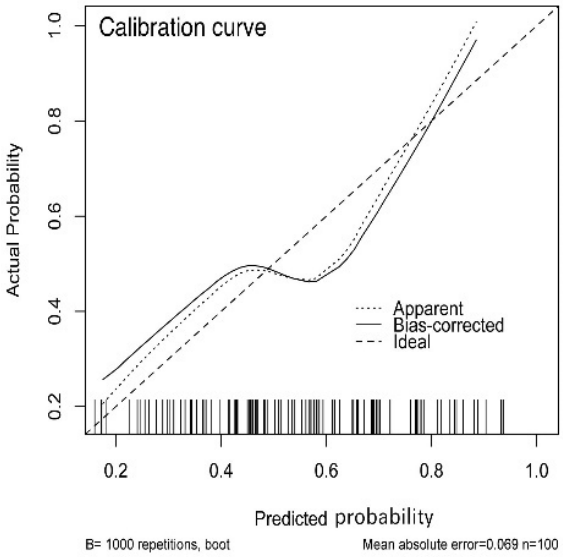
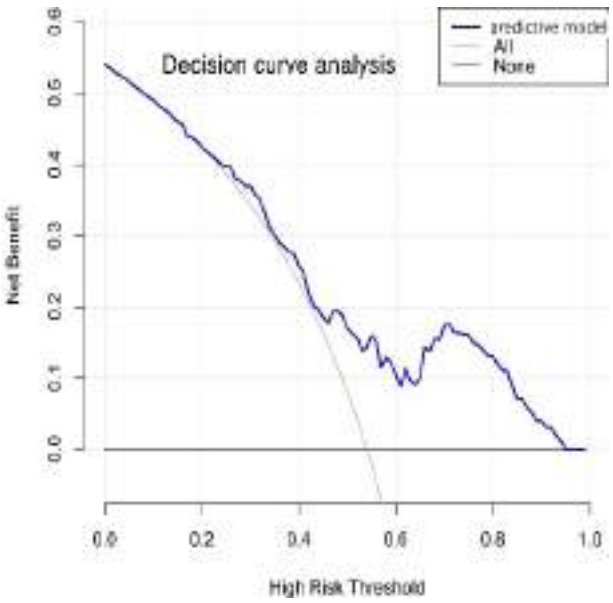
Background: To analyze patterns of failure for patients with local advanced non-small cell lung cancer (LA-NSCLC) receiving definitive chemoradiotherapy and to build a nomogram for predicting the failure patterns in these patients. **Method:** Clinicopathological materials of patients between 2013 and 2016 with LA-NSCLC who receiving definitive chemoradiotherapy and following-up in our hospital were collected. The endpoint was the first failure after definitive chemoradiotherapy. Based on logistic regression, the predictive value of each factor was evaluated and nomogram was built. This model was validated by ROC curve, calibration curve and decision curve analysis (DCA). **Result:** With a median follow-up of 28 month, 100 patients were observed failure. Local failure and distant failure were 46 and 54, respectively. Univariate and multivariate analysis indicated that age (p = 0.016, OR (95%CI): 0.936 (0.887-0.987)), tumor location (p = 0.025, OR (95%CI): 2.732 (1.137-6.567)) and epidermal growth factor receptor (EGFR) mutation status (p = 0.020, OR (95%CI): 3.747 (1.234-11.381)) were independent predictors of distant failure, which were included in the nomogram (Figure 1). ROC curve showed that area under the ROC curve (AUC) of the nomogram was 0.713, which was better than any factors along. Calibration curve revealed a satisfactory consistency between the predicted distant failure and actual observation. DCA showed the majority of the threshold probabilities in this model were with good net benefits (Figure 2).









Conclusion: We concluded that age, tumor location and EGFR mutation status could predict failure pattern in patients with LA-NSCLC receiving definitive chemoradiotherapy. A nomogram was built and validated based on these factors, showing a potential predictive value in clinical practice.

Keywords: local advanced non-small cell lung cancer, failure, predictor

POSTERS

P1.18-14 THE PROGNOSTIC SIGNIFICANCE OF SIGNIFICANT WEIGHT LOSS IN STAGE III NSCLC UNDERGOING DEFINITIVE CRT AFTER FDG-PET STAGING

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Background: In the pre-PET era, weight loss is a harbinger of occult metastatic disease in patients with stage III NSCLC. Identifying the relationship between weight loss and pattern of relapse (POR), may enable stratification of patients into prognostic groups associated with increased risk of relapse. We sought to identify if weight loss remains a negative independent prognostic factor after FDG-PET staging. **Method:** A retrospective audit (using web-based and electronic databases) was conducted in all patients with stage III NSCLC treated with definitive CRT between 01/07/2013 and 30/06/2018 at the Royal Brisbane and Women's Hospital and The Prince Charles Hospital, Queensland, Australia. A descriptive analysis was applied to describe the primary end-point of PFS and secondary end-points of OS and POR, in relation to the percentage of pre-treatment weight loss (0-10% vs >10-20% vs >20%). A subset analysis looked at other prognostic factors identified in NSCLC to account for potential confounders. **Result:** Of the 127 patients (mean age 65 years, mean weight 76kg, 57% male, 42% current smokers) who commenced treatment during the study period, 24% lost > 10% and 3% lost > 20% weight. Median TTP for the entire cohort was 9 months. Based on multivariable modelling, risk of PD or death was 45% higher with > 10% loss of body weight (p=0.004), and risk of death was 36% higher with > 10% loss of body weight (p=0.05). Of the 54% that died during follow-up, 31 had distant PD, 18 had locoregional PD, 6 had local PD, and 10 had no PD. Males were at increased risk of PD. **Conclusion:** A prognostic link continues to be identified between significant (> 10%) weight loss and risk of progressive disease or death in stage III NSCLC treated with definitive CRT despite pre-treatment FDG-PET. These findings identify a sub-group of patients where weight loss could still be a surrogate for micro-metastases not detected on PET, or other adverse prognostic markers. Other treatment strategies or improved diagnostic strategies are warranted.

Keywords: stage III NSCLC, weight loss, prognostic significance

P1.18-15 DOSIMETRIC AND TOXICITY BENEFITS OF ADAPTIVE IMRT IN PATIENTS WITH STAGE III NON-SMALL CELL LUNG CANCER

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Background: Multiple studies observed anatomical changes or tumor shrinkage during concurrent chemoradiotherapy in patients with non-small cell lung cancer (NSCLC). Mid-treatment CT based adaptive radiotherapy targeting to the shrunken tumor can reduce the dose to adjacent normal tissue or potentially deliver a higher dose to the tumor. We aimed to quantitatively analyze the benefit of intensity-modulated radiotherapy (IMRT) adapting to CT changes at the 20th fraction in stage III NSCLC patients. **Method:** We retrospectively evaluated consecutive patients with unresectable stage III NSCLC treated with adaptive IMRT from November 2017 to August 2018. The eligibility criteria included a mid-treatment CT simulation for replanning at the 20th fraction and a follow-up of at least 6 months. The prescribed dose was 64-66 Gy in 30 fractions unless exceeding the dose limit. Normal tissues were delineated according to RTOG1106 atlas on organs at risk under the supervision of a senior physician. Dose-volume histograms were calculated for the initial plans, composite adaptive plans, and lung isotoxic boost plans. Radiation pneumonitis (RP) and esophagitis (RE) were graded per CTCAE v4.03. Univariate logistic regression was applied to analyze the correlation between dosimetric factors and adverse events. **Result:** 53 patients were eligible in this study. The average GTV shrinkage was -40.9% at the 20th fraction. Comparing the dosimetric factors of the composite adaptive plans to the initial ones, the GTV coverage was found marginally higher (P=0.002). The doses to normal tissues were significantly lower (all Ps<0.001) in heart mean dose by 109.5 cGy, esophagus V60 by 1.53%, cord maximum dose by -272.7 cGy, lung V20 and mean lung dose (MLD) by 1.11% and 79.2 cGy, respectively. The tumor targets could potentially get an average lung isotoxic boost of 481 cGy. Eight patients (15.1%) had grade 2 RP while no grade 3 or higher RP occurred. Twenty-three patients (43.4%) developed grade ≥ 2 RE. MLD was significantly associated with grade 2 RP with an odds ratio of 1.39 per 100 cGy increase (95% CI, 1.01 to 1.91; P=0.042). Esophagus V60 was significantly associated with grade ≥ 2 RE with an odds ratio of 1.15 per 1% increase (95% CI, 1.04 to 1.28; P=0.009). (Table 1)

Factors		Initial Plans	Adaptive Plans	Mean difference	95%CI		P Value
Targets	PGTV (%)	92.96	93.81	0.85	0.33	1.37	0.002
	PTV(%)	94.13	94.54	0.41	0.35	0.80	0.033
Lung	V5(%)	46.77	45.72	-1.05	-0.70	-1.41	<0.001
	V20(%)	25.15	24.04	-1.11	-0.80	-1.42	<0.001
	V30(%)	18.62	17.60	-1.02	-0.77	-1.27	<0.001
	MLD (cGy)	1411.4	1332.2	-79.2	-60.1	-98.4	<0.001
Heart	V30(%)	17.40	15.11	-2.29	-0.94	-3.62	0.001
	V40(%)	10.87	9.06	-1.81	-0.98	-2.64	<0.001
	V55(%)	4.06	2.79	-1.27	-0.76	-1.77	<0.001
	Mean Dose(cGy)	1504.5	1395.0	-109.5	-67.88	-151.22	<0.001
Pericardium	V30(%)	32.17	30.43	-1.74	-0.77	-2.70	0.001
	V40(%)	25.70	24.00	-1.7	-0.76	-2.64	0.001
	V55(%)	13.87	11.87	-2	-1.34	-2.66	<0.001
	Mean Dose(cGy)	2192.9	2091.2	-101.7	-60.00	-143.3	<0.001
Esophagus	V40(%)	39.43	36.49	-2.94	-1.62	-4.27	<0.001
	V50(%)	27.89	24.08	-3.81	-2.36	-5.27	<0.001
	V60(%)	7.57	6.04	-1.53	-0.96	-2.09	<0.001
	Max Dose(cGy)	6498.3	6336.7	-161.6	-101.99	-221.3	<0.001
Cord	Max Dose(cGy)	4113.0	3840.3	-272.7	-209.51	-335.93	<0.001

Conclusion: By adapting to the changes on CT scans at the 20th fraction, the adaptive IMRT approach provides significant dosimetric benefits and has the potential to lower the risk of symptomatic pneumonitis and esophagitis in stage III NSCLC.

Keywords: Adaptive Radiotherapy (ART), Radiation esophagitis (RE), Radiation pneumonitis (RP)

P1.18-16 IS TUMOR SHRINKING DURING CHEMORADIATION FOR LA-NSCLC A BIOMARKER FOR OUTCOME?

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Background: Adaptation of dose distribution to tumor reduction during radiotherapy is an innovative approach. Even if the advantage for lung toxicity is intuitive, some concerns exist about the risk of tumor recurrences in the area of target reduction. Recent data reported no increased local relapse and low pulmonary toxicity so, waiting for the ongoing phase III trial investigating this issue (RTOG 1106-ACRIN 6697), the aims of this study is to compare the long term outcome for patients treated or not with the adaptive approach. **Method:** LA- NSCLC patients enrolled in a prospective study, where they were treated with concomitant chemoradiation and underwent to replanning in case of tumor shrinkage, have been compared with patients without tumor shrinkage treated with the concurrent treatment in the same period. Toxicity was evaluated with the RTOG/ EORTC scale. The differences between groups were compared by Fisher's exact test (two tail) or χ^2 when appropriate. The "time to event" curve was calculated with the Kaplan-Meier method, and log-rank test was used to perform between-group comparisons. **Result:** Patients in the adaptive group (AG) were more likely to receive a total radiation dose equal or higher than 59.4Gy (58% vs 27%, p=0.003). No statistical differences were reported in local recurrences, even if in non-adaptive (NAG) and AG were 48% and 31%, respectively. Distant recurrences were documented in the 55% and 46% of patients. Acute ≥G2 esophageal and pulmonary toxicity was similar, but G3 acute lung toxicity was lower than a third in AG (2% vs 7%) and G3 chronic lung damage reduced by half (7.5% vs 4%). Median follow up for alive patients was 57.8 months. Median OS were 26,6 and 30,5 months and PFS 7,6 and 8.3 months between NAG and AG, respectively. Survival was affected by the rate of shrinking with better result for patients reducing 25-50% of the initial volume (median not reached) in comparison with no-reduction or until 25% patients (median 25 months) (p=0.016). An apparent contra-intuitive result was the lower survival in case of reduction >50% (median 23 months). PFS reflects the same observation with median values of 7,5 and 7,4 months for patients shrinking 0-25% and >50%, respectively and 13,8 months for patients reporting a tumor reduction in the range of 25-50%. **Conclusion:** Waiting for randomized phase III results, adaptive approach confirms its role in escalating dose and reducing toxicity without compromise outcome. The worse outcome in patients with >50% reduction could be explained by high proliferating aggressive tumor behavior. The value of the shrinking rate as a biomarker for survival deserves to be investigated in future trials at the aim to intensify treatment in selected population.

P1.18-17 SURVIVAL AFTER ADJUVANT CHEMOTHERAPY IN COMPLETELY RESECTED N1 NON-SMALL CELL LUNG CANCER

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Background: Upfront surgery is the standard of care for patients with clinical stage I or II non-small cell lung cancer (NSCLC), but the relapse rate remains high, and 5-year survival is unsatisfactory. Randomized controlled trials, including the International Adjuvant Lung Cancer trial published in 2014, showed that adjuvant chemotherapy (ACT) after surgery increased overall survival at 5 years. However, ACT is seldom well tolerated, and often patients do not complete treatment. The goal of this study was to analyze the effects of adjuvant therapy in patients with N1 disease to better understand the effectiveness of ACT in a real-world surgery series. **Method:** This is a retrospective study from a prospectively maintained database at our institution. Patient with NSCLC were included in the study if they underwent surgery with complete resection (R0) from January 2006 to December 2017 and had pathological N1 NSCLC. **Result:** We identified 207 patients with pN1 NSCLC; their mean age was 64.5 ± 8.9 years. Most (71.2%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Eight patients (3.9%) were never-smokers. Over 50% of the patients had a video-assisted thoracoscopic surgery (VATS) lobectomy. Mean tumor size was 31.6 ± 15.4 mm, and most tumors (70.5%) were adenocarcinomas. Although 139 patients (65.7%) underwent ACT using the BR.10 chemotherapy regimen, only 59 patients (42.4%) completed all cycles of the treatment. Five years after surgery, overall survival was 55±4%, and disease-free survival was 39.3±4%. There was no statistically significant difference in disease-free survival between the patients who received ACT and those who did not (median 4.0 vs 2.8 years, hazard ratio [HR] = 0.74 (95% confidence interval, 0.49, 1.11), p = 0.1463), but there was a trend toward improved overall survival in patients who underwent ACT (median 8.6 vs 5.0 years, HR = 0.66 (0.41, 1.05), p = 0.0763). (Figure 1) **Conclusion:** Adjuvant chemotherapy was completed in only 42% of patients in this single-center, retrospective study. No statistically significant differences in disease-free survival or overall survival as a result of ACT were observed, likely a result of the small cohort. This study highlights the difficulties patients encounter in completing ACT, and the need for alternative ACT regimens to improve survival in patients with pN1 NSCLC after surgery.

Keywords: adjuvant chemotherapy, Non-Small Cell Lung Cancer

P1.18-18 FEASIBILITY OF HYPOFRACTIONATED CHEMORADIATION FOR PATIENTS WITH STAGE III NON-SMALL CELL LUNG CANCER

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Background: The standard treatment for fit patients with stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiation often consisting of a platinum doublet and 60-66Gy. In the Netherlands an alternative is mildly hypofractionated radiotherapie (66Gy in 24 fractions of 2.75 Gy) combined with daily low dose Cisplatinum. This schedule aims to improve local tumor controle and overall survival by reducing overall treatment time. We investigated the feasibility of three weekly full dose platinum doublet chemotherapy combined with hypofractionated radiotherapy. The rational for full dose platinum doublet chemotherapy is to reduce the incidence of distant metastases. **Method:** A retrospective observational study was performed including patients with stage III NSCLC (<70 years old, WHO performance score 0-1, estimated length of the oesophagus receiving 66Gy ≤12cm) who were treated with full dose platinum doublet chemotherapy and 66Gy/24 fractions. All patients were staged with a PET-scan and brain MRI. Chemotherapy generally consisted of 1 cycle of Cisplatin/Alimta or Cisplatin/Gemcitabine followed by 2-3 cycles of Cisplatin/Etoposide. Radiotherapy mostly started on day two of the second cycle of chemotherapy. Patients with a single mediastinal lymphnode metastasis who were selected for surgery after chemoradiation are not included in this analysis. Toxicity was scored using the common criteria for adverse events (CTCAE v4.0): acute if it occurred ≤90 days, late >90 days. **Result:** Between 2012-2019, 40 patients were treated with hypofractionated radiotherapy and platinum doublet chemotherapy. The median age was 58 years (SD 8.9), all had a WHO 0-1, and 58% were male. The median follow-up was 3.3 years (IQR 1.7 – 3.9). The median overall survival was 1.6 years (IQR 0.6-3.2). The rate of distant metastases was 30% at two years, and the median progression free survival was 0.9 years. Grade ≥3 acute oesophageal toxicity occurred in 14 patients (35%) and late oesophageal toxicity in 7 patients (17.5%). Five patients died: all due to oesophagus perforation or broncho-oesophageal fistula. **Conclusion:** In selected fit patients with locally advanced stage III NSCLC hypofractionated radiotherapy with concurrent full dose Cisplatin based chemotherapy resulted in an unexpected high rate of severe acute and late esophageal toxicity.

Keyword: NSCLC hypofractionated chemoradiation

P1.18-19 INVASIVE MEDIASTINAL STAGING IS MANDATORY FOR UPFRONT SURGERY FOR N2 DISEASE

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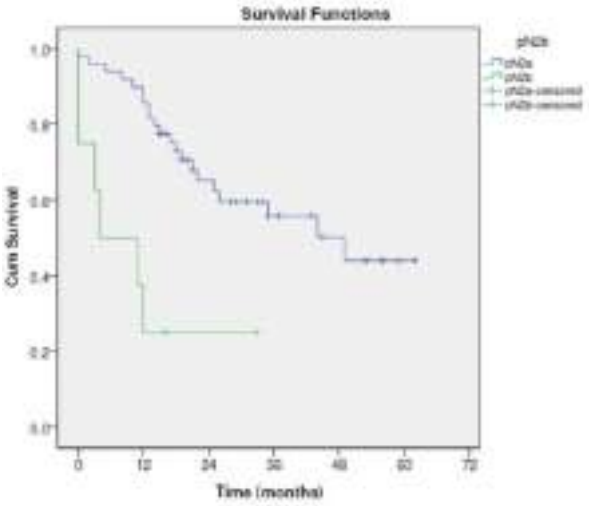
Background: There is debate about the management of stage IIIA(N2) lung cancer. We evaluated our policy of upfront surgery for limited N2 disease. **Method:** Of 821 resections for primary lung cancer from January 2014 to December 2017, 57(7%) patients [39 male, 19 female, mean age 67.7] had postoperative N2 disease. All patients had standard staging with PET-CT with selective mediastinal biopsy (nine EBUS). We compared the survival of upfront N2 surgery with unexpected pN2 disease. **Result:** Preoperatively 44% had cN2 disease and 56% had cN0/1 with unexpected pN2 disease postoperatively. 23(40.4%) patients had pN2a1, 26(45.6%) pN2a2 and 8(14%) pN2b disease. Majority (63.2%) had adenocarcinoma and lobectomy (94.8%), Unexpected pN2 (cN0-1) had similar overall survival to those with cN2 disease (median survival 49 months vs 44 months, p=0.75). For patients with N2a disease, there was no survival difference between those with pN2a1 and pN2a2 (median survival 49 months vs 44 months p=0.71). Survival was significantly worse with multizone N2b disease than with single-zone N2a disease (figure 1, median survival 49 months vs 4 months, p<0.001) and the effect persisted following multivariate adjustment for age, T-stage and chemotherapy (HR 6.73, p<0.001).



Conclusion: Our data further support the resection of cN2a lung cancer but N2b must be excluded preoperatively.

Keyword: Management of Limited N2 disease

P1.18-20 THE RELATIONSHIP BETWEEN THE RECURRENCE TIMING AND INFLAMMATION-BASED PROGNOSTIC SCORES IN RESECTED NON-SMALL-CELL LUNG CANCER

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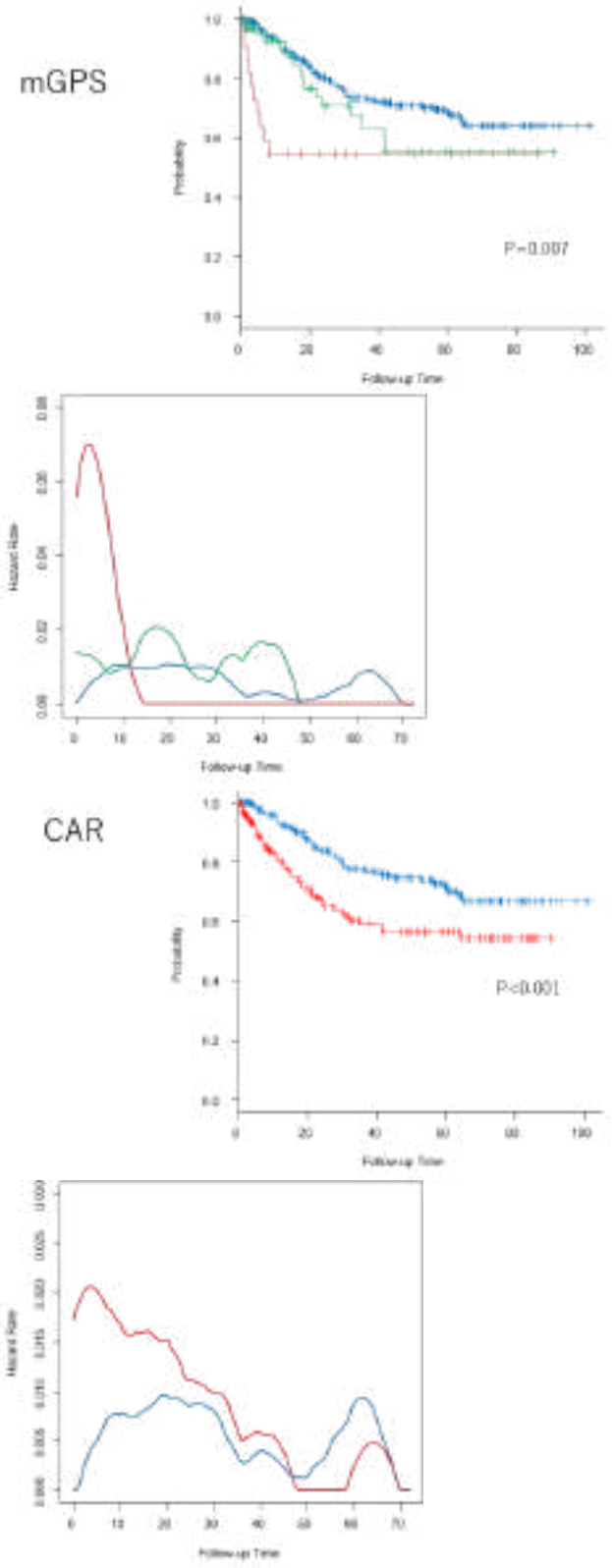
Background: Several inflammatory markers are reported to be useful in predicting the surgical outcomes in patients with various cancers. We evaluated the influence of inflammation-based prognostic scores on the postoperative recurrence timing using survival curves and hazard curves for non-small cell lung cancer (NSCLC) patients. **Method:** Total 356 patients with NSCLC who underwent pulmonary resection were retrospectively studied. The study subjects included 217 males and 139 females with a mean age of 70.0 years at the time of the surgery. We divided the population as per the Glasgow prognostic score (GPS), modified GPS, neutrophil-to-lymphocyte ratio (NLR, cut-off: low ≤ 3.75 and high > 3.75), platelet-to-lymphocyte ratio[A1] (low ≤ 200 and high > 200), and C-reactive protein-to-albumin ratio (CAR, low ≤ 0.028 and high > 0.028). Hazard curves and changes in the hazards [A2] over time were evaluated. **Result:** GPS, mGPS, high NLR, and high CAR were significantly associated with poor recurrence-free survival (RFS) in the univariate analysis. Multivariate analysis revealed that only mGPS (Hazard ratio [HR]: 1.569, 95% confidence interval [CI] 1.149–2.144, p = 0.005) and high CAR (HR: 1.751, 95%CI 1.002–3.061, p = 0.049) remained independently associated with RFS. The resulting hazard curves indicated that the recurrence risk pattern correlated with inflammation, with an early sharp peak within a year of surgery for patients with mGPS 2 or a high CAR and some late gentle humps [A1] for patients with mGPS 0 or a low CAR.



Conclusion: Patients with mGPS 2 or a high CAR have a high risk of early recurrence in resected NSCLC. These findings are useful for postoperative follow-up strategy, allowing the identification of patients who would specifically obtain a clinical benefit from intensive surveillance.

Keyword: mGPS, CAR, Hazard curves

POSTERS

P1.18-21 SHORT AND MID-TERM OUTCOMES OF MULTIMODAL TREATMENT FOR LOCALLY-ADVANCED NON SMALL CELL LUNG CANCER IN ELDERLY PATIENTS

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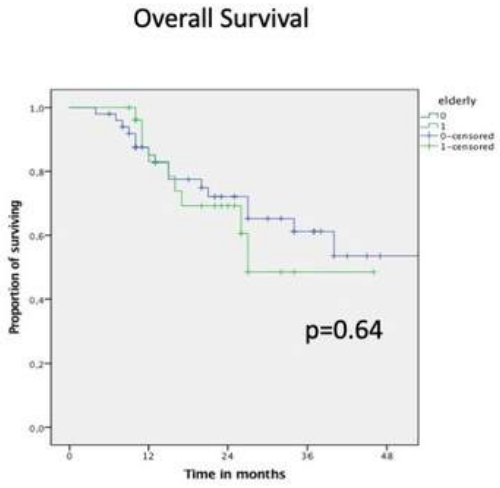
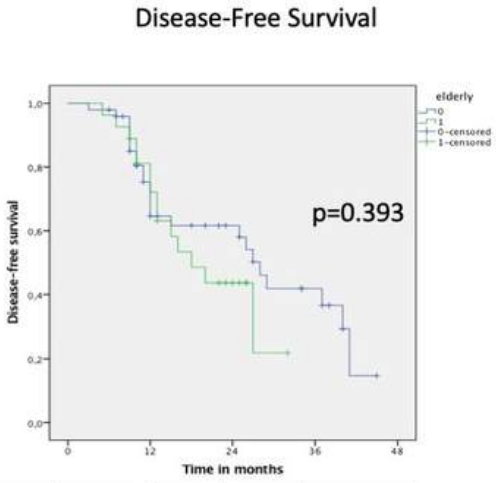
Background: Multimodality treatments are effective for locally advanced non-small cell lung cancer (LA-NSCLC) and have demonstrated clinical benefits in terms of overall (OS) and disease-free survival (DFS), but these options are frequently denied to elderly patients due to the fear of fatal complications. **Method:** The objectives of this retrospective study were: to investigate mortality, morbidity, short and mid-term oncological outcomes of pulmonary resection after induction therapy (IT) for NSCLC in elderly patients (>70 years) treated between June 2014 to December 2018. We divided the study population in two groups based on age at time of the treatment: patients <70 years (group A) and patients >70 years (group B). A multivariable logistic regression was built to identify factors associated with overall morbidity, including a set of variables chosen on clinical relevance. **Result:** 77 patients underwent pulmonary resection after IT; among these, 27 were aged >70 years. Platinum-based chemotherapy was administered to 73 patients and chemoradiation was used more frequently in group A (24% vs 3.7%; p=0.02). Surgical procedures were similar in both groups, although chest wall resections were more frequent in group A (20% vs 11%). Pathological stages and pathological responses were comparable. In-hospital mortality (2% vs 0%) was similar, while the percentage of patients with complication (38% vs 48.1%, p=0.47) and the complication rate (50% vs 77%, p=0.01) were higher in group B, but the severity of complications was comparable between the two groups. The multivariable analysis demonstrated the absence of any significant factors associated with overall morbidity. OS at 3 years and DFS at 2 years were not different between the two groups (61% vs 48.5%, p=0.64; 61.7% vs 44%, p=0.393).



	0	12	24	36	48
Younger	50	43	38	35	36
Elderly	27	23	20	18	



	0	12	24	36
Younger	50	35	34	31
Elderly	27	20	14	

Conclusion: Lung resection for LA-NSCLC after IT can be performed safely in appropriately selected elderly patients with favorable post-operative and mid-term oncological results.

Keywords: locally-advanced NSCLC, induction therapy, elderly

P1.18-22 IMPACT OF USING VOLUMETRIC MODULATED ARC THERAPY ON RADIATION PNEUMONITIS IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The administration of durvalumab after radical chemoradiotherapy has been shown to improve the outcome of locally advanced non-small cell lung cancer (NSCLC); however, it cannot be used when Grade 2 or higher radiation pneumonitis (RP) occurs. Although the use of volumetric modulated arc therapy (VMAT) is widespread, there is concern about the expansion of low doses to the lungs, causing an increase in RP. The concern is stronger for Asians, since RP may be frequent in Asians as with gefitinib-induced pneumonitis. The purpose of this study was to evaluate the impact of using VMAT on lung dose–volume histogram (DVH) and incidence of Grade 2 or higher RP compared with three-dimensional conformal radiotherapy (3D-CRT) in Asians. **Method:** We retrospectively evaluated 63 patients who underwent radical chemoradiotherapy for locally advanced NSCLC at our hospital from 2010 to 2018. RP was evaluated using the common terminology criteria for adverse events version 4.0. Regarding the lung DVH, the mean lung dose (MLD)and V5Gy–V70Gy were analyzed. Student's t test was used to compare the mean value between the two groups and the chi-squared test was used to compare the incidence of toxicities between the two groups. P values < 0.05 were considered statistically significant. **Result:** The total dose was 60–74 Gy/24–35 fractions (median 70 Gy/35 fractions). Thirty-nine patients underwent 3D-CRT (3D-CRT group), and 24 patients underwent VMAT (VMAT group). Of the 63 cases, Grade 2 or higher RP was observed in 41 cases (65.1%). The incidence of Grade 2 or higher RP tended to be lower in the VMAT group, although there was no significant difference (54.2% vs. 74%, p = 0.10). Regarding DVH comparisons between the 3D-CRT and VMAT groups, planning target volumes (PTVs) tended to be large in the VMAT group (451 cc vs. 357 cc, p = 0.14). There were no significant differences in MLD and V10Gy–V50Gy. Lung V5Gy was significantly higher in the VMAT group (49.7% vs. 39.2% p = 0.007), while V60Gy tended to be lower (6.0% vs. 8.5%, p = 0.053) and V70Gy was significantly lower (1.5% vs. 4.0% p = 0.009) in the VMAT group. **Conclusion:** Although VMAT increased the low dose area to the lungs, it could reduce the high dose area and could be performed without increasing RP for relatively larger PTVs in Asians.

Keywords: volumetric modulated arc therapy, Radiation pneumonitis

P1.18-23 USE OF PERFUSION SPECT TO PRESERVE FUNCTIONAL LUNG IN RADIOTHERAPY FOR NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Radiation treatment related pneumonitis (RP), is one of the most common dose-limiting adverse effects of treatment. The rate of G3 or higher pneumonitis was reported in literature in the range of 8%- 11% with the 3D Conformal Radiotherapy (3DCRT). Lung perfusional imaging, such a SPECT, can reflect patient pulmonary function as the perfused areas could coincide with the functional sites. It is possible identify and used different functional regions in treatment planning, using co-registered SPECT images, in order to reduce the radio-induced damage or consent dose escalation. In this study we explore the adaptive approach on organ at risk, using lung functional imaging (SPECT) to guide the dose distribution in lung cancer radiotherapy treatment plans. **Method:** Patients with medically operable stage II-III A-B, undergoing neoadjuvant chemo-radiotherapy from April to December 2017, were included in this dosimetric study. Lung perfusion SPECT images were performed within a week before radiotherapy. The CT and SPECT scans were co-registered. Functional lung volumes were classified in three groups according to their relative tracer uptake in SPECT/CT images: Low Perfusion (LP) (0-40%), Medium Perfusion (MP) (40-70%) and High Perfusion (HP) (70-100%). Two different 3D-conformal plan, with co-planar e non co-planar fields, were generated, in a photon regimen with 6/15 MV nominal energies. The first plan was created without function Lung information (Anatomic Plan, A) the other one using the functional data (Functional Plan, F). Each plan was performed with Varian Eclipse treatment plan System and calculated with Anisotropic Analytical Algorithm (version 10.0.28). To estimate difference between dose coverages, 3 variables were reported, PTV minimum dose, $D_{min,}$ as the minimum dose to the PTV, Conformity Index (CI) as ratio between the volume covered by isodose of 95% and the PTV Homogeneity Index (HI), as the ratio between the maximum dose in the PTV and the prescription dose. Paired t-test was performed to assess differences between groups. **Result:** Eighteen plan were available for analysis (nine patients included). The median volume of PTV was 156 cm^3 (88.8 cm^3- 253.5 cm^3), the median volume of Whole Lung was 3767 cm^3. Most of patients had Low Perfusional areas or perfusion defects in PTV region (64%) or near this area (22%). The functional plans produced a significant reduction of dose in HP areas, in particular the reduction of HPV_{20Gy} values ranging from 15% to 8% (p=0,046), while the $ipsiHPV_{20Gy}$ was reduced by an average of 38% to 22% (p=0,028) and $ipsiHPD_{mean}$ reduction varied between 16Gy and 12Gy (p=0,039). There were no significant differences for Dmean, V38Gy and V42Gy of Heart and Dmean, V35Gy and V50Gy of Esophagus and Dmax of Spinal Canal PTV's Homogeneity and Conformity Index. **Conclusion:** Our results seem to suggest a benefit to use functional imaging in the treatment planning. With Functional Plans, it is possible to avoid HP areas and reduce dose in the HP regions of healthy Lung, especially in homo-lateral lung. This goal is achieved without worsening in OAR irradiation, and with comparable PTV coverage regardless of the technique applied. Further studies are needed in this setting.

Keyword: Functional imaging, Locally advanced NSCLC, Radiation pneumonitis

P1.18-24 NEOADJUVANT THERAPY VERSUS UPFRONT SURGERY FOR NSCLC PATIENTS WITH CLINICALLY SUSPECTED SUBAORTIC OR PARAAORTIC LYMPH NODES

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Background: Subaortic lymph nodes (#LN5) and para-aortic lymph nodes (#LN6) cannot be accessed by routine mediastinoscopy and E(B)US-FNA but need additional invasive surgical staging methods such as VATS or anterior mediastinotomy. Therefore, a considerable number of patients with suspected #LN5 or #LN6 receive multimodal treatment or, upfront surgery based on imaging staging only. We investigated survival outcomes of each therapeutic strategy. **Method:** An institutional lung cancer database of consecutive patients between 2007 and 2016 (N=134) was reviewed retrospectively. Eligible patients had pathologically confirmed non-small cell lung cancer with clinically suspected #LN5 or #LN6 involvement by CT or PET-CT without clinical or pathological evidence of other N2 station involvement. Excluded are those with involvement of other N2 stations, unexpected N2, low grade malignancy, and prior history of cancer. Patients in group 1 received neoadjuvant therapy followed by surgery (n=68) and those in group 2 underwent upfront surgery (n=66). **Result:** Group 1 consisted of patients with clinically suspected (n=39, 57%), and biopsy-proven #LN5 or #LN6 (n=29, 43%) by VATS (n=19), anterior mediastinotomy (n=6), or EUS-FNA (n=4). They received preoperative chemoradiation (n=62, 91%) and the rest received chemotherapy (n=6, 9%). Nodal down-staging was occurred in 36 (53%) patients whereas persistent N2 in 32 (47%). On the contrary, group 2 consisted of patients with clinically suspected #LN5 or 6 (n=66). After surgery, 30 (45%) patients were confirmed to have pathologic N0 or N1. The rest 36 (55%) patients were confirmed pathologic N2, and 29 (81%) of them received adjuvant therapy: chemoradiation in 23, and chemotherapy in 6. Overall survival rate at 5-year (5YOS) were 50.5% in group 1 versus 58.9% in group 2 (p=0.55); recurrence-free survival at 5-year (5YRFS) was 42.2% versus 46.7% (p=0.98), respectively. In subgroup, the 5YOS were 44.6% in pathologic N2 in group 2, which were similar to persistent N2 (52.8%, p=0.6), down-staged (49.2%, p=0.89), or biopsy-proven N2 (57.8%, p=0.54) in group 1. The 5YRFS were 26.7% in pathologic N2 in group 2, which were similar to persistent N2 (30.3%, p=0.89) and biopsy-proven N2 (43.9%, p=0.15), but lower than down-staged (53%, p=0.03) in group 1. **Conclusion:** Upfront surgery or omission of invasive mediastinal staging for #LN5 or 6 may not compromise survival outcomes. Each therapeutic strategy is effective in terms of oncologic outcomes.

Keywords: Non-Small Cell Lung Cancer, upfront surgery, N2

P1.18-25 THE IMPACT OF RADIATION PNEUMONITIS ON PROGNOSIS OF PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH CHEMORADIOTHERAPY

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Background: Concurrent chemoradiotherapy (CRT) is the standard treatment for patients with locally advanced non-small cell lung cancer (LA-NSCLC). The radiation pneumonitis after CRT is one of the most serious problems in clinical practice. Moreover, the prognosis of the patients with driver mutation who received CRT remains unclear. **Method:** The medical records of LA-NSCLC patients treated with CRT at Hirosaki University Hospital and Aomori Prefectural Central Hospital between January 2008 and June 2018 were reviewed. This study was approved by the ethics committee of Hirosaki University Graduate School of Medicine (No. 2018-1157). **Result:** A total of 257 patients were enrolled. The median age was 67 years (range, 36-84). One hundled six patients (41.2%) had adenocarcinoma, 130 (50.6%) squamous cell carcinoma, and 21 (8.2%) NSCLC not otherwise specified. Response rate was 79.4%. Median progression free survival (PFS) was 13.6 months (95%CI: 11.3-17.8 months) and median overall survival (OS) was 64.2 months (95%CI: 47.5-122.5). There was no difference in PFS between the histological subtypes. Thirteen patients had EGFR mutation. The median PFS after CRT was not significantly different between EGFR mutant and wild type (9.0 vs 11.9 months, p= 0.831). The 2- and 5-yrear OS rate was 66.4% and 47.5%, respectively. Pneumonitis within 42 days after CRT was observed in 84 patients (32.7%), of whom 28 (10.9%) showed grade 3 or over. After 42 days of CRT, 133 patients (51.8%) developed pneumonitis. The patients with radiation pneumonitis within 42 days after CRT had a significantly shorter OS than those who developed pneumonitis after 42 days (38.6 vs 122.5 months, p=.0002). Pulmonary emphysema and fibrosis on baseline CT were correlated with radiation pneumonitis of grade 3 or more. Radiation over 60 Gy significantly prolonged OS than the lower dose (median OS: 64.3 vs 10.1 months, p=0.0002). **Conclusion:** Early pneumonitis after CRT might be suggestive of a poor prognosis, and the EGFR mutation status might not affect PFS after CRT.

Keywords: locally advanced non-small cell lung cancer, Radiation pneumonitis, chemoradiotherapy

POSTERS

P1.18-26 PRETREATMENT RISK FACTORS FOR POSTOPERATIVE PULMONARY COMPLICATION AFTER NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY FOR NSCLC

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Background: An occurrence of postoperative pulmonary complication (PPC) after neoadjuvant concurrent chemoradiotherapy (CCRT) might be fatal. It is important to stratify the risk of PPCs before the beginning of CCRT to decide treatment plans. This study is performed to investigate characteristics and pretreatment risk factors for PPCs after neoadjuvant CCRT in patients with non-small cell lung cancer (NSCLC). **Method:** We retrospectively reviewed 95 patients who received curative resection after neoadjuvant CCRT for NSCLC from 2007 to May 2018. Data of pulmonary function test and body mass index (BMI) at the time of the beginning of CCRT were used. **Result:** The mean age was 59.6 ± 9.7, and male patients were 69.5%. Twenty-one patients suffered from PPCs more than grade II. Pneumonia/adult respiratory distress syndrome (n=13) is the most common PPCs following bronchopleural fistula (n= 6) and atelectasis (n=4). Patient with PPCs had significantly longer hospital stay (with Vs without PPCs, median 8 days [Interquartile range {IQR}, 6-10] vs. 17 days [IQR, 9.5 – 30.5], p<0001), and more operative mortalities (0 % vs. 38.1 %, p<0.001). In multivariate analysis, Age-adjusted charlson comorbidity index score (CCI) (Odd ratio [OR] = 2.967, p=0.002), lower diffusing capacity for carbon monoxide (DLCO) (%) (OR = 0.939, p=0.017), and lower BMI (OR, 0.612, p = 0.006) were adverse risk factors for PPCs (concordance index 0.897).

Multivariate logistic regression analysis for PPCs

	OR (95 CI)	p value
Male	15.136 (0.059 – 3876.117)	0.337
Age-adjusted CCI	2.967 (1.488 – 5.914)	0.002
Smoking	0.085 (<0.001 – 21.643)	0.383
FEV1 (%)	0.973 (0.930 – 1.019)	0.248
DLCO (%)	0.939 (0.892 – 0.989)	0.017
BMI (kg/m^2)	0.612 (0.433 – 0.867)	0.006
C index	0.897 (0.818 – 0.976)	

Conclusion: Age-adjusted CCI, lower DLCO, and lower BMI were related to PPCs in patients with NSCLC treated neoadjuvant CCRT and surgery. These risk factors should be considered when to decide neoadjuvant CCRT.

Keywords: Postoperative pulmonary complication, Non-Small Cell Lung Cancer, Neoadjuvant chemoradiotherapy

P1.18-27 CHEMORADIOTHERAPY OF INOPERABLE NON-SMALL CELL LUNG CANCER (NSCLC) WITH IGRT TECHNIQUE USING TOMOTHERAPY HD

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Background: Concurrent chemoradiotherapy (CCRT) of locally advanced NSCLC is considered a standard of care last two decades without important improvement except of adjuvant check-point inhibitor therapy. We present one-institutional results of chemoradiotherapy of inoperable NSCLC using daily 3D IGRT with TomoTherapy HD unit. **Method:** A total of 39 patients with inoperable NSCLC staged by UICC7 and treated since April 2015 till September 2018 were included. Clinical data and radiation plans were retrospectively reviewed. Survival was analysed using Kaplan-Meier method, univariate analysis was done using Cox regression model. Our preferential chemotherapy regimen was cisplatin/vinorelbine three-weekly, carboplatin doublet with vinorelbine or paclitaxel was acceptable as well. Standard radiation dose was 66Gy/33fractions/6.5 weeks, daily MVCT was done. Minimal and median follow-up was 7/30 months, respectively. **Result:** Patient characteristics were as follows: mean age 66 years, male 46%, stage II+IIIA/IIIB/locoregional recurrences 44%/33%/23%, respectively. PET/CT was done in 77% of patients. Histology: adenocarcinoma 41%, squamous 38.5%, NOS 20.5%. All patients had chemotherapy, 59% cisplatin-based, 41% carboplatin-based, full radiation dose of 66Gy was delivered to 69% of patients, mean size of PTV was 366ml. CCRT had 69% patients. Subsequently, only one patient passed radical surgery, check-point inhibitors were used in 5 patients as second line palliative therapy. We observed low treatment toxicity, radiation esophagitis grade 1-2 in 64%, grade 3 in one patient. Radiation pneumonitis of grade 1-2 started in 13% of patients. Median survival and median time to progression (TTP) was 35.3 and 22.3 months, 2-year survival and TTP 63% and 44%, respectively. The reason of progression was mainly distant metastases alone (26%) or with locoregional failure (15%). Only locoregional progression occurred in 8% of patients. Univariate analysis did not find any difference in survival or TTP by age, gender, tumour location, regimen and length of chemotherapy, or concurrent treatment delivery. Non-significant trend of better outcome of stage II+IIIA, squamous cancer, higher dose of radiation and shorter interval between chemotherapy and radiotherapy start was observed. Only significant variable was size of PTV. With cut-off 440ml the patients having greater size of PTV had significantly worse survival in compare with those with smaller one (HR 4.209, 95%CI: 1.519;11.665). **Conclusion:** Chemoradiation of inoperable NSCLC with IGRT technique using TomoTherapy HD has excellent results with 77% of durable local control, 63% of 2-year survival and nearly 3-year median survival. Only negative prognostic factor was higher size of PTV.

Keywords: image guided radiation therapy, concurrent chemoradiotherapy, Non-Small Cell Lung Cancer

P1.18-28 SALVAGE SURGERY FOR RESIDUAL LESION/ LOCAL REPROGRESSION AFTER INITIAL MEDICAL TREATMENT IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: There is no clear definition of salvage surgery, although the numbers of reports according to salvage surgery in non-small cell lung cancer (NSCLC) have been recently increasing. **Method:** A total of 29 patients underwent lung resection for residual lesion or local reprogression after definitive chemoradiotherapy (median 60Gy) (dCRT) or after systemic chemotherapy (CTx) and/or tyrosine kinase inhibitor (TKI) in our department between January 2005 and March 2019. Among them, the surgeries for small cell lung cancer (6 patients) and post-treatment complications (3 patients) were excluded. We divided the remaining 20 patients into the following two groups: dCRT in 11 patients and CTx/TKI in 9 patients. We evaluated the clinicopathological findings and surgical outcomes in both groups to assess the perioperative safety and survival benefit of these salvage surgeries. **Result:** The median age was 58 years (range, 38-72) in dCRT (male 7, female 4), whereas the median age was 68 years (range, 49-80) in CTx/TKI (male 3, female 6). The majority of clinical stage before initial treatment was stage III in dCRT (91%). In contrast, that was stage IV in CTx/TKI (56%). The median interval between initial treatment and salvage surgery was 20 months (range, 8-119) in dCRT and 31 months (range 4-93) in CTx/TKI (P = 0.94). There was no significant difference in the proportion of lobectomy/pneumonectomy; 8 patients (73%) in dCRT and 5 patients (56%) in CTx/TKI, respectively (P = 0.64). Combined resection with adjacent organ was required more frequently in dCRT than in CTx/TKI (64% vs 0%, P = 0.005). The median operative time was significantly longer in dCRT compared to CTx/TKI (333 min vs 213 min, P = 0.038). The median blood loss was more in dCRT than in CTx/TKI (220 mL vs 90 mL), but the difference was not statistically significant (P = 0.37). Postoperative complications (≧grade II in Clavien-Dindo classification) were significant more frequently observed in dCRT than in CTx/TKI (46% vs 0%, P = 0.038). Perioperative mortality was 0% in both groups. Three-year overall survival was 71% in dCRT and 58% in CTx/TKI (P = 0.38), and 3-year disease-free survival was 62% in dCRT and 39% in CTx/TKI (P = 0.59), respectively. In both groups, 3-year disease-free survival were significantly worse in patients with ypN positive compared to

in patients with ypN negative (in dCRT, 0% vs 76%, $P < 0.001$; in CTx/TKI, 0% vs 53%, $P = 0.017$). **Conclusion:** Although there was limited data, salvage surgery after dCRT or CTx/TKI was associated with acceptable operative mortality and morbidity, and favorable long-term outcomes in highly selected patients. Postoperative N status might potentially be a poor predictive factor for disease-free survival.

Keywords: NSCLC, salvage surgery, Lung cancer

P2.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.01-01 CEMIPLIMAB, A HUMAN PD-1 MONOCLONAL ANTIBODY, VERSUS CHEMOTHERAPY IN FIRST-LINE TREATMENT OF ADVANCED NSCLC WITH PD-L1 ≥50%

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Background: Most patients (pts) with non-small cell lung cancer (NSCLC) present with advanced disease at diagnosis. Despite initial response to platinum-based doublet chemotherapy, an established first-line treatment for pts with advanced NSCLC whose tumours do not have *EGFR*, *ALK*, or *ROS 1* mutations, pts often progress and require additional treatment options. In recent years, anti-programmed death-1 (anti–PD-1) therapies have emerged as an effective treatment option for advanced NSCLC, potentially allowing some patients with PD-L1 expression ≥50% to avoid chemotherapy. However, there is currently only one PD-1 inhibitor approved as monotherapy in first-line treatment of NSCLC. In a Phase 1 trial of pts with advanced malignancies, including NSCLC, cemiplimab exhibited anti-tumour activity with a safety profile similar to those described for other anti–PD-1 agents. Cemiplimab-rwlc is the only Food and Drug Administration-approved treatment for patients with advanced cutaneous squamous cell carcinoma. **Method:** This is a randomised (1:1), multicentre, open-label, Phase 3 study of cemiplimab versus platinumbased doublet chemotherapy in systemic treatmentnaïve pts (≥18 years) with stage IIIB, IIIC or IV squamous or nonsquamous NSCLC whose tumours express PDL1 in ≥50% of tumour cells (NCT03088540). Pts will be stratified by histology and geographic region. Pts will receive cemiplimab 350 mg every 3 weeks intravenously (for up to 108 weeks) or 4–6 cycles chemotherapy with (i) paclitaxel + cisplatin or carboplatin, (ii) pemetrexed + cisplatin or carboplatin with or without pemetrexed maintenance, (iii) or gemcitabine + cisplatin or carboplatin. Crossover from chemotherapy to cemiplimab and addition of chemotherapy to cemiplimab at the time of disease progression is allowed. The primary objective is to evaluate progression-free survival (PFS) as determined by blinded independent review committee. Key secondary objectives include assessment of overall survival and objective response rate. An independent data monitoring committee will monitor safety data during study conduct. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: non-small-cell lung cancer, anti–PD-1, cemiplimab

P2.01-02 CANOPY-A: A PHASE 3 STUDY OF CANAKINUMAB AS ADJUVANT THERAPY IN PATIENTS WITH SURGICALLY RESECTED NSCLC

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Background: Overexpression of interleukin (IL)-1β has been described in solid tumors, including lung. IL-1β can promote angiogenesis, tumor invasiveness, and induces tumor-associated immunosuppression through myeloid-derived suppressor cell (MDSC) accumulation in tumors. Pre-clinical data has shown that IL-1β inhibition reduced tumor growth, by limiting pro-tumorigenic inflammation and polarization of MDSCs into M1 phenotype. Canakinumab is a human monoclonal antibody with high affinity and specificity for IL-1β. Recently, it was found that canakinumab was associated with a significant and dose-dependent reduction in incidence and mortality from lung cancer based on CANTOS study. **Method:** CANOPY-A (NCT03447769) is a phase III, randomized, double-blind, placebo-controlled study designed to evaluate efficacy and safety of adjuvant canakinumab versus placebo in patients with surgically resected NSCLC. This trial will enroll adult patients, with completely resected (R0) AJCC/UICC v.8 stages II-IIIA and IIIB (T >5 cm and N2) NSCLC, who have completed standard-of-care adjuvant treatments, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable). Prior treatment with neoadjuvant chemotherapy or neoadjuvant radiotherapy is not permitted. Approximately 1500 patients will be randomized 1:1 to receive canakinumab (200 mg Q3W, s.c) or placebo (Q3W, s.c.) for 18 cycles or until disease recurrence, unacceptable toxicity, treatment discontinuation at the discretion of the investigator or patient, death, or loss to follow-up. Randomization will be stratified by AJCC/UICC v.8 stage, tumor histology, and region. The primary objective is disease-free survival, per investigator assessment. Secondary objectives include overall survival (key secondary objective), lung cancer-specific survival, safety, pharmacokinetics and immunogenicity of canakinumab, and patient-reported outcomes. Enrollment is ongoing.CANOPY-A (NCT03447769) is a phase III, randomized, double-blind, placebo-controlled study designed to evaluate efficacy and safety of adjuvant canakinumab versus placebo in patients with surgically resected NSCLC. This trial will enroll adult patients, with completely resected (R0) AJCC/UICC v.8 stages II-IIIA and IIIB (T >5 cm and N2) NSCLC, who have completed standard-of-care adjuvant treatments, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable). Prior treatment with neoadjuvant chemotherapy or neoadjuvant radiotherapy is not permitted. Approximately 1500 patients will be randomized 1:1 to receive canakinumab (200 mg Q3W, s.c) or placebo (Q3W, s.c.) for 18 cycles or until disease recurrence, unacceptable toxicity, treatment discontinuation at the discretion of the investigator or patient, death, or loss to follow-up. Randomization will be stratified by AJCC/UICC v.8 stage, tumor histology, and region. The primary objective is disease-free survival, per investigator assessment. Secondary objectives include overall survival (key secondary objective), lung cancer-specific survival, safety, pharmacokinetics and immunogenicity of canakinumab, and patient-reported outcomes. Enrollment is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: IL-1β, Canakinumab, ACZ885

POSTERS

P2.01-03 TUMOR TREATING FIELDS PLUS STANDARD OF CARE TREATMENT IN STAGE 4 NON-SMALL CELL LUNG CANCER (NSCLC): PHASE 3 LUNAR STUDY

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Background: Tumor Treating Fields (TTFields) are a non-invasive, anti-mitotic treatment that disrupts the formation of the mitotic spindle and dislocation of intracellular constituents. TTFields plus temozolomide significantly extended survival in newly diagnosed glioblastoma. Efficacy of TTFields in NSCLC has been shown in preclinical models. Safety of TTields in combination with pemetrexed has been reported in a phase 2 clinical study. Robust efficacy of concurrent application of TTFields and anti PD-1 therapy has been demonstrated in a mouse model of lung cancer. These data suggest that combining TTFields with anti-PD-1 may achieve tumor control by further enhancing antitumor immunity. In this Phase 3 LUNAR study [NCT02973789], we investigated if the addition of TTFields to immune checkpoint inhibitors or docetaxel increases overall survival (OS). **Method:** Patients (N=534), with squamous or non-squamous NSCLC, are stratified by their selected standard therapy (immune checkpoint inhibitors or docetaxel), histology and geographical region. Key inclusion criteria are disease progression, ECOG 0-2, no electronic medical devices in the upper torso, and absence of brain metastasis. TTFields (150 kHz) are applied to the upper torso for ≥18 hours/day until progression in the thorax and/or liver. The primary endpoint is superiority in OS between patients treated with TTFields in combination with the standard of care treatments versus standard of care treatments alone. Key secondary endpoints compare the OS in patients treated with TTFields and docetaxel versus docetaxel alone, and patients treated with TTFields and immune checkpoint inhibitors vs those treated with immune checkpoint inhibitors alone. An exploratory analysis will test non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Secondary endpoints include progression-free survival, radiological response rate, quality of life based on the EORTC QLQ C30 questionnaire. The sample size is powered to detect a HR of 0.75 in TTFields-treated patients versus control group. In January 2019, an independent Data Monitoring Committee (DMC) performed a review of the LUNAR trial data collected to that point. The DMC concluded that no unexpected safety issues could be found in patients treated with the combination of immune checkpoint inhibitors and TTFields, and recommended continuation of the LUNAR study as planned. **Result:** “Section not applicable” **Conclusion:** “Section not applicable”

Keywords: Tumor Treating Fields plus PD1 inhibitors, Tumor Treating Fields, stage 4 non-small cell lung cancer (NSCLC):

P2.01-04 NCI-NRG ONCOLOGY ALK PROTOCOL (NRG-LU003): A BIOMARKER-DRIVEN PROTOCOL FOR PREVIOUSLY TREATED ALK-POSITIVE NON-SQUAMOUS NSCLC PATIENTS

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Background: Currently, the 1st generation ALK inhibitor crizotinib and 2nd generation ALK inhibitors ceritinib, alectinib and brigatinib are FDA-approved for the treatment of advanced ALK-positive NSCLC. The 3rd generation ALK inhibitor *lorlatinib* recently received accelerated approval for patients after failure of a 2nd generation inhibitor. 2nd generation ALK inhibitors are widely used in crizotinib-resistant patients and have recently replaced crizotinib as first-line therapy for newly diagnosed patients. There is an urgent need to define the optimal therapy for patients who have become resistant to a second-generation ALK inhibitor. Pre-clinical data and small case series suggest that the presence/absence of ALK resistance mutations or the specigic ALK mutation may serve as a critical biomarker to guide selection of therapy, particularly in the setting of relapse on a 2nd generation ALK inhibitor when ALK resistance mutations are more common, **Method:** NRG-LU003 proposes to study ALK-positive non-squamous NSCLC patients who develop resistance to a second-generation ALK inhibitor, in order to establish a treatment algorithm for these patients based on resistance mechanisms.Patients will undergo tissue biopsy along with blood sampling for cfDNA analysis. One of the aims of the study is to establish the concordance between tissue and liquid biopsies; liquid biopsy may replace tissue biopsy after the first 200 patients enrolled, depending on the concordance and in consultation with CDRH/FDA. Treatments will be selected based on preclinical and clinical data demonstrating activity of treatment particular inhibitor against the specific ALK mutation or resistance mechanism identified. If no ALK resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not previously received or pemetrexed-based therapy with cisplatin or carboplatin. Target accrual is 660 patients and primary objective is to assess whether ALK kinase domain mutations (e.g., G1202/C1156/I1171/L1196/V1180/F1174 mutations) associated with drug resistance are predictive of objective response to subsequent ALK inhibitor therapy, to assess whether subsequent pemetrexed based chemotherapy improves objective response compared to ALK inhibitor therapy for patients with no ALK resistance mutations, and to evaluate objective responses of patients with specific genetic alterations (e.g., ALK L1198F, compound mutations, or high-level *MET* amplification) treated with crizotinib.

Mutation	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG
G1202, G1202del, G1202R	lorlatinib			brigatinib			
C1156Y	lorlatinib		alectinib	brigatinib			
I1171	lorlatinib	ceritinib		brigatinib			
L1196, L1196M	lorlatinib	ceritinib	alectinib	brigatinib	ensartinib		
V1180	lorlatinib	ceritinib		brigatinib			
F1174	lorlatinib		alectinib	brigatinib			
Compound mutation	lorlatinib						
ALK L1198F (alone/ in combination with another ALK mutation)						crizotinib	
MET amplification						crizotinib	
No ALK-resistance mutations*	lorlatinib	ceritinib	alectinib	brigatinib	ensartinib		Pemetrexed + Cisplatin or Carboplatin

Result: "Section not applicable" **Conclusion:** This study has been approved and is open for enrollment through the National Clinical Trials Network (NCTN). This project is supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC) from the National Cancer Institute (NCI)

Keywords: ALK Resistance mutation Trial, liquid biopsy, advanced ALK Positive Lung Cancer

P2.01-05 MAGELLAN: PHASE 1B STUDY OF DURVALUMAB WITH NOVEL ONCOLOGY THERAPIES, WITH/WITHOUT CHEMOTHERAPY, IN UNTREATED STAGE IV NSCLC

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Background: Immunotherapy with anti-PD-1/PD-L1 antibodies, with or without chemotherapy, is the standard of care in the first-line (1L) treatment for metastatic NSCLC. Despite advances, patients treated with anti-PD-1 directed regimens in metastatic NSCLC have demonstrated median PFS of <1 year. Targeting novel mechanisms in the tumor may improve response rates and survival. For example, danvatirsen is an antisense oligonucleotide that downregulates *STAT3*, a master regulator of immune suppression, and oleclumab is an anti-CD73 monoclonal antibody that alleviates adenosine-mediated immunosuppression. MAGELLAN is a Phase 1B, open-label, multicenter, biomarker-enriched, multicohort study (NCT03819465), designed to assess the safety and efficacy of durvalumab in combination with novel oncology therapies (danvatirsen, oleclumab), with or without chemotherapy, as 1L treatment for patients with Stage IV NSCLC. Additional novel therapies will be added to this study as supportive preclinical/clinical datasets emerge. **Method:** Adult patients with Stage IV NSCLC (histologically/cytologically documented), tumors lacking activating *EGFR* mutations and *ALK* rearrangements, WHO/ECOG PS 0–1, and no prior chemotherapy or systemic therapy for Stage IV NSCLC are eligible. Eligible patients will be assigned to the PD-L1 tumor cell (TC) ≥50% or PD-L1 TC<50% cohorts, as confirmed by the VENTANA PD-L1 (SP263) Assay. Immunohistochemical staining with the SP263 assay is concordant with that for the 22C3 assay, another PD-L1 diagnostic assay. Patients in the PD-L1 TC≥50% cohort will be assigned to durvalumab monotherapy (1500 mg q4w), durvalumab+danvatirsen, or durvalumab+oleclumab. Patients in the PD-L1 TC<50% cohort will be assigned to durvalumab+chemotherapy (1500 mg durvalumab q3w up to 4 cycles [+chemotherapy], then q4w [–chemotherapy]), durvalumab+chemotherapy+danvatirsen, or durvalumab+chemotherapy+oleclumab. All therapy will be administered intravenously until disease progression. Oleclumab (1500 mg starting dose) and danvatirsen (200 mg starting dose) in combination with durvalumab or durvalumab+chemotherapy will be administered using a rolling 6-patient design to evaluate for toxicity. The chemotherapy backbone for use with immunotherapy, per investigator's choice, will be nabpaclitaxel+carboplatin for squamous and non-squamous NSCLC, gemcitabine+cisplatin/carboplatin for squamous NSCLC, and pemetrexed+carboplatin/cisplatin for non-squamous NSCLC. Patients receiving pemetrexed+carboplatin/cisplatin who do not progress after 4 cycles of chemotherapy will receive pemetrexed maintenance therapy and immunotherapy, unless contraindicated. The primary endpoint is safety and tolerability. Secondary endpoints are objective response rate and PFS (both RECIST v1.1), duration of response, OS, and pharmacokinetics and immunogenicity of durvalumab, oleclumab, and danvatirsen. Identification of candidate biomarkers from blood and tissue samples that may correlate the likely clinical benefit with the treatments under investigation will also be explored. Enrollment is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: durvalumab, Non-Small Cell Lung Cancer, PD-L1

P2.01-06 PHASE I STUDY OF NIVOLUMAB AND IPILIMUMAB COMBINED WITH NINTEDANIB IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Cancer-associated fibroblasts (CAFs) in the tumor microenvironment (TME) inhibit tumor infiltrating lymphocyte activation and are potentially immunosuppressive. Targeting the TME may represent an important synergistic approach in immunotherapy (IO). Combination IO with nivolumab and ipilimumab has proven clinical activity in NSCLC. Nintedanib is an orally available triple kinase inhibitor that is active against NSCLC, inhibits CAFs, and targets VEGFR, FGFR and PDGFR. We report the preliminary results of a phase 1 dose escalation trial evaluating the combination of nintedanib with nivolumab and ipilimumab (N+N+I) in advanced NSCLC pts. **Method:** This is single center, investigational, non-randomized trial of IO naïve or IO pretreated pts with locally advanced or metastatic NSCLC. Primary endpoint is to determine the safety and tolerability of concurrent administration of the proposed regimen. Key secondary endpoints include RR, DOR, OS, PFS. Five dose levels of nintedanib (dose level -1, 0, 1, 2 and 3 with nintedanib given at dose 100 mg once daily,150 mg once daily and 100mg, 150 mg and 200 mg twice daily respectively) are given with fixed dose of nivolumab (3mg/kg every 2 weeks) and ipilimumab (1mg/kg every 6 weeks). Dose escalation was achieved by the 3+3 design. Blood and tumor biopsies are obtained to evaluate potential predictive and resistance mechanisms. **Result:** Enrollment to phase I dose escalation was started on 29th January 2018 and to date 13 patients have been treated on dose level -1 (3), 0 (5) and 1(5). 54% (7) were IO pretreated and 46% (6) were IO naive. Median age is 65 with 62% (8) female patients, ECOG 1 62% (8) and 15% (2) never smoker/ 85% (11) prior or current smokers. Most common AE of any grade were transaminitis and rash in 23% (3). Most G3 AE was transaminitis 8% (1). There were no G4/5 AEs or DLTs. There was no treatment discontinuation due to AEs. PD-L1 expression was < or = 1% in 46% (6), 1-49% in 8% (1) and >/= 50% in 46% (6) pts. Amongst the 12 patients evaluable for confirmed response, 17% (2) had PR, 50% (6) had SD and 33% (4) had PD. In the IO pretreated group, 14% (1) had PR, 57% (4) had SD and 28% (2) had PD. **Conclusion:** The combination of N+N+I was well tolerated. The regimen demonstrates antitumor activity despite progression on prior IO. The updated and mature data of the phase I dose escalation trial will be presented at the meeting. Clinical trial information: NCT03377023.

Keywords: tumor microenvironment, Combination immunotherapy, advanced non small cell lung cancer

P2.01-07 OPEN-LABEL, BIOMARKER-DIRECTED PLATFORM STUDY IN NSCLC PATIENTS WHO PROGRESSED ON AN ANTI-PD-(L)1-CONTAINING THERAPY (HUDSON)

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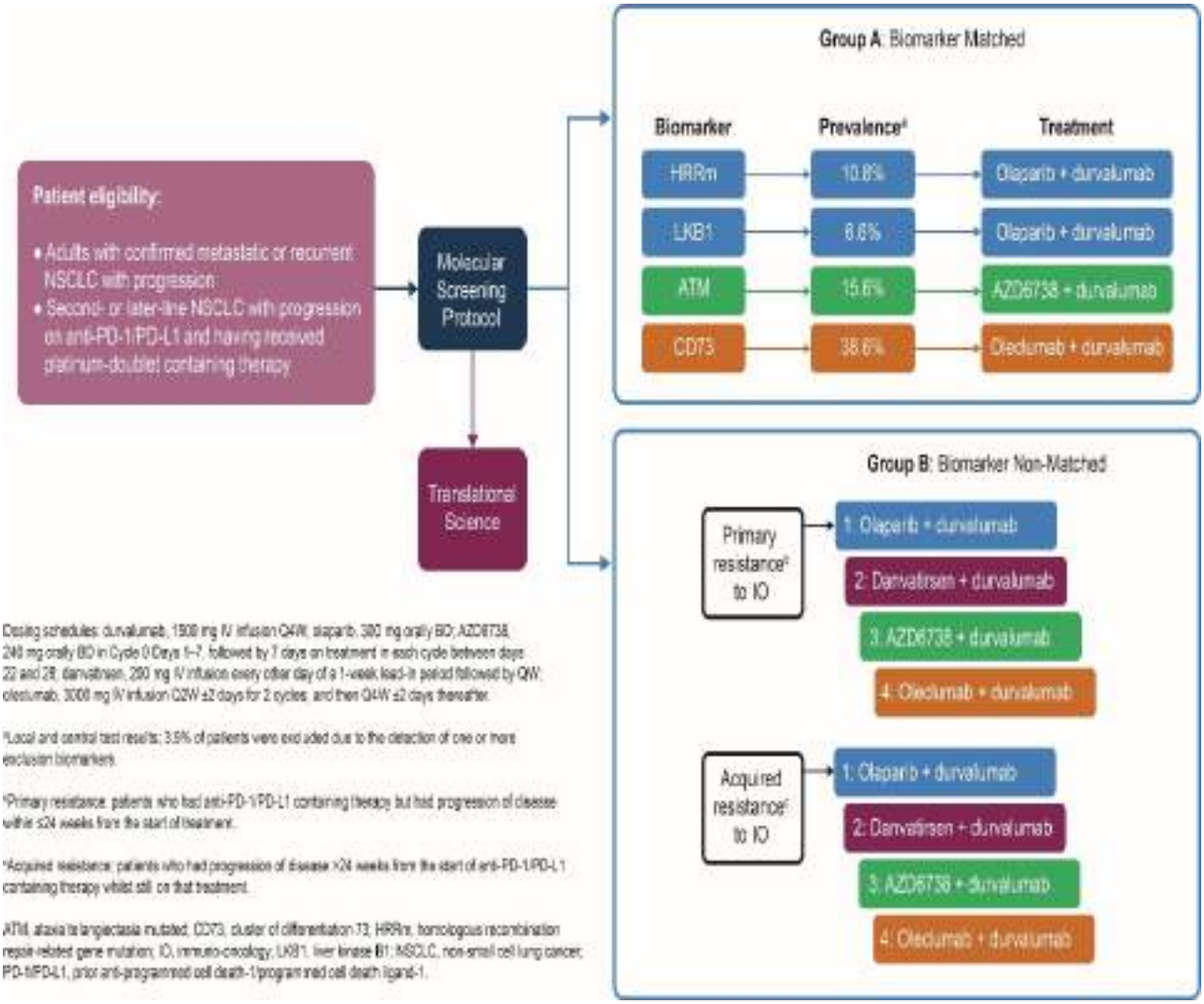
Background: Immune checkpoint inhibitor (ICI)-containing regimens have significantly improved survival outcomes in first- and second-line non-small cell lung cancer (NSCLC). However, few patients have-durable responses to anti-programmed cell death1/ programmed cell death-ligand 1 (anti-PD-[L]1)-containing therapy (primary resistance) or other patients progress during anti-PD-(L)1-containing therapy (acquired resistance). HUDSON addresses the urgent need to identify new treatments and understand ICI resistance for patients who progressed after receiving anti-PD-(L)1-containing therapy. **Method:** HUDSON is a multi-centre, international, multi-arm, platform study (NCT03334617), which will 1) evaluate therapies to reverse ICI resistance and 2) define mechanisms of ICI resistance in patients with NSCLC who have progressed following standard-of-care platinum- and ICI-based therapies. HUDSON consists of biomarker matched and non-matched groups (Figure). Allocation is guided by tumour molecular profile, using a pre-specified algorithm. Pre-existing local next generation sequence (NGS) data enables rapid patient allocation to biomarker-matched groups. Central molecular profiling comprises NGS and immunohistochemistry data. New groups will be added as new translational hypotheses emerge. Translational research will employ serial peripheral blood samples (including ctDNA) and tumour biopsies. Figure. Study design and biomarker prevalence



Dosing schedules: durvalumab, 1500 mg IV infusion Q4W; olaparib, 300 mg orally BID; AZD6738, 240 mg orally BID in Cycle 0 Days 1–7, followed by 7 days on treatment in each cycle between days 22 and 28; danvatirsen, 200 mg IV infusion every other day of a 1-week lead-in period followed by Q2W; oleclumab, 3000 mg IV infusion Q2W ±2 days for 2 cycles, and then Q4W ±2 days thereafter.

*Local and central test results; 3.5% of patients were excluded due to the detection of one or more exclusion biomarkers.

†Primary resistance: patients who had anti-PD-1/PD-L1 containing therapy but had progression of disease within ≤24 weeks from the start of treatment.

‡Acquired resistance: patients who had progression of disease >24 weeks from the start of anti-PD-1/PD-L1 containing therapy whilst still on that treatment.

ATM, ataxia telangiectasia mutated; CD73, cluster of differentiation 73; HRRm, homologous recombination repair-related gene mutation; IO, immuno-oncology; LKB1, liver kinase B1; NSCLC, non-small cell lung cancer; PD-1/PD-L1, prior anti-programmed cell death-1/programmed cell death ligand-1.

Result: Enrolment is ongoing; as of 01 April 2019, patients have been dosed in each of the drug combinations currently open for recruitment. Analyses of tissue and blood samples collected for exploratory research are ongoing, including genomic, transcriptomic and chemistry biomarkers such as tumour mutation burden, human leukocyte antigen status, T-cell receptor repertoire, and peripheral immune activation signatures. **Conclusion:** Specific differences between patients on individual HUDSON arms that inform anti-PD(L)1 resistance mechanisms, plus learnings from the implementation of this innovative and complex platform study will be presented.

Keyword: metastatic NSCLC; biomarkers; immunotherapy resistance

P2.01-08 CLINICAL TRIAL IN PROGRESS: CONCORDE - A PHASE 1B STUDY OF NOVEL AGENTS IN COMBINATION WITH CONVENTIONAL RADIOTHERAPY IN NSCLC

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Background: The majority of patients with locally advanced non-small cell lung cancer (NSCLC) treated with curative intent receive radiotherapy (RT) as part of their treatment. Despite considerable technological advances in RT delivery, the survival of these patients has barely changed over the last 60 years. A major factor in this failure to improve outcomes is the relative radioresistance of NSCLC. Attempts to overcome radioresistance by escalating RT doses have demonstrated inferior outcome likely secondary to normal tissue toxicity. Therefore an alternate approach is to exploit genetic dependencies in the DNA damage response of NSCLC, using biological inhibitors to selectively radiosensitise tumours whilst sparing normal tissues. The CONCORDE study is a multi-arm phase 1B platform study to investigate the combination of radical RT with DNA damage response inhibitors (DDR-i) targeting five different proteins: PARP, ATR, WEE1, ATM, DNA-PK. **Method:** CONCORDE is a hypothesis-driven combination study of novel therapeutics and RT using an innovative adaptive early-phase trial design. The study will address two main research questions: - What are the recommended

phase 2 doses (RP2D) of individual DDR-i in combination with curative RT in patients with stage IIB/III NSCLC? - What are the safety profiles of individual DDR-i combined with curative RT in this population? Key inclusion criteria are stage IIB and III NSCLC planned to receive curative intent RT doses (+/- neoadjuvant chemotherapy) and PS 0-1. Participants will be randomised on a 3:1 basis between DDR-i with RT or RT alone. Patients receiving RT alone will be pooled across the arms to provide contemporary data on toxicity. All patients will receive external beam RT with a planned dose of 60 Gy in 30 fractions. The study will use a Bayesian adaptive model-based approach to dose-escalation, with separate Time-To-Event Continual Reassessment Method (TiTE-CRM) models in each experimental arm. The primary endpoints are dose-limiting toxicities occurring within 12 months of the start of radiotherapy. Secondary endpoints include safety and toxicity (acute and late toxicity up to 2 years including using patient reported outcome (PRO) measures), treatment compliance, and best overall response (using RECIST 1.1, progression-free, and overall survival). Correlative studies will be carried out to identify biomarkers of toxicity and response. We have secured high-level agreement from leading pharmaceutical partners to invest in 5 treatment arms and funding approval from Cancer Research UK is pending. The first participant is estimated to commence treatment in late 2019 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Radiotherapy / drug combinations, Phase 1b, DNA damage response

P2.01-09 VINMETATEZO: PHASE II TRIAL OF METRONOMIC ORAL VINORELBINE WITH ATEZOLIZUMAB FOR RECURRENT STAGE IV NSCLC (GFPC*04-08)

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Background: Immunotherapy is recommended as second-line treatment for advanced Non-Small Cell Lung Cancer (NSCLC) progressing after a platinum doublet treatment. However, response rates remain low and some patients have rapid progression. Novel concepts of synergic action between immunotherapy and chemotherapy have emerged recently. Metronomic oral vinorelbine (MOV) is defined as low-dose and frequent chemotherapy administration. There is no data of the association of immunotherapy and metronomic chemotherapy. The main objective of this trial was to assess safety and efficacy of this combination of MVO and atezolizumab. **Method:** An open label phase 2 trial (NCT 03801304) in two steps. -First step: a safety run-in phase: 12 patients will be enrolled and will receive atezolizumab in combination with MOV (40 mg/day 3 times a week, every week). After 12 patients have received study treatment and completed at least 1 cycle of study treatment (21 days), enrollment will be interrupted and an independent Data Safety Monitoring Board (DSMB) will review the number and percentage of adverse events (AEs). The dose will be considered toxic when Grade ≥ 3 immune-related AEs (>20%) or vinorelbine-related AEs (>20%) occurs. In this case the dose will be decreased to 30 mg, 3 times a week. AEs will be assessed with the same procedure that will be applied to the next 12 patients. - Second step: phase II design as defined by A'hern. The main outcome is PFS rate at 4 months. Minimal efficacy hypothesis (p1) is set at 55% event-free rate of PFS at 4 months, (p0), which would indicate that the strategy is clearly ineffective, is set at 40% PFS at 4 months. With a 5% alpha risk (unilateral perspective) and a 20% beta risk, the number of assessable subjects is set at 71. **Result:** The trial started on 2019 January 24th. 12 patients have been included in 4 centers. The run in step ended at the beginning of April, with no grade 3 or more immune related AEs or vinorelbine related AEs. The DSMB decided to expand the study to the second step, which will start on April, 17th. **Conclusion:** Combination of atezolizumab and MOV appears as a feasible association without major toxicities. The phase 2 is ongoing; complementary results on safety and efficacy will be presented at the meeting.

Keywords: relapsed advanced NSCLC, Immunotherapy, Chemotherapy

P2.01-10 REAL CLINICAL PRACTICE STUDY TO EVALUATE 2 LINE TREATMENT BASED ON COMPRENHENSIVE GENOMIC PROFILING IN NSCLC. LUNGONE STUDY

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Background: Cancer is a genomic disease and molecular-targeted therapy plays an increasingly important role in the treatment of advanced NSCLC. The current standard of care (SoC) indication for NSCLC is defined by genomic biomarkers to classify the tumor as a carrier of a therapeutic approved target. However, the current standard of practice for molecular testing in NSCLC in Spain is highly heterogeneous, depending on several factors such as hospital size, resources, laboratory equipment and experience. In addition, there are several other markers and/or genomic signatures which are not determined due to the current lack of scientific evidence, i.e. MSI, TMB, KRAS, BRAF, RET, MET, HER2 and NTKR, which could guide physician second line treatment choice, including clinical trial options. The aim of this study is to evaluate the impact on decision making in the 2nd line treatment using a comprehensive genomic profiling (CGP) in advanced/metastatic NSCLC with adenocarcinoma histology. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** This is a multicenter, prospective, single-cohort study to describe the clinical management of the 2nd line SoC treatment in patients with locally advanced/metastatic NSCLC with adenocarcinoma histology, when a comprehensive genomic profile based on FoundationOne®CDx or FoundationOne® Liquid test, is provided. 12 academic institutions in Spain were selected and 180 patients were planned to be recruited. The principal objective is to evaluate if there is any change in planned 2nd line treatment decisions after receiving the CGP report. Secondary objectives for this study are:1) to identify non-previously detected actionable molecular aberrations by conventional molecular assays; 2) to evaluate the economic impact in terms of use of healthcare resources of the CGP *vs.* standard diagnostic panels; and 3) to describe each patient's status 2 years after the inclusion of the last patient in the study. Patients will follow usual clinical pathways for biomarker analysis and a comprehensive genomic profiling in the remaining tissue through FoundationOne® CDx, will be conducted or liquid biopsy with FoundationOne® Liquid, if exhausted. To be enrolled in the study, patients must have an ECOG between 0 and 2 and biomarkers ALK, EGFR, ROS1 must have been assayed (negative or unknown results). Enrolment begun on October 2018 and, to date, a total of 110 patients have been included.

Keywords: F1CDx, F1Liquid, Foundation Medicine

P2.01-11 ALKTERNATE: A PROOF OF CONCEPT STUDY IN ALK-REARRANGED NSCLC ALTERNATING LORLATINIB WITH CRIZOTINIB AFTER DISEASE PROGRESSION

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Background: Standard frontline therapy for patients with advanced *ALK*-NSCLC has rapidly evolved to 2nd generation ALK TKIs based on superior survival. Regardless, resistance to treatment is inevitable. Most will receive multiple lines of TKIs +/- chemotherapy before eventually dying from the disease. Lorlatinib is a 3rd generation ALK TKI active against a broad range of acquired ALK kinase domain (KD) resistance mutations. A recent report demonstrated re-sensitisation to crizotinib by the lorlatinib ALK resistance mutation L1198F.

Increased knowledge of resistance mechanisms is key to overcoming and preventing its emergence. Based on knowledge of the varying patterns of resistance to different ALK TKIs, ALKternate will test the hypothesis that treatment with alternating TKIs will re-equilibrate the selection pressure for enrichment of resistant clones. This hypothesis has been tested preclinically in accompanying abstracts #2072 and #2074. **Method:** ALKternate is a proof of concept open label multi-centre translational study alternating lorlatinib (100mg OD) with crizotinib (250mg BD) (Figure 1. including eligibility). The aim is to identify whether this fixed alternating schedule of ALK TKI is: safe; feasible and active, resulting in prolonged systemic and intracranial disease control via delaying the emergence of ALK TKI resistance. A secondary aim is to investigate whether plasma *ALK*-dependent and independent resistance profiles can be used to monitor therapy effectiveness. The primary outcome measure is time to treatment failure (TTTF) with alternating therapy. Secondary end points include best OR, PK analysis, PFS, DCR (systemic and CNS) after lorlatinib induction and the first cycle of alternating therapy, OS, toxicity, PROs and QOL measures. Plasma ctDNA and proteomic biomarkers will be analysed. Enrolled patients must demonstrate disease control after induction lorlatinib to continue alternating therapy. Imaging occurs more frequently initially (Figure 1.), before 12 weekly after two alternating cycles in those with disease control. Status: Trial in Progress. Enrollment began Q3 2019, ethics approval NSLHD ETH00389.

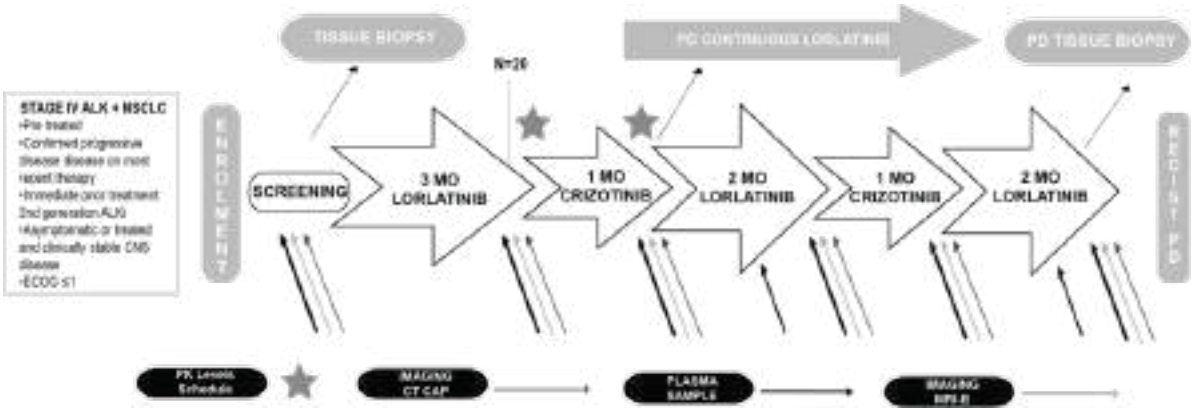

Figure 1. ALKternate trial schema

Result: Section not applicable **Conclusion:** Section not applicable

Keyword: NSCLC, ALK, resistance

P2.01-12 A PHASE I/II TRIAL OF IO102 AND PEMBROLIZUMAB WITH/WITHOUT CHEMOTHERAPY AS FIRST-LINE TREATMENT OF METASTATIC NSCLC

M. Provencio[1], J. Spicer[2], P. Garrido[3], J.M. Trigo Perez[4], S. Viteri[5], J. Bosch-Barrera[6], A. Insa[7], E. Felip[8], J. De Castro Carpeno[9], E. Coart[10], E. Schmidt[11], A. Christiansen[12], M. Hald Andersen[12], M.-B. Zocca[12], E. Ehrnrooth[12], L. Paz-Aras[13]

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Background: Immunotherapy has significantly changed the treatment landscape of non-small cell lung cancer (NSCLC) with no driver mutations. However, despite the addition of anti-PD-1/PD-L1 therapies to the clinical armamentarium only a subset of patients derives durable benefit. IO102 is a novel, second generation, HLA-A unrestricted immune modulating T-win® vaccine targeting IDO. IO102 has a dual mode of action; remodulation of the tumour micro-environment through elimination of immune suppressive cells, and induction of CD8 T-cell mediated killing of IDO-expressing tumor cells. Our first-generation IDO vaccine (IO101) has shown promising antitumor activity and a favorable safety in heavily pretreated NSCLC patients (*Iversen, CCR 2013)*. **Method:** Phase I/II, international, multicenter, open-label, randomized trial with two parallel cohorts. Cohort A: IO102 (100µg s.c.) and pembrolizumab (200 mg) (PD-L1 ≥ 50%); Cohort B: IO102, pembrolizumab and carboplatin plus pemetrexed (PD-L1 < 50%). The maximum treatment duration is 35 cycles (app. 2 years). Key eligibility criteria include metastatic NSCLC or non-squamous NSCLC (cohort B) with no prior treatment for metastatic NSCLC and no driver mutations. Phase I is a non-randomized safety run-in with 6 patients per cohort investigating one dose level of the experimental arms. Only one DLT is allowed in each cohort. Phase II is following Sargent's two-stage, three-outcome optimum design (*Sargent, ClinTrial2001*) with a 2:1 randomization in the cohorts. Cohort A: IO102 and pembrolizumab versus pembrolizumab alone; Cohort B: IO102, pembrolizumab and chemotherapy vs. pembrolizumab and chemotherapy. Provision of blood and tumour tissue is required for biomarker studies. The primary endpoint is safety and objective response rate (ORR) per RECIST 1.1 in Phases I and II, respectively. Secondary endpoints include ORR per iRECIST, duration of response, progression free survival, overall survival, and biomarkers including immunoscore in tissue, tumour mutational burden and immunomonitoring in blood. The study is enrolling in Europe. First patient was entered in September 2018 and recruitment is expected to continue throughout 2019: EudraCT Number 2018-000139-28 / IND Number: 018081. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: NSCLC, Vaccine, Pembrolizumab

P2.01-13 THE DAIL TRIAL: DIETETIC ASSESSMENT AND INTERVENTION IN LUNG CANCER

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Background: Clinical Trial in Progress Lung Cancer related weight loss has a complex aetiology. It includes 3 overlapping but distinct syndromes: cachexia, sarcopenia and malnutrition. ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines suggest that everyone with a new diagnosis of cancer is screened for malnutrition, but there is minimal evidence to support this recommendation. We have opened the DAIL trial to further investigate the proportion of patients with newly diagnosed Non-Small Cell Lung Cancer (NSCLC) who should be referred to a dietitian, and the proportion of patients who had cachexia, sarcopenia and malnutrition. **Method:** Primary objectives are: 1. To identify the proportion of patients diagnosed with NSCLC who are malnourished, cachectic and have sarcopenia before anti-cancer treatment. 2. To identify the proportion of lung cancer patients who would require dietetic review before anti-cancer treatment. Secondary objectives are: 1. To identify whether malnutrition, cachexia or sarcopenia affects overall survival in metastatic NSCLC. 2. To identify whether sarcopenia predicts for a poor outcome in NSCLC. In the study we use patient generated questionnaires, physical assessments and radiological tests to define malnutrition, sarcopenia and cachexia. The specific assessments are: Patient generated subjective global assessment (PG-SGA) G8 EORTC QLQC30 EORTC LC13 Performance status Hand grip strength Spirometry Psoas muscle assessment from diagnostic cross sectional imaging Charlson Co-morbidity Index Inclusion criteria are: Patients >18 years old who are able to consent to entry into a clinical trial Biopsy confirmed Advanced NSCLC (stage IIIb and IV). Patient receiving first line systemic palliative anti-cancer treatment. Exclusion criteria are: Inability to consent to treatment Patient declines anti-cancer treatment **Result:** Section not applicable **Conclusion:** It is anticipated that the results will clarify if a nutritional screening tool such as the PG-SGA can identify patients at risk of malnutrition prior to starting anti-cancer treatment, as well as highlight those who require dietetic intervention. It is hoped that this research will inform a randomised clinical trial of dietetic counselling in lung cancer.

Keywords: Dietitian, weight loss, cachexia

P2.01-14 PHASE 3 TRIAL OF SITRAVATINIB PLUS NIVOLUMAB VS DOCETAXEL FOR TREATMENT OF NSCLC AFTER PLATINUM-BASED CHEMOIMMUNOTHERAPY

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Background: Sitravatinib is a tyrosine kinase inhibitor (TKI) that targets multiple closely-related receptor tyrosine kinases (RTKs), including the split RTKs VEGFR-2 and KIT as well as the TAM (TYRO3, AXL, and MER) RTKs. Inhibition of the split RTKs may reduce immunosuppressive regulatory T (T_{reg}) cells and myeloidderived suppressor cells (MDSCs) within the tumor microenvironment (TME), while inhibition of TAM RTKs may, in addition to promoting depletion of MDSCs, repolarize tumor associated macrophages towards the M1 phenotype that is associated with secretion of pro-inflammatory cytokines. Given these pleiotropic immunestimulating effects, sitravatinib may augment the antitumor immune response of nivolumab in patients (pts) with non-small cell lung cancer (NSCLC). An ongoing Phase 2 study demonstrates clinical activity of this combination in pts with metastatic non-squamous NSCLC after progression on a checkpoint inhibitor (CIT). **Method:** This randomized, open-label, Phase 3 study (N=664) compares the efficacy and safety of sitravatinib in combination with nivolumab vs docetaxel in pts with advanced non-squamous NSCLC who have radiographically documented disease progression on or after platinum-based chemotherapy in combination with CIT. Pts are randomized (1:1) to receive sitravatinib administered orally once daily in continuous 28-day cycles at 120 mg combined with nivolumab IV at 240 mg every 2 weeks or 480 mg every 4 weeks vs treatment with docetaxel 75 mg/m^2 IV every 3 weeks. Patients will be stratified based on duration of previous CIT treatment, ECOG performance status, and presence of brain metastases at baseline. Key eligibility criteria include duration of treatment of CIT for at least 4 months, discontinuation of prior treatment with CIT < 90 days prior to the date of randomization, and absence of symptomatic or uncontrolled brain metastases. The primary endpoint is Overall Survival (OS). Key secondary endpoints include safety and tolerability, ORR, PFS, PROs, and PK. OS will be analyzed using Kaplan-Meier methods and the stratified log-rank test to estimate and compare the median OS between the two treatment arms with 95% CI. An IDMC will be established to review safety at regular intervals and to review efficacy data at the planned interim analysis for futility and possible sample size adjustment based on OS. Recruitment begins May 2019. NCT number NCT03906071 **Result:** Section not applicable **Conclusion:** Section not applicable.

Keywords: advanced NSCLC, Immunology

P2.01-15 PHASE II SINGLE ARM STUDY OF CABOZANTINIB IN NON-SMALL CELL LUNG CANCER PATIENTS WITH MET DEREGULATION (CABINMET)

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Background: Mesenchymal-Epithelial Transition gene (*MET*) amplification and exon 14 skipping mutations are established oncogenic drivers in non-small cell lung cancer (NSCLC), both occurring in about 4% of cases. In patients with *MET* amplified or mutated lung cancer, oral MET tyrosine kinase inhibitors (TKI) showed promising activity. The American Food and Drug Administration has recently granted crizotinib a breakthrough therapy designation for *MET* exon 14 mutation positive NSCLC. Cabozantinib is a novel oral inhibitor of MET and other receptor tyrosine kinases that has shown preliminary activity in *MET* deregulated NSCLC patients pretreated with crizotinib, although definitive data on its therapeutic role are still missing. **Method:** CABinMET (NCT03911193) is a phase II, single arm, multicenter study assessing the efficacy of cabozantinib in subject with *MET* amplification or *MET* exon 14 skipping mutation pretreated or not with MET inhibitors. The primary endpoint of the trial is overall response rate. Secondary efficacy endpoints are progression free survival, overall survival and disease control rate. Main inclusion criteria include histologically/cytologically confirmed diagnosis of advanced stage NSCLC, presence of *MET* exon 14 skipping mutation or *MET* amplification (MET/CEP7 ratio ≥2.2 on FISH analysis) on archival formalin-fixed paraffin-embedded (FFPE) tumor tissue or circulating tumor DNA, measurable disease, ECOG PS 0-1, at least 1 prior line of standard therapy, adequate organ function. Patients with co-existent driver events or with symptomatic brain metastases are excluded from the trial. Cabozantinib is administered orally at 60 mg once daily until disease progression, patient refusal or unacceptable toxicity. Disease is assessed every 8 weeks. Exploratory biomarker analyses are conducted on archival FFPE tumor tissue and on blood samples collected at baseline, at the time of the first disease assessment and at progression. **Result:** The study is currently running in 9 Italian centers. Recruitment started in September 2018 and 6 of the planned 25 patients have been enrolled. **Conclusion:** Enrollment will be completed in 24 months.

Keywords: NSCLC, MET, cabozantinib

P2.01-16 TACTICAL: A PHASE I/II TRIAL TO ASSESS THE SAFETY AND EFFICACY OF MSCTRAIL IN METASTATIC LUNG ADENOCARCINOMA

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Background: Mesenchymal stromal cells (MSCs) migrate to and incorporate into tumour stroma, acting as vehicles for delivering anti-cancer therapies. TNF-related apoptosis inducing ligand (TRAIL) selectively induces apoptosis in malignant cells, however its short biological half-life has limited therapeutic efficacy. We have transduced MSCs with a lentiviral vector to express TRAIL (MSCTRAIL), demonstrating efficacy *in vitro* using co-culture assays and *in vivo* in orthotopic lung metastasis murine model, showing regression of metastases following treatment with intravenous MSCTRAIL [1] and synergistic activity with other systemic anti-cancer therapies. Given their immune-privileged nature we are now delivering *ex vivo* MSCTRAIL from pooled third party umbilical cord donors without tissue matching or immunosuppression. **Method:** TACTICAL is a phase I/II trial assessing safety and efficacy of MSCTRAIL in combination with first line standard of care (SOC); pemetrexed (500mg/m2) and cisplatin (75mg/m2) and/or pembrolizumab (200mg), in treatment-naive patients with stage IIIB/IV metastatic lung adenocarcinoma. Patients have no actionable driver mutations and ECOG performance status 0-1. Phase I is a dose de-escalation study; patients receive SOC on day 1 and $4x10^8$ MSCTRAIL cells on day 2 of a 21-day cycle for 3 cycles, with a Bayesian adaptive design recommending dose reductions if severe toxicities occur (Fig.1A). Primary outcomes are recommended phase II dose (RP2D), safety and tolerability of MSCTRAIL. In phase II, 46 patients will be randomised (1:1) in a double-blind trial to receive SOC and either RP2D of MSCTRAIL or placebo (Fig.1B). Primary outcome is tumour response rate by RECIST (v1.1) at 12 weeks.

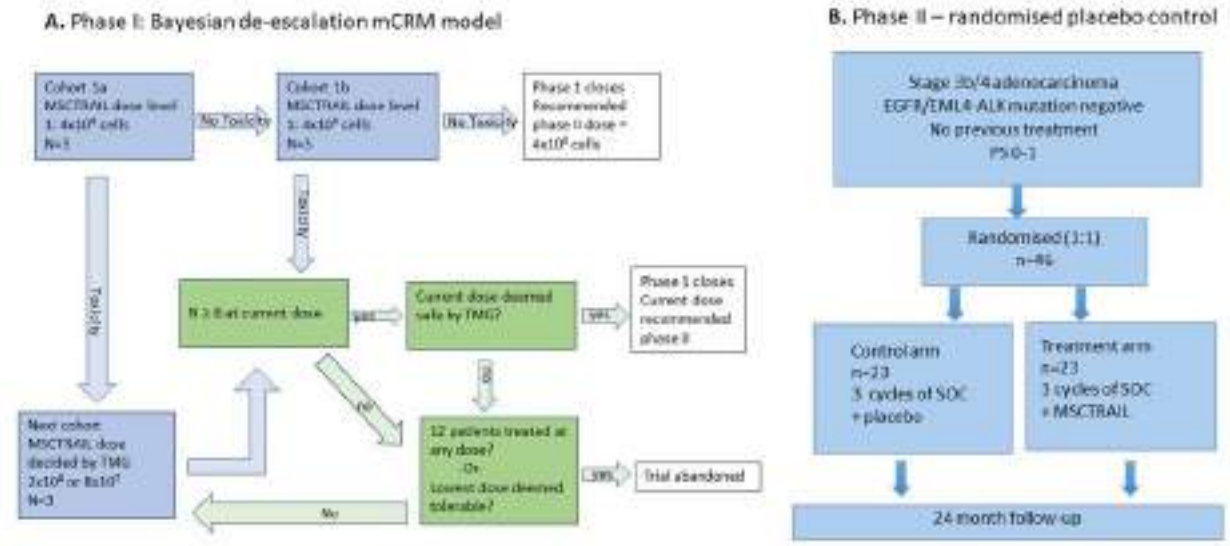

Figure 1: Schematic of TACTICAL Trial
A) Phase I Bayesian de- escalation model. B) Phase II randomised double-blind placebo control

Result: Translational work will include measuring: biomarkers of response; T, B, NK cell function in reaction to allogeneic MSCs; tracking migration of MSCs radiolabelled with ^{89}Zirconium-oxine through serial PET imaging. **Conclusion:** TACTICAL is the first clinical trial of this novel cell and gene therapy and if successful will pave the way for future allogeneic MSC cancer therapies. 1. Loebinger, M.R., et al., *Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer.* Cancer Res, 2009. 69(10): p. 4134-42.

Keywords: Mesenchymal Stromal Cells, cell and gene, novel therapy

POSTERS

P2.01-17 CANOPY-1: PHASE 3 STUDY OF CANAKINUMAB/PLACEBO+PEMBROLIZUMAB+PLATINUM-CHEMOTHERAPY IN UNTREATED STAGE IIIB-IV NSCLC PTS

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Background: Interleukin-1β (IL-1β) inhibition with canakinumab reduced the incidence of and mortality due to lung cancer among patients with atherosclerosis in CANTOS trial. Inhibition of IL-1β driven inflammation may lead to a tumor microenvironment more susceptible to anti-PD-(L)1 therapies. Recent studies have shown that low levels of CRP at baseline or decreased levels over time correlated with improved responses to anti-PD-(L)1 agents, providing rationale for combination of canakinumab and Pembrolizumab (PEM). **Method:** CANOPY-1 (NCT03631199) is a double-blind, randomized, placebo (Pb)-controlled, phase III trial to determine efficacy and safety of PEM + platinum-based chemotherapy (Ctx) ± canakinumab in untreated stage IIIB/IIIC-IV squamous and non-squamous NSCLC pts. It is a 2 part study- In Part 1 [open-label safety run-in with 3 cohorts of ~9 pts each to confirm recommended phase 3 canakinumab regimen], pts will receive canakinumab 200 mg s.c (Q3W) + PEM 200 mg i.v (Q3W) + platinum-based Ctx [Cohort A (non-squamous), carboplatin (CBCDA) + pemetrexed (PTX); Cohort B (non-squamous), cisplatin + PTX; Cohort C (squamous or non-squamous), CBCDA + paclitaxel]. In Part 2 [with ~600 pts) to evaluate efficacy and safety of canakinumab combination], pts will be randomized to receive canakinumab/Pb + PEM + platinum-based Ctx (non-squamous, CBCDA or cisplatin + PTX; squamous, CBCDA + paclitaxel or nab-paclitaxel). PEM and platinum-based Ctx will be administered at their approved doses. Randomization (1:1) will be stratified by PD-L1 status, region and histology. In both parts, pts will receive 4 cycles of induction therapy (canakinumab/Pb + PEM + Ctx) followed by maintenance therapy (PEM + canakinumab/Pb +/- PTX) until progressive disease. Primary objectives: confirm recommended phase 3 regimen for canakinumab combination (Part 1), compare PFS and OS between treatment arms (Part 2). Secondary objectives (Part 1 and 2): ORR, DCR, safety, PK and DOR. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: IL-1β, Canakinumab, NSCLC

P2.01-18 ORION: DURVALUMAB+OLAPARIB VERSUS DURVALUMAB ALONE AS MAINTENANCE THERAPY IN STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Systemic chemotherapy for first-line (1L) metastatic NSCLC shows mixed outcomes. Results from studies using immunotherapy alone or combined with chemotherapy as 1L treatment in patients (pts) with metastatic NSCLC represent a substantial advance, but further improvement is needed. Increased deoxyribonucleic acid damage triggered by polyadenosine 5'diphosphoribose polymerase inhibition may confer antitumour activity, modify tumour immunogenicity and further sensitise tumours to immune checkpoint inhibition, thus promoting a more durable antitumour response. This Phase 2, randomised, multicentre, double-blind study (NCT03775486) is designed to assess the efficacy and safety of durvalumab+olaparib versus durvalumab alone as maintenance therapy in pts whose stage IV NSCLC has not progressed following 1L platinum-based chemotherapy+durvalumab. **Method:** Adult pts with stage IV NSCLC with tumours lacking activating *EGFR* mutations and *ALK* fusions are eligible. In the initial therapy phase, all pts will receive durvalumab (1500 mg intravenously [IV]) concurrent with platinum-based doublet therapy. Durvalumab+chemotherapy will be administered for 4 cycles for both squamous NSCLC (nanoparticle albumin-bound [nab]-paclitaxel+carboplatin or gemcitabine+carboplatin/cisplatin) and nonsquamous NSCLC (nab-paclitaxel+carboplatin or pemetrexed+carboplatin/cisplatin). Pts whose disease does not progress (complete or partial response [CR/PR] or stable disease [SD]; investigator-assessed RECIST 1.1) will be randomised (1:1) to durvalumab (1500 mg IV, every 4 weeks) + either olaparib (300 mg, oral, twice daily) or its matching placebo until disease progression. Randomisation will be stratified based on objective response to durvalumab+chemotherapy (CR/PR or SD) during the initial therapy phase and histology (squamous or nonsquamous). **Result:** The primary endpoint is progression-free survival (PFS) (investigator-assessed, RECIST 1.1). Secondary endpoints are overall survival, PFS in pts with homologous recombination repair-related gene mutation, objective response rate, duration of response, health-related quality of life, pharmacokinetics and immunogenicity of durvalumab, as well as safety. **Conclusion:** The study start date was 21 December 2018 and patient enrolment is ongoing. All patients will be followed for survival until the end of the study. The estimated primary completion date is 5 October 2020 and the estimated study completion date is 2 June 2022.

P2.01-19 PHASE 2 STUDY OF TELISOTUZUMAB VEDOTIN (TELISO-V) IN PREVIOUSLY TREATED C-MET+ NON-SMALL CELL LUNG CANCER: TRIAL IN PROGRESS

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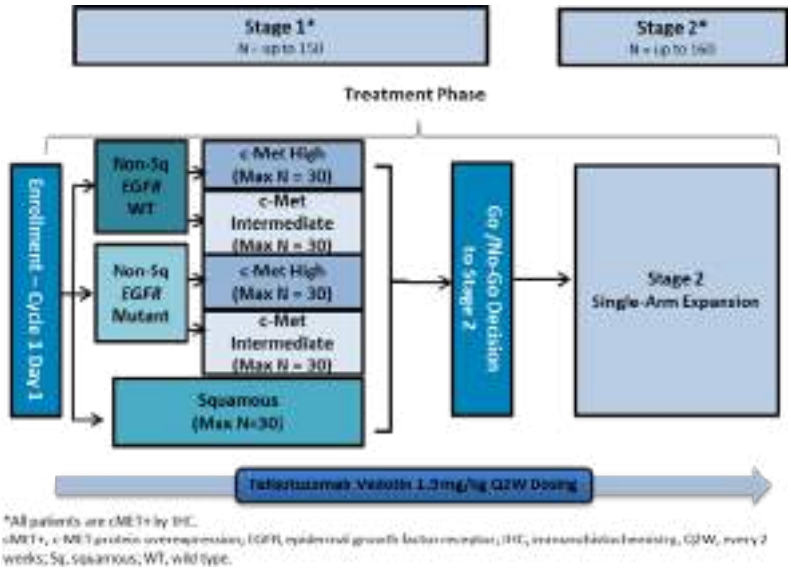
Background: Telisotuzumab vedotin (ABBV-399; teliso-v), an anti–c-Met antibody-drug conjugate, demonstrated favorable antitumor activity in a phase 1/1b trial (NCT02099058) in patients with non-small cell lung cancer (NSCLC) and c-MET protein overexpression (c-MET+). Evidence from this study supported additional analysis of teliso-v in patients with c-MET+ NSCLC. Herein, we describe the first phase 2 study of teliso-v. The aim of this study is to evaluate the potential activity and safety profile of teliso-v as a later line of therapy in a biomarker-selected population(s) of patients with NSCLC. **Method:** This is a 2-stage (Figure) multicenter, non-randomized, single-arm phase 2 study (NCT03539536) in patients (≥18 years; Eastern Cooperative Oncology Group performance status 0–1) with c-MET+ locally advanced or metastatic histologically confirmed NSCLC. Stage 1 is designed to identify the target c-MET+ NSCLC population(s) best suited for teliso-v therapy in the second- or third-line setting using a novel multifactor Bayesian hierarchical model. In Stage 2, the group(s) that demonstrate promising results during Stage 1 will be expanded in a single-arm cohort to further evaluate teliso-v efficacy in the selected population(s). Teliso-v will be administered intravenously at a dosage of 1.9 mg/kg every 2 weeks until disease progression/intolerable toxicity. The primary endpoint is overall response rate according to Response Evaluation Criteria In Solid Tumors version 1.1. Secondary endpoints include duration of response, disease control rate, duration of disease control, progression-free survival, overall survival, safety, and tolerability. Pharmacokinetic samples will be collected pre-treatment and at specific timepoints during the study. Tumor samples will be collected pre-treatment for biomarker analysis. The trial is active, with the first patient screened on 11/05/2018. As of 3/11/2019, 13 centers in 5 countries have enrolled 3 patients.



Result: Section not applicable **Conclusion:** Section not applicable

Keywords: c-MET protein, antibody-drug conjugate, Non-Small Cell Lung Cancer

P2.01-20 ANLOTINIB VS. DOCETAXEL IN ADVANCED NON-SQUAMOUS NSCLC (EGFR WILD-TYPE) AFTER PROGRESSION ON PLATINUM-BASED CHEMOTHERAPY: A TRIAL PROTOCOL

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Background: Anlotinib, an oral VEGFR, FGFR, PDGFR and c-Kit tyrosine kinase inhibitor, showed significantly longer overall survival in a phase 3 trial. In the multi-center, open-label, randomized controlled ALTER-L023 trial, we compared anlotinib with docetaxel as second-line treatment in patients with advanced non-squamous EGFR wild-type non-small cell lung cancer (NSCLC) previously given platinum-based doublet chemotherapy. **Method:** This multi-center, open-label, randomized controlled ALTER-L023 trial was conducted at 10 hospitals in China. Eligible patients with previously treated non-squamous EGFR wild-type NSCLC were randomly assigned (1:1) to receive anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) or docetaxel (75mg/m2, on day 1 of a 21-day cycle) till progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS), that was defined as the time from randomization to disease progression or death. The secondary endpoints included objective response rate, disease control rate, duration of response and safety. Based on a two-sided log-rank test at 5% significance level, a power of 80% and a median PFS of 6 months for anlotinib versus 3 months for docetaxel,the simple size was estimated at 77 patients. Allowing for 15% dropouts, the sample size was set at 88 patients (44 patients in both groups). Clinical trial information: NCT03703596 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Anlotinib, non-squamous NSCLC (EGFR wild-type), platinum-based doublet chemotherapy

P2.01-21 EFFICACY AND SAFETY OF COMBING ANLOTINIB AND ERLOTINIB AS A FIRST-LINE THERAPY IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: As a promising multi-target tyrosine kinase inhibitor (TKI), anlotinib hydrochloride significantly improved overall survival (OS) and progression-free survival (PFS) in advanced NSCLC patients in the phase 3 trial ALTER0303. Antiangiogenesis therapy combined with EGFR-TKI has shown excellent efficacy and survival benefits in patients with EGFR mutations. This is the first trial evaluating anlotinib plus erlotinib in treatment-naive advanced NSCLC patients and is one arm of Phase II anlotinib-based trial (NCT03628521). **Method:** Patients with previously untreated, EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC were enrolled. Eligible patients received anlotinib (10 mg QD from day 1 to 14 of a 21-day cycle) combined with erlotinib (at a dose of 150 mg once daily) until disease progression or treatment intolerance. The primary outcome was objective response (ORR) and secondary outcomes were PFS, disease control rate (DCR) and OS. **Result:** Until the 21st March 2019, 26 patients were enrolled. All are under treatment and 17 have received at least one tumor assessment. Among these patients, fifteen of them achieved PR (9 confirmed, the rest waiting for next assessment), two of them achieved SD and no patient developed to disease progression. The objective response rate was 88.2 % while the disease control rate was 100 %.The most common Grade 3 TRAE were rash (15.38 %), oral mucositis (11.54%) and albuminuria (7.69 %), and no grade 4/5 observation. **Conclusion:** The combination of anlotinib and erlotinib showed the promising efficacy for previously untreated, EGFR mutation–positive advanced NSCLC patients with a manageable safety profile. Table 1: Response rates

Response	Assessed
CR	0
PR	15/17(88.2%)
SD	2/17(11.76%)
PD	0
ORR, n/N(%)	15/17 (88.2%)
DCR, n/N(%)	17/17 (100.0%)

Keywords: combination of anlotinib and erlotinib, NSCLC, first-line therapy

POSTERS

P2.01-22 ORCHARD: A PHASE II PLATFORM STUDY IN PATIENTS WITH ADVANCED NSCLC WHO HAVE PROGRESSED ON FIRST-LINE OSIMERTINIB THERAPY

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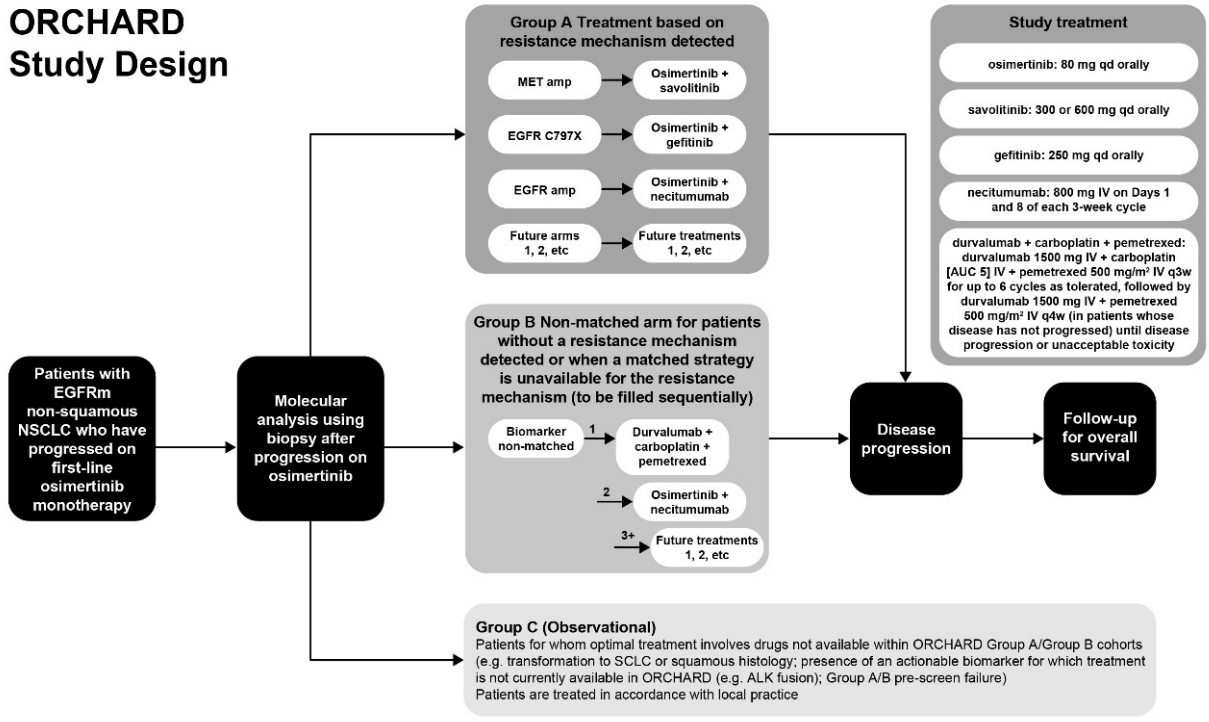
Background: Osimertinib is a third-generation, central nervous system (CNS)-active, irreversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that potently and selectively inhibits both EGFR-TKI sensitising mutations (EGFRm) and EGFR T790M. First-line osimertinib has demonstrated superiority in progression-free survival (PFS) compared with first-generation EGFR-TKIs in patients with EGFRm advanced NSCLC (Soria et al, NEJM 2018). The most common resistance mechanisms to first-line osimertinib identified from plasma samples are MET amplification (15%) and EGFR C797S (7%) (Ramalingam et al, Ann Oncol 2018). Further clinical studies are needed to better understand resistance mechanisms and evaluate post-progression targeted treatment options. **Method:** ORCHARD is an open-label, multicentre, biomarker-directed, Phase II platform study evaluating the optimal treatment for individual patients with EGFRm NSCLC depending on their underlying resistance mechanism to first-line osimertinib. Adult patients with EGFRm locally advanced/metastatic NSCLC and radiological progression on first-line osimertinib monotherapy will be eligible. Treatment assignment will be based on molecular characterisation of the tumour at progression from a mandatory tissue biopsy. ORCHARD will comprise of three groups assigned by tumour molecular profile (Figure). An adaptive design allows addition of new treatments based on emerging findings. Tumour assessments (RECIST 1.1) will be performed every 6 weeks for the first 24 weeks and every 9 weeks thereafter until progression. An interim analysis of each cohort will be performed when ≈16 patients have reached the second on-treatment RECIST assessment. Based on preliminary signals, the cohort may be stopped or expanded to 30–40 patients for further evaluation. The primary outcome is investigator-assessed objective response rate; secondary outcomes include PFS, duration of response, overall survival, and pharmacokinetics of each treatment module, evaluated independently. Exploratory outcomes include tumour and plasma biomarker and resistance analyses, and correlation between biomarker profiles and treatment effect. Safety data will also be reported.



ALK, anaplastic lymphoma kinase; amp, amplification; AUC, area under curve; EGFR, epidermal growth factor receptor; EGFRm, EGFR-tyrosine kinase inhibitor (TKI) sensitising mutation; IV, intravenous; MET, hepatocyte growth factor receptor (HGFR); NSCLC, non-small cell lung cancer; q3(4)w, once every 3(4)-week cycle; qd, once a day; SCLC small cell lung cancer

Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Osimertinib, NSCLC, resistance

POSTERS

P2.01-23 DUBLIN-3, A PHASE (PH) III TRIAL COMPARING THE PLINABULIN (P)/DOCETAXEL(D) COMBINATION WITH D ALONE IN STAGE IIIB/IV NSCLC

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Background: In 2018, practice patterns changed in untreated metastatic NSCLC, as platinum-based chemotherapy (Chemo) started to be combined with pembrolizumab. Prior to 2018, checkpoint inhibitors (C-I) were given sequentially with Chemo. In C-I refractory metastatic NSCLC, single agent D is standard of care. Although effective, D induces AEs (Neutropenia (N) that may require dose reduction to sub-therapeutic levels. The addition of Plinabulin (P) to D (D+P) reduced D-induced grade 4 (Gr4) N (frequency of 33% vs 5% for D vs D+P; p<0.0003) and thrombocytopenia (P<0.02) vs D alone (Blayney ASH 2018; IASLC 2018) in Ph 2. Importantly, P added to D improved median overall-survival (OS) with 4.6-month, and duration of response (DoR) with 1-year (p<0.05) vs D alone (Mohanlal ASCO-SITC 2017) in pts with a measurable lesion (per RECIST 1.1) located in the lung. P induces Dendritic Cell (DC) maturation and CD40 upregulation and facilitates DC-dependent T-cell proliferation in an antigen (Ag) specific manner (Lloyd AACR 2016). Therefore, P is predicted to be the most effective in a setting that harbors novel Ags, that can stimulate the immune system. Subclonal lung lesions can induce novel Ags (De Bruin Science 2014), but clonal lung lesions can also harbor Ags that can stimulate the immune system, as long as immune tolerance is not yet developed. There is a high concordance in mutation status (thus Ags) between clonal primary and metastatic lesions in NSCLC (Sherwood J Exp & Clin Canc Res 2015), but the distant lesions had more time to induce immune tolerance development. Hence, we required the presence of measurable lesion present in the lung in DUBLIN-3. We combined P with D since D can release Ags which in turn can be presented by P-modulated DCs to cytotoxic CD8 T-cells. **Method:** DUBLIN-3 (NCT02504489), is an ongoing global PhIII study in EGFR wild-type advanced or metastatic NSCLC pts (target n=554) receiving 2nd- or 3rd-line systemic therapy with D+P or D in a 1:1 ratio. The primary endpoint is OS. Key secondary endpoints are incidence of Gr 4 N on day 8 of Cycle 1, D dose modification due to N, QoL (EORTC QLQ-C30), ORR, PFS, and DoR. The study is single-blinded (for pts) to more reliable allow for QoL assessments. Pts must have at least one measurable lesion located in the lung and must have failed a prior platinum-based regimen. Prior PD1/PD-L1 use is allowed. A pre-specified first Interim Analysis (IA) occurred at reaching ~150 events and a second pre-specified IA is to occur at ~ 300 events. **Result:** ~400 patients have been enrolled to date with more than 200 events achieved. Based on the data at the 1st IA, the study will continue, unmodified, to the 2nd IA. **Conclusion:** The D+P combination holds the promise of a novel 2nd or 3rd line treatment option with superior efficacy and safety over D alone. The 2nd IA of DUBLIN-3 is expected to occur later in 2019.

Keywords: NSCLC, Plinabulin/Docetaxel Combination, PD1-Failures

P2.01-24 CANOPY-2: PHASE 3 STUDY OF CANAKINUMAB PLUS DOCETAXEL AS SECOND/THIRD LINE THERAPY IN LOCALLY ADVANCED/METASTATIC NSCLC

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Background: Pembrolizumab, a PD-1 inhibitor combined with platinum-based chemotherapy is standard first-line therapy for eligible patients without a targetable mutation, stage IIIB/IV NSCLC. Currently, there is no data to guide treatment following progression on sequential/concomitant use of platinum-based chemotherapy and PD-1 inhibitors. Activation of inflammation and elevated baseline C-reactive protein (CRP) levels are associated with lower response/resistance to immunotherapies. Canakinumab is a high-affinity anti-IL-1β monoclonal antibody that demonstrated a significant reduction in incidence of fatal and nonfatal lung cancer in patients with increased CRP levels (CANTOS study). **Method:** CANOPY-2 (NCT03626545) is a multicenter, phase 3 study evaluating safety and efficacy of docetaxel ± canakinumab in patients with squamous/non-squamous, stage IIIB-IV NSCLC. This study includes a safety run-in part (part 1 – open label) to confirm recommended phase 3 regimen (RP3R) to be used in randomized phase 3 part (part 2 – double blind, placebo-controlled). Key inclusion criteria: adult patients pretreated with one prior platinum-based chemotherapy and one prior PD-(L)1 inhibitor therapy for locally advanced/metastatic disease, either together/sequentially and then progressed; ECOG PS 0-1. In part 1, ~9 patients will be enrolled to have at least 6 evaluable patients and ~226 patients will be randomized (1:1, stratified by number of prior lines of therapy and histology) in part 2 to docetaxel ± canakinumab. Primary objectives: to confirm RP3R of canakinumab + docetaxel, as determined by incidence of DLTs in first 42 days of administration (part 1) and overall survival (part 2). Secondary objectives are to assess efficacy (overall response rate, disease control rate, duration of response, time to response, progression-free survival by investigator per RECIST v1.1), safety, pharmacokinetics, immunogenicity of canakinumab, and patient reported outcomes. Enrollment is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Canakinumab, Docetaxel, IL-1β

P2.01-25 TOURIST: THORACIC UMBRELLA RADIOTHERAPY STUDY IN STAGE IV NSCLC: A PHASE III RANDOMIZED TRIAL IN DEVELOPMENT

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Background: Non Small Cell Lung Cancer (NSCLC) is the leading cause of cancer mortality throughout the world with an incidence exceeding 1.2 million. 70% of NSCLC patients present with incurable disease with treatment aimed at alleviating symptoms, maintaining / improving quality of life as well as prolonging survival. In the last decade there have been dramatic changes in systemic therapy (chemotherapy, immunotherapy, Tyrosine kinase Inhibitors (TKIs)). Despite these advances, many patients suffer from lororegional symptomatic relapse. This may benefit from local radiotherapy in addition to other standards of care such as symptom control. Radiotherapy remains widely used in the management of stage IV NSCLC but strategies vary hugely because the data originates from a series of dose fractionations trials in the 1990s when systemic therapy options were limited. There is therefore limited evidence regarding the use and place of palliative radiotherapy in conjunction with modern systemic treatments and there is a need to assess benefits of advanced radiotherapy techniques in this population. The TOURIST trial aims to establish the utility of palliative thoracic radiotherapy in the primary treatment of stage IV NSCLC. **Method:** This is a phase III platform that currently has 2 study arms, to cover the needs of differing patient populations, defined by the use of first line systemic therapy. Study 1 (PRINCE) Patients receiving first line systemic therapy as standard of care, who have not progressed after 2-4 cycles are randomised 1:1 to either high dose palliative radiotherapy to the thorax, or to no radiotherapy while continuing on their standard systemic therapy. Co-primary endpoints: overall survival, PROMs recorded QOL, with progression free survival and time to next line of therapy, as secondary endpoints. Study 2 (QUARTZ Lung) Asymptomatic patients unsuitable for standard systemic therapy randomised 1:1 to low dose palliative radiotherapy dose to the thorax or no radiotherapy. Telephone follow up will be used for PROMs data collection to measure QOL improvements. Stratification factors for

both studies will include bulk of thoracic disease, use of advanced radiotherapy techniques and performance status. The TOURIST trial intends to recruit 750 patients and is anticipated to open in 2020. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: advanced non-small cell lung cancer, radiotherapy, trials in progress

P2.01-26 EMPOWER-LUNG 3: PHASE 3 STUDY OF COMBINATIONS OF CEMIPLIMAB AND CHEMOTHERAPY IN FIRST-LINE TREATMENT OF ADVANCED NSCLC

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Background: Most patients (pts) with non-small cell lung cancer (NSCLC) present with advanced disease at the time of diagnosis. Until recently, platinum-based doublet chemotherapy regimens were the standard of care first-line treatment for pts with advanced NSCLC whose tumors lack an *EGFR*, *ALK*, or *ROS1* mutation. Despite chemotherapy, patients with metastatic NSCLC had a median overall survival (OS) of 8 to 12 months and a 5-year survival rate of approximately 18%. With the introduction of programmed cell death-1 (PD-1) inhibitors to NSCLC, this prognosis has improved. Cemiplimab, a human PD-1 monoclonal antibody, has exhibited antitumor activity and safety in a Phase 1 trial of advanced malignancies including NSCLC and was approved recently in the US as cemiplimab-rwlc for advanced cutaneous squamous cell carcinoma (CSCC). Based on their unique modes of action, combining cemiplimab with platinumbased chemotherapy has the potential for a synergistic effect in pts with advanced NSCLC of both histologies and irrespective of PD-L1 expression. **Method:** EMPOWER-lung 3 is a randomised, global, two-part, Phase 3 study of first-line treatment of pts with advanced squamous or non-squamous NSCLC (NCT03409614). Part 1, as previously described (IASLC 19th WCLC; Abstract 13347), is open-label and aims to describe the efficacy and safety of combinations of cemiplimab, ipilimumab, and platinum-based doublet chemotherapy in pts whose tumors express PD-L1 in <50% of the tumor cells. The updated primary endpoint of Part 1 is objective response rate. Here we introduce the recently added Part 2. This part is double-blinded and will compare the efficacy and safety of cemiplimab versus placebo, both in combination with investigator's choice of standard chemotherapy, in all pts irrespective of PD-L1 expression status. Chemotherapy options include: paclitaxel + carboplatin or cisplatin for squamous cell NSCLC and pemetrexed + carboplatin or cisplatin for non-squamous NSCLC. The investigator may choose from one of these regimens provided that it is consistent with the local standard-of-care. Pts will be randomized (2:1) to cemiplimab 350 mg Q3W plus up to four cycles of chemotherapy or placebo Q3W plus up to four cycles of chemotherapy. Pts will be stratified by histology and PD-L1 expression levels. The co-primary endpoints for Part 2 are OS and progression-free survival (PFS). **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: non-small-cell lung cancer, Anti-PD-1, cemiplimab

P2.01-27 APPARENT DIFFUSION COEFFICIENT (ADC) CHANGE ON REPEATED DIFFUSION-WEIGHTED MRI DURING CHEMOTHERAPY FOR STAGE IV LUNG NSCLC

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Background: Diffusion-weighted magnetic resonance imaging (DWI) depicts the random Brownian movement of water molecules in biological tissues. The net displacement of these molecules diffusing across an area of tissue per second is the apparent diffusion coefficient (ADC). ADC has proven useful in detection, characterization and treatment response monitoring of malignant diseases and is used routinely in the investigation of cancer of the prostate. The role of MRI in the follow up of treated lung cancer remains unclear. Previous publications have suggested that it could function as a biomarker in chemoradiotherapy treated NSCLC. Very little has been published about chemotherapy treated tumours. **Method:** 20 patients with stage IV adenocarcinoma were enrolled between September 2014 and April 2017. They received treatment with carboplatin/placitaxel and bevacizumab (7,5mg/kg) with maintenance bevacizumab if response. Two patients, in whom the lesion proved to be too small to measure (<2ml), were excluded. Characteristics of the remaining 18 patients: 8 f/10m, median age 69 (51 -77), median survival 9 month (1-NR, follow up 60months) and median time to treatment failure 6 month (1-37). DWI was performed at baseline, 2w, 4w and 16w. Four patients did not participate in the full study program. Two examinations were incomplete due to technical problems, and 8 MRI examinations were excluded due to the tumors becoming too small in size (<2ml). A total of 57 MRI examinations were included. **Result:** The ADC value at baseline varied between 950 and 1584mm2/s (median 1228). ADC values both increased and decreased during treatment (% change at week 2 range -11 to 24%, at w4 -14 to 34%, at 16 w -27 to 10%). The evolution of the ADC values at the different timepoints did not show any statistical significant increase or decrease (using Mean Comparison with Student t's test, Prob>Chisq 0,2159). Proportion Hazard analysis did not show any statistical correlation between the baseline ADC value, the change in ADC value and overall survival, nor between ADC values, change in ADC values and time to treatment failure. **Conclusion:** Repeated MRI in lung cancer is feasible. The clinical value of ADC measurements in the follow up of chemotherapy treated lung cancer needs further investigations.

Keywords: MRI, DWI, Bevacizumab

P2.01-28 THE PREDICTIVE FACTOR FOR PROLONGED AIR LEAKAGE OVER 48 HOURS USING LOG DATA OF DIGITAL DRAINAGE SYSTEM

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Background: Air leakage is one of the most common complications after pulmonary resection and many risk factors of air leakage have been reported in the past. However, there are few studies about the objective predictive factors. Digital drainage system (DDS) has enabled us to measure the flow of air leakage after pulmonary resection objectively and quantitatively. We aimed to elucidate the predictive factors of prolonged air leakage (PAL: continuing air leakage over 48 hours) after surgery using the log data of DDS. **Method:** The presence of air leakage was defined as being 20ml/min or more and/or spike in the flow on DDS. Chest tubes were removed at the time of continuing for 8 hours at less than 20ml/min and pleural effusion of less than 300ml/day. The 593 patients underwent pulmonary resection and monitored by DDS postoperatively from May 2016 to January 2018. The 92 patients had air leakage at the time of transferring to intensive care unit or recovery room (postoperative air leakage: POAL). The log data of these 89 patients were analyzed retrospectively and We examined their characteristics using univariate and multivariate manners in logistic regression analysis. **Result:** The median age at the time of pulmonary resection in these 89 patients (72 men and 17 women) was 72 years (range, 40 to 86 years). The 75 patients (84%) had smoking history. The 17 patients (19%) had diabetes mellitus. The 49 patients (55%) had emphysema. Surgical procedures were a lobectomy in 71 patients, a segmentectomy in 4 patients, and a wedge resection in 14 patients. Fibrin glue was used during surgery in 45 patients (51%). The mean flow of POAL was 70.4 ml/min (range, 20.2-1267.9). The mean duration of air leakage was 60 hours (range, 9-257). In univariate analysis, diabetes mellitus (DM, p=0.0284, OR; 3.450), use of fibrin glue (p=0.0452, OR; 0.411), and POAL (p=0.0101) were statistically significant. In the final multivariate model, DM (p=0.0441) and flow of POAL (p=0.0228) were independently associated with PAL. In ROC curve, considering less than 20% false positive rate, the optimal cutoff in patients with DM was 100ml/min (sensitivity; 67%, specificity; 82%). The optimal cutoff in patients without DM was 150ml/min (sensitivity; 53%, specificity; 84%). **Conclusion:** The POAL flow of 150ml/min or more in patients without DM and that of 100 ml/min or more in patients with DM will be likely to develop PAL with high probability. Pleurodesis may be considered earlier for this population.

Keywords: prolonged air leakage, digital drainage system

P2.01-29 THE CORRELATION BETWEEN K-RAS MUTANT SUBSETS WITH TP53 MUTATION AND PD-L1 IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Despite its role in non-small cell lung cancer (NSCLC), K-ras gene mutations are considered is a non-targetable with no established predictive value. And so far, programmed death ligand-1 (PD-L1) is the only approved predictive marker for immunotherapy in NSCLC patients and has been associated with smoking, while TP53 mutations has been linked to neoplasms with aggressive nature. Meanwhile, K-ras mutation has been identified with smoking and linked to aggressive NSCLC. Accordingly, we hypothesized that k-ras mutant NSCLC has higher PD-L1 expression which suggests an improved response to immunotherapy in these patients. **Method:** The CARIS database from 2016 - 2018 was queried and patients with NSCLC were identified. PD-L1 antibody 22c3 ≥1% was considered positive. PD-L1 expression as well as k-ras and TP53 mutation status were analyzed and correlation between different variables were identified using ANOVA. **Result:**

Table 1: showing the percentage expression of PD-L1 in each K-ras mutation subtype

K-ras mutation sub-type	PD-L1 negative (n,%)	PD-L1 positive (n,%)	Total (n,%)
G12V	205 (20.8%)	239 (18%)	444 (19.2%)
G12D	142 (14.4%)	194 (14.6%)	336 (14.5%)
G12A	56 (5.7%)	72 (5.4%)	128 (5.5%)
G12C	337 (34.2%)	566 (42.7%)	903(39.1%)
G13C	51 (5.2%)	46 (3.5%)	97 (4.2%)
Q6H	54 (5.5%)	67 (5.1%)	121 (5.2%)
G12R	18 (1.8%)	18 (1.4%)	36 (1.6%)
G12S	18 (1.8%)	16 (1.2%)	34 (1.5%)
Non-Specified	104 (10.6%)	108 (8.1%)	212 (9.2%)
Total	985 (100%)	1326 (100%)	2311 (100%)

We identified 8,471 patients with NSCLC. TP53 mutation was detected in 66% where k-ras mutation in 26.9%. Combined K-ras and TP53 mutations was detected in 12% where 71.48% were PD-L1 positive in this combined category. There was female predominance with a female to male ratio of 1.4:1. We looked for the eight main K-ras mutation subsets and G12C was the most common identified mutation. G12C was associated with a higher occurrence of PD-L1 positivity (42.7%), followed by G12V (18.0%) with a significant difference in PD-L1 expression among K-ras mutations subtypes with P value of 0.004. (table 1). PD-L1 expression in wild type K-ras tumors was 69.4% and although high, wild type K-ras cases showed higher percentage of PD-L1 expression negativity (76.2%). **Conclusion:** Patients with G12C, amongst other k-ras mutation subsets, have higher occurrence of PD-L1 expression which is suggestive of improved response to immunotherapy. The subset of combined K-ras and p-53 mutations showed 71.48% positive PD-L1 expression.

Keywords: PD-L1, NSCLC, K-ras

P2.01-30 HEPATITIS B INFECTION OR AMINOTRANSFERASE INCREASE ASSOCIATE WITH POOR OUTCOME OF ANTI-PD-1 MONOTHERAPY IN PATIENTS WITH ADVANCED NSCLC

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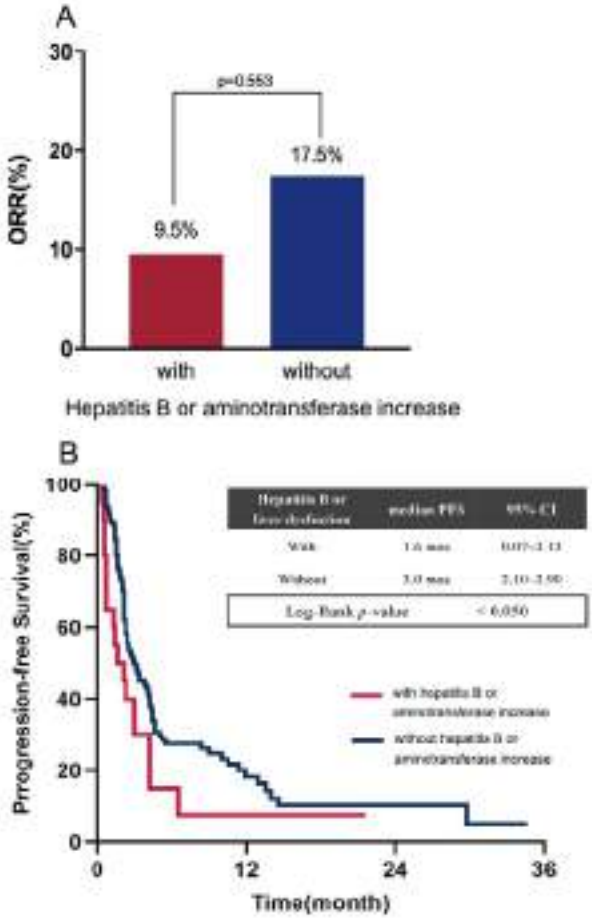
Background: Previous study demonstrated that the existence of liver metastases at the commencement of immunotherapy was associated with poor response. Since hepatitis B infection and liver dysfunction were higher prevalent in China, this study aimed to investigate the efficacy and safety of PD-1/PD-L1 inhibitor in Chinese NSCLC patients with hepatitis B infection or liver dysfunction. **Method:** We retrospectively collected the patients who were diagnosed with non-small cell lung cancer and received anti-PD-1 monotherapy at Shanghai Pulmonary Hospital, Tongji University School of Medicine, China, from January 2016 to February 2019. Detailed clinicopathologic characteristics, therapeutic outcomes, hepatitis biomarker test and liver function test were collected. **Result:** 135 patients were enrolled with 73(54.1%) aged <65 years old. Among them, 113(83.7%) were male, 84(62.2%) were smoker, 57(42.2%) were squamous, 69(44.4%) received anti-PD-1 monotherapy (Pembolizumab n=28, Nivolumab n=21) as 2nd line setting, 5(3.7%) patients had hepatitis B infection and 17(12.6%) had increased ALT or AST. The baseline characteristics such as age, gender, smoking status, histology, PD-1 mono-antibodies, line of therapy was similar between hepatitis infection or liver dysfunction group vs. normal group. Hepatitis infection or liver dysfunction group had a lower ORR (9.5% vs. 17.5%, p=0.553, Figure A), significantly shorter PFS (1.6 months vs. 3.0 months, p<0.050, Figure B) when compared with these patients without. Out of the 22 patients with hepatitis or increase transaminase, 35.7% deteriorated the grading of alanine or aspartate aminotransferase increased.



Conclusion: NSCLC patients with hepatitis B infection or increased transaminase showed a high incidence of hepatic disfunction and poor outcome to anti-PD-1 monotherapy.

Keywords: Hepatitis B infection, Immunotherapy, aminotransferase increase

POSTERS

P2.01-31 PRELIMINARY RESULTS OF SECOND GENERATION ALK INHIBITOR PLB1003: A PHASE LA STUDY

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Background: ALK rearrangements have been described in approximately 4-5% of patients with non-squamous non-small cell lung cancer (NSCLC). Crizotinib is initially effective in the treatment of ALK-rearranged NSCLC, but the disease eventually progresses. PLB1003, a high-efficiency second generation ALK inhibitor, was developed due to the increased resistance of EML4-ALK fusion genes. Preclinical data show that PLB1003 is safe and effective in cell-based assays and Crizotinib-resistant animal models. This is the ongoing phase Ia study of PLB1003. **Method:** An open-label, multicenter phase I clinical trial was conducted in patients with locally advanced or metastatic NSCLC who had previously failed or were intolerable to Crizotinib or chemotherapy. It consisted of dose-escalation cohorts and dose-expansion cohorts. In the dose-escalation cohorts, patients were orally given 50-500mg/d of PLB1003 at 6 dose levels . In each cohort, patients' plasma were collected for pharmacokinetic evaluation. The safety, tolerability, pharmacokinetics, maximum tolerated dose (MTD), dose limiting toxicities (DLT) and recommended phase 2 dose (RP2D) of PLB1003 were determined. **Result:** A total of 21 patients were enrolled in dose-escalation cohorts as of 31 August 2018. The dose-escalation cohort is ongoing at the dose of 200 and 250 mg BID. A lipase elevation of DLT event was observed at 250 mg BID. MTD has not been reached in this study. Additionally, the most common treatment-emergent adverse events (TEAEs) (>10%) were grade1/2, including: (1) gastrointestinal toxicities: diarrhea (24%), vomiting (14%); (2) hepatotoxicity: increased GGT (g-glutamyltransferase) (48%), increased ALP (33%), elevated ALT (43%) and AST (33%); (3) others: increased blood glucose level (43%), hyperuricemia (24%), increased creatinine (19%), anemia (19%), hypercholesterolemia (14%). All the treatment-related adverse events (TRAEs) were reversible. TRAEs of grade 3, increasing of GGT (-glutamyl transferase) (33%), alkaline phosphatase (10%) and lipase (10%), mostly appeared during 7-13 weeks of initial study. Patients all recovered from TRAEs of grade 3 with symptomatic treatments. Among the 14 evaluable patients in ≥200mg/d cohorts, 10 patients had PR (71%), 2 patients had SD (14%), and the disease control rate (DCR) was 86%. Among the 7 patients who progressed with previous treatment of Crizotinib, 5 patients had PR (71%), 1 patient had SD (14%), and the DCR was 86%. **Conclusion:** PLB1003 is safe, tolerable and has potential clinical benefit to locally advanced or metastatic NSCLC patients with ALK rearrangement mutation and had disease progression or were intolerable to previously treatment of Crizotinib or chemtherapy. (ClinicalTrials.gov number, NCT03130881)

Keywords: Non-small cell lung cancer (NSCLC), advanced anaplastic lymphoma kinase (ALK), lung adenocarcinoma

P2.01-32 THE IMPACT OF SEGMENTECTOMY VERSUS LOBECTOMY ON PULMONARY FUNCTION OF PATIENTS WITH NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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Background: Lobectomy with lymph node dissection is considered the standard surgical procedure for non-small cell lung cancer (NSCLC). Recently segmentectomy has been regarded as an alternative in early peripheral NSCLC owing to its theoretical advantages of lung function preservation. However, Segmentectomy presents some oncological risk. Thus, we performed a meta-analysis with the aim of evaluating whether segmentectomy offers an advantage in lung function preservation compared with lobectomy. **Method:** We searched and retrieved studies from four databases. Postoperative results and lung functional index and were synthesized. The odds ratio (OR) or Standard Mean Difference (SMD) and its 95% CI were calculated using a random effects model. Subgroup division was conducted according to different time points. Single-arm meta-analysis for lung function of each visit time was conducted. Repeated-measures analysis of variance (ANOVA) was used to compare the lung function between each visit. **Result:** A total of 16 eligible studies including 6,098 patients were recruited. Two groups showed no significant difference based on baseline characteristics before surgery between groups (Segmentectomy and Lobectomy). Segmentectomy correlated with a greater postoperative preserved pulmonary function than Lobectomy in FVC (SMD=0.23, p=0.009) and FEV1 (SMD=0.27, p=0.002), especially within 12 months after surgery. ANOVA showed no difference between FVC (p=0.647) and FEV1 (p=0.468) of the two groups according to visit time. The segmentectomy group showed no significant difference of postoperative complications compared with the Lobectomy groups(OR=0.95, p=0.618) and the recurrence rates were similar between groups (OR=0.90, p=0.644). **Conclusion:** Segmentectomy offers a better short-term but similar long-term lung functional preservation compared with Lobectomy, with similar surgical and oncological safety.

Keywords: segmentectomy, lobectomy, Non-Small Cell Lung Cancer

P2.01-33 SURVIVAL BENEFIT OF DEPLETING HIGH SERUM EGF CONCENTRATION IN ADVANCED NSCLC PATIENTS AS SWITCH MAINTENANCE THERAPY

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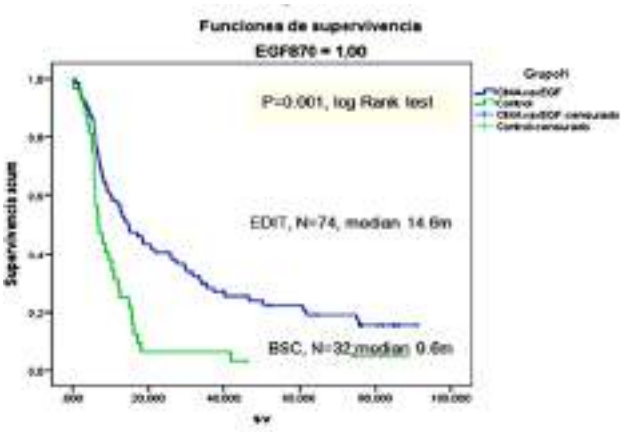
Background: Serum EGF depleting immunotherapy (EDIT) with CIMAvax-EGF has shown to be safe and effective in the treatment of advanced NSCLC patients after first line of treatment with platinum based chemotherapy. The rationale of its use is to create an immune response against circulating serum EGF and by doing this prevent its binding to EGFR. Previous studies have shown that serum EGF levels above 870 pg/mL and response to chemotherapy (at least stable disease) are independent predictors of the response to EDIT. In this study we aimed to better estimate the benefit of this therapy in the population of first line responders with high basal serum EGF concentration **Method:** To know the benefit of EDIT in overall survival compared to Best Support Care in this selected population, we pooled data data from three late stage clinical trials of CIMAvax-EGF in patients with advanced NSCLC (IC RD-EC056, IC RD-EC081, and IC RD-EC0120) after First Line Platinum based chemotherapy. The main outcome was overall survival. **Result:** Out of 523 patients included in the study, 484 were responders (at least stable disease) to FLC. sEGF concentration above 870 pg/mL was measured in 106 patients, (74 and 32 in the EDIT and Control group, respectively). All 106 patients carrying these two protective distinctive features were included in the analyses. A significant benefit in median overall survival was found (14.6 m vs 9.6 m, p=0.001; 5 y survival rate: 22% vs 3%) favouring EDIT therapy.



Conclusion: EGF Depleting Immunotherapy (EDIT) induces a survival benefit as Switch Maintenance in avanced NSCLC patients with high serum EGF concentration.

Keywords: EDIT, NSCLC,Immunotherapy, s EGF depleting therapy, Non Small Cell Lung Cancer, Immunotherapy

POSTERS

P2.01-34 ENDOSTAR COMBINED WITH WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH NSCLC BRAIN METASTASES

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Background: Brain metastasis (BM) is the leading cause of poor prognosis, recurrence, and death in non-small-cell lung cancer (NSCLC) patients. The effectiveness of whole-brain radiotherapy is unsatisfactory. Endostar was reported as an anti-angiogenic agent, which could promote vascular normalization in tumor. This study is to investigate the influence of endostar combined with cranial radiation to survival, cerebral blood flow, immune status and quality of life of the patients. **Method:** 28 NSCLC patients with multiple brain metastasis(more than four)were randomly divided into two groups. The experimental group (n = 14) received WBRT (30Gy/10F) combined with Endostar (15mg/m2, 7days), and the control group (n=14) received WBRT (30Gy/10F) alone. Tumor progression and survival of the patients were established by certified oncologists based on whole brain MRI scan. Magnetic resonance perfusion imaging was carried out pre- and one month post-radiation to detect regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), mean transit time (MTT) and transit time to peak (TTP) of the contrast medium. The changes of blood T lymphocyte subpopulation, the cognitive function and overall healthy level were evaluated pre- and post- radiation every two months against the MMSE, MoCA and EORTC QLQ-C30 scales. **Result:** The median progression free survival (mPFS) was 211 days vs. 84 days (*P*=0.2204), while the median intracranial PFS (miPFS) was 333 days vs. 192 days (*P*=0.1882) and the median extracranial PFS (mePFS) was 311 days vs. 84 days (*P*=0.0873) between the Endostar group vs. the control group, but neither with significant difference, may for the limit of sample size. Moreover, compared with the control group, rCBF of the lesion in the Endostar group decreased more evidently (-69.0286±87.4532 *vs.* -25.3444±233.4, *P*=0.6158), rCBV decreased slightly (-13.1286±389 *vs.* -510.8±800.1, *P*=0.1545), MTT increased (69.0571±1190.7 *vs.* -483.3±1885.1, *P*=0.5108) and TTP increased (156.6±1232.8 *vs.* 102.1±864.1, *P*=0.9185), indicating that endostar group had a better control of the cerebral perfusion and the tumor. The T lymphocyte subpopulation increased in the Endostar group, especially the CD3+CD8+ T lymphocyte but without significant difference compared with the control group(*P*=0.1447). At the same time, after cranial radiation, the cognitive function, physical, role, social and emotional functions improved in the endostar group, while a small fluctuation in the control group with significant difference(*P*<0.05). **Conclusion:** Our study showed that endostar could improve survival of the patients, adjust cerebral perfusion and promote control of lesions, ameliorate the immune status, while improve cognitive function and quality of life of the patients at the same time.

Keywords: Brain metastases, endostar, brain radiotherapy

P2.01-35 ACQUIRED MET-ABERRANCE IS A MECHANISM OF RESISTANCE TO ALK INHIBITORS IN ALK-POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK-TKI) is standard of care in *ALK*-positive advanced non-small-cell lung cancer (NSCLC). Unfortunately *ALK*-positive NSCLC patients treated with ALK TKIs inevitably develop resistance mediated by complex mechanisms including *ALK* mutations, *ALK* amplification, or activation of alternative signaling pathways. However, there are few reports about Mesenchymal-epithelial transition factor (MET) signal in NSCLC. **Method:** Totally 136 *ALK*-positive advanced NSCLC patients were screened for *ALK* rearrangement detected by tumor tissue or plasma Next-generation sequencing(NGS) at the Guangdong Lung Cancer Institute from January 2016 to December 2018 .*MET*-aberrance was defined as c-Met overexpression performed by immunohistochemical(IHC) staining method with SP44 antibody and *MET* amplification assessed by tumor tissue or plasma Next-generation sequencing (NGS) or fluorescent in situ hybridization(FISH). **Result:** Totally 5.89% (8/136) of patients were identified with *MET*-aberrance in 136 *ALK*-rearranged cases. Among the 8 patients,there were 6 with *de novo MET*-aberrance and 2 with acquired *MET*-aberrance.The median progression-free survival (PFS) in *ALK*-rearranged patients with *de novo MET*-aberrance was 9.6 months (95% CI 0.0 to 19.2months).The other 2 patients gained *MET*-aberrance after the treatment with alectinib. Both of them received lorlatinib, but the PFS only lasted for 2months. One achieved partial remission with crizotinib, which was originally developed as an inhibitor of the *MET* gene. **Conclusion:** Acquired *MET*-aberrance maybe a mechanism of acquired resistance to the second-generation ALK-TKIs for *ALK*-rearranged advanced NSCLC patients.

Keyword: non-small-cell lung cancer (NSCLC);MET-aberrance;ALK positive by NGS

P2.01-36 A PILOT STUDY ON CEREBROSPINAL FLUID CELL-FREE DNA SEQUENCING IN LEPTOMENINGEAL METASTASIS FROM NON-SMALL CELL LUNG CANCER

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Background: Leptomeningeal metastasis (LM) is a devastating complication of non-small cell lung cancer (NSCLC) with poor prognosis. It is difficult to determine the genomics alternations and assess the therapeutic responses. The purpose of this study was to detect the cell-free DNA (cfDNA) in cerebrospinal fluid (CSF) from NSCLC patients with LM, and to explore the whole genome and chromosomal alterations information of tumors. **Method:** From 2016 October to 2019 February, a total of 40 lung adenocarcinoma patients with LM were enrolled. Paired 10 ml CSF and 10 ml blood samples were collected before intrathecal chemotherapy. Gene mutations of cfDNA in plasma and CSF were detected by second-generation sequencing (NGS). Three cases of NSCLC-LM CSF cfDNA were sequenced by whole genome sequencing (WGS) to screen chromosome instability (CIN). **Result:**

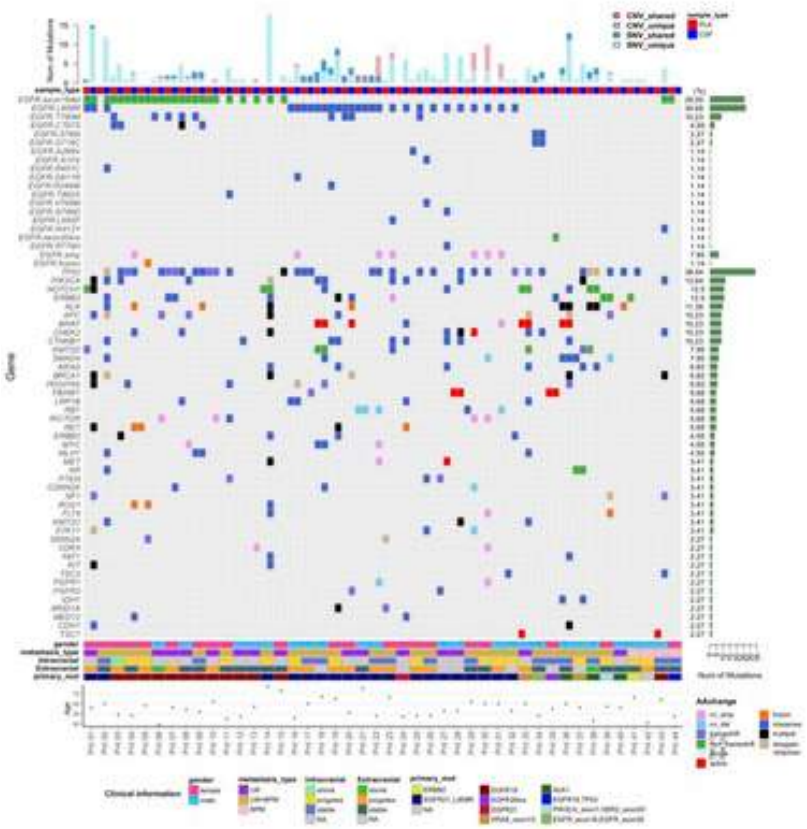

Fig1 Gene mutation landscapes of CSF cfDNA and plasma cfDNA in patients with LM from lung adenocarcinoma

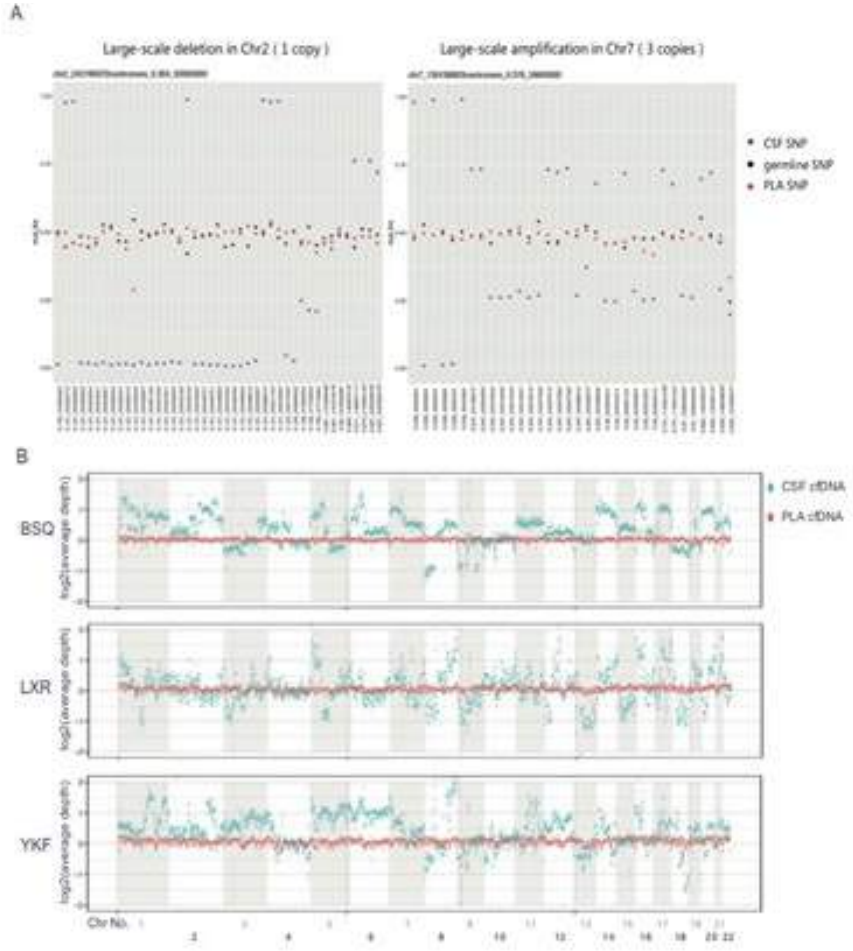

Fig 2 Examples of Chromosome Structural Variation of CSF cfDNA

Among 40 patients with LM from NSCLC, median age was 56 (range, 39-77), 47.8% were female, 85.0% had EGFR mutation, 7.5% ALK rearrangement and 7.5% other activating mutations. Driver genes were detected much higher in CSF cfDNA than plasma cfDNA (100% vs 57.5%). 237 specific genetic mutations were captured in CSF cfDNA, while only 48 specific mutations were detected in plasma. Copy number variations(CNV)were totally identified in CSF cfDNA, however, no CNV was detected in plasma. The three NSCLC-LM CSF cfDNA samples had either short arm deletion on chromosome 8 or short arm amplification on chromosome 5. **Conclusion:** Compared with plasma cfDNA, CSF cfDNA was more sensitive to the detection of LM genomic alterations. We suggest that CSF cfDNA would representative to the LM lesions, it could dynamically monitor the disease progression and guide precision therapies. Whether genome wide doubling (WGD) and CIN can predict overall survival or recurrence risk needs further exploration.

Keywords: cerebrospinal fluid, cell-free DNA, leptomeningeal metastases

POSTERS

P2.01-37 LOWER RISK OF HYPERCOAGULABILITY IN NON-SMALL CELL LUNG CANCER PATIENTS WITH EGFR MUTATIONS

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Background: Hypercoagulability is sometimes observed in cancer patients, including non-small cell lung cancer (NSCLC) patients. Plasma levels of fibrinogen or D-dimer are used as markers for hypercoagulability, and several previous studies have reported that upregulation of these markers are poor prognostic factors in NSCLCs. On the other hand, recent studies have highlighted clinical differences between NSCLCs with EGFR mutation and those without. However, there is no data about the difference in hypercoagulability between NSCLCs with EGFR mutation and those without. **Method:** Between January 2007 to December 2016, 270 surgically resected NSCLC patients received EGFR mutation testing and were included in this study. Plasma fibrinogen and D-dimer levels were examined as one of pre-surgical examinations in all patients. We analyzed the correlation between plasma fibrinogen / D-dimer levels and EGFR mutation status. **Result:** Among 270 patients in our cohort, 123 patients had EGFR mutation and 147 patients were wild type (WT) for the EGFR. In our cohort, plasma fibrinogen level was upregulated in 39 patients, while plasma D-dimer level was upregulated in 75 patients. Plasma fibrinogen was upregulated in 9 patients (7%) and in 30 patients (20%) in EGFR mutation group and in WT EGFR group, respectively (p = 0.0017). Plasma D-dimer was upregulated in 27 patients (22%) and in 48 patients (33%) in EGFR mutation group and in WT EGFR group, respectively (p = 0.049). These correlations were still significant after the adjustment with clinical factors including smoking status, age, and histology. In multivariate analysis, odds ratio and 95% CI in EGFR mutation group for upregulated plasma fibrinogen were 0.40 and 0.17 – 0.94, respectively (p = 0.037). On the other hand, odds ratio and 95% CI in EGFR mutation group for upregulated plasma D-dimer were 0.48 and 0.26 – 0.90, respectively (p = 0.022). **Conclusion:** Plasma levels of fibrinogen and D-dimer were significantly lower in NSCLCs with EGFR mutation.

Keywords: EGFR, NSCLC

P2.01-38 GENE EXPRESSION PROFILING OF CNS METASTASES IN NON-SMALL CELL LUNG CANCER - MATCHED ANALYSES WITH PRIMARY TUMORS

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Background: Dissemination of non-small cell lung cancer (NSCLC) in the central nervous system (CNS) is a frequent and challenging clinical problem. Systemic or local therapies rarely prolong survival and have modest activity regarding local control. Alterations in gene expression in brain metastasis (BM) versus primary tumour may increase aggressiveness and could explain the worse prognosis of brain metastatic NSCLC. **Method:** We identified patients with surgically removed BM from NSCLC in two cohorts. The first cohort consisted of 725 patients with surgically removed NSCLC and the second of 280 patients who had received whole brain radiotherapy during the course of their disease. Gene expression analysis with nanoString PanCancer IO 360 panel was performed in BM and primary tumour samples. A minimum of 50 ng of total RNA was used as input for each sample. Identification of differentially expressed genes was conducted on normalized data using the nSolver analysis software. **Result:** 30 patients with surgically removed BM were identified from both cohorts. For 13 of these patients primary tumour samples were available. We compared gene expressions in BM with primary tumour samples and found a statistically significant downregulation of certain genes, especially genes related to immune response and immune cell activation. Gene expression profiles from BM samples displayed a distinct clustering pattern compared to primary tumour samples. Results from KEGG-term analysis on differentially expressed genes revealed a concomitant enrichment of multiple KEGG-terms associated with the immune system. **Conclusion:** We identified a unique gene downregulation pattern in BM samples compared to primary tumour. This finding may explain the lower clinical efficacy of systemic therapy, especially immunotherapy, in BM of NSCLC patients.

Keyword: brain metastasis, gene expression, non-small cell lung cancer

P2.01-39 SERIAL PLASMA CTDNA TESTS IDENTIFY GENOMIC ALTERATIONS FOR EARLY PREDICTION OF OSIMERTINIB TREATMENT OUTCOME IN T790M+ NSCLC

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Background: Recent advances in detection of genomic DNA from plasma samples allow us to follow the alteration of shedding tumor DNA in plasma before and after systemic treatment with multiple biopsies. Osimertinib is the standard of care for NSCLC patients with T790M mutations. We plan to use serial plasma cfDNA genomic alteration to predict osimertinib efficacy and search for possible resistance mechanisms. **Method:** We prospectively collected plasma from patients of *EGFR* mutation-positive NSCLC who harbored acquired *EGFR* T790M mutation following prior EGFR-TKI therapy. Plasma samples were collected before starting osimertinib treatment, 4 weeks following osimertinib treatment and upon disease progression. ctDNA were detected by Guardant360 gene panel test. **Result:** Fifteen patients (median age 62 [range 48-77], 53% men, 53% exon 19 deletion and 47% exon 21 L858R mutation) received osimertinib treatment. Acquired T790M mutation was diagnosed by using plasma sample only (Cobas® or digital PCR) (n = 11), tissue or pleural effusion only (n = 2), and both tissue and plasma samples (n = 2). Before starting osimertinib treatment, activating mutations were detected in plasma in all patients, T790M was detected in 93% (n = 14) and *TP53* mutation was detected in 47% (n = 7) of the patients by using Guardant360. After osimertinib treatment, 11 out of the 14 patients had non-detectable plasma T790M at the 4th week. Follow-up CT at least 8 weeks following osimertinib treatment of the 11 patients disclosed decreased tumor size (6 confirmed PR, 1 unconfirmed PR and 5 SD by RECIST criteria). The remaining 3 patients who had detectable plasma T790M (n = 2) or increased activating mutation allele frequency (n = 1) at the 4th week had progressive disease within 16 weeks. The first patient had initial PR but later developed C797S on progression. The second patient developed new liver tumor following prior stable disease. This patient had baseline *TP53* and *CDKN2A* mutations detected in the plasma, and allele frequencies decreased at the 4th week and increased on progression. The last patient had rapid progression on osimertinib treatment, and alterations in *PTEN* and *TP53* were detected on baseline and increased at the 4th week and on progression. In that patient, T790M mutation was not detectable at the 4th week but activating mutation increased in allele frequency at the 4th week and on progression. Regarding patients with baseline *TP53* mutation, 4 (57%) patients who had non-detectable plasma *TP53* mutation at the 4th week achieved disease control, and 2 (29%) patients had detectable or increased *TP53* mutation allele frequency had PD within 16 weeks. **Conclusion:** 4 week plasma ctDNA following osimertinib treatment may predict early progression within 16 weeks.

Keywords: T790M, Osimertinib, ctDNA

P2.01-40 NORMALIZATION OF CARCINOEMBRYONIC ANTIGEN LEVELS IS ASSOCIATED WITH SURVIVAL IMPROVEMENT IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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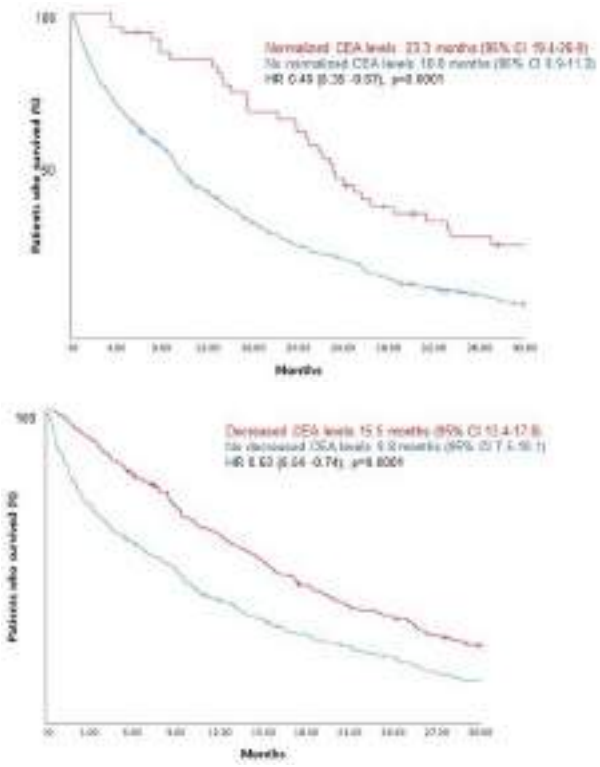
Background: Serum carcinoembryonic antigen (CEA) levels are elevated in approximately 65% of the Non-small cell lung cancer (NSCLC) patients with adenocarcinoma histology. Elevated CEA levels are an independent prognostic factor for overall survival (OS) in early and advanced NSCLC stages. Previous reports from our group suggest that the decrease or increase in CEA serum levels

is strongly associated with response and progression to systemic treatment. However, determination of CEA levels is not included in standard guidelines, such as National Comprehensive Cancer Network (NCNN). The aim of this study is to analyze the progression-free survival (PFS) and overall survival (OS) in NSCLC patients with elevated CEA levels at diagnosis and its association with systemic treatment response. **Method:** We performed a retrospective analysis of patients with advanced NSCLC with an elevated serum level baseline of CEA (>20 ng/ml) that received treatment according to international guidelines. The serum CEA levels were measured every two cycles of platinum-based chemotherapy or a tyrosine kinase inhibitor (TKI) treatment. The change in serum CEA levels in response to treatment and the association with overall survival and progression free survival was evaluated. **Result:** Between March 2004 and February 2018, 748 patients with diagnosis of advanced NSCLC and CEA levels >20 ng/mL were included in the analysis. Median age was 60.2 years old, 631 patients (84.4%) had adenocarcinoma histology. From 338 patients evaluated for EGFR mutations, 139 (31.3%) harbored an EGFR mutation. The median OS was 23.3 months (95% CI 19.4-26.9) in patients who completely normalized CEA vs 10.0 months (95% CI 8.9-11.2) in patients who did not achieved CEA normalization, with a HR 0.48 95% CI (0.35 -0.67) p <0.0001. The median OS was 15.5 months (95% CI 13.4-17.6) in patients who showed a decrease in CEA levels vs 8.8 months (95% CI 7.5-10.1) in those who did not. Reduction in CEA levels was associated with better OS, either in patients treated with TKI or platinum-based chemotherapy.

Overall survival according to changes in CEA levels



Conclusion: The normalization or decrease of the serum CEA levels is a biological marker that serves as tool associated with OS. Based on these findings and previous reports, CEA determination should be included in the clinical guidelines for NSCLC as response biomarker. Serum CEA levels should be part of the standard follow-up of NSCLC patients.

Keywords: NSCLC, biomarkers, Carcinoembryonic antigen

P2.01-41 EGFR MUTATION POSITIVE NON-SMALL CELL LUNG CANCER: MANAGEMENT APPROACH AND SURVIVAL OUTCOMES FROM THE HOSPITAL OF LEON

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Background: Approximately 10-16% of non-small cell lung cancer (NSCLC) cases have the EGFR mutation. Studies have shown that EGFR tyrosine kinase inhibitors (TKIs) significantly prolong progression-free survival (PFS) in patients with advanced NSCLC in comparison to those treated with platinum-based chemotherapy doublets. Our aim is to perform a real world analysis of patients treated with TKI as first line therapy at the Hospital of Leon (CAULE). **Method:** We retrospectively reviewed a total of 74 patients diagnosed with EGFR mutation positive NSCLC between March 2011 to June 2018 in the CAULE. Data was obtained from their medical records. The impact of comorbidities and smoking status on the survival rate were evaluated, in addition to the PFS and overall survival (OS) outcomes in patients treated with first line TKI. The follow-up schedule for computed tomography (CT) imaging was realized every 8 to 12 weeks. **Result:** A total of 74 patients were included in the study, out of which 55 were treated with a first line TKI. Exon 19 deletion was the most prevalent mutation subtype accounting for 53% of cases. 67% of patients were women. The average age was 69 years old. 44% had metastasis to more than 2 sites at the time of diagnosis; 6 patients had brain metastasis, 4 of which received prior whole brain radiotherapy, 1 surgical treatment, and 1 didn't receive local treatment. 22% of patients had no medical comorbidities (including cardiovascular, pulmonary, neurological or psychiatric history). Results revealed that the presence of comorbidities had no statistical significance when analyzing its impact on survival outcomes (HR=0.85, 95%CI 0.37-1.83 p=0.64). Similar results were obtained when non-smokers (71%) were compared to smokers or former smokers, suggesting that smoking had no statistical significance when analyzing survival data (HR=0,94 95%CI: 0.43- 2.02 p=0.87). 50% (n= 28) of patients were treated with first line gefitinib, 32% (n=18) with erlotinib and 10% (n= 6) with afatinib. There was no statistical significance in survival rates amongst patients treated with gefitinib vs afatinib or erlotinib (HR=1.6 P=0.56 95%CI 0.84-3.2). When analyzing best response to treatment, 63% of patient had a partial response, 20% demonstrated stable disease and 10% had progression of disease. Median OS was 31 months (95%CI: 20,5-31,4 months) and the PFS was 17 months (95%IC 13,9-20,6 months). 30% were alive at the time of analysis. The main cause of death was disease progression. **Conclusion:** This real-world analysis of the data gathered from the Hospital of Leon confirms that treatment with TKI is beneficial for patients diagnosed with EGFR mutation positive NSCLC. In fact, our OS outcomes are similar than those reported in clinical trials. We have not observed significant differences amongst TKI treatment options, nor was there an impact on global survival rates in patients with underlying medical comorbidities. Given the prevalence of EGFR mutation positive lung cancer, more clinical data is required in order to expand scientific evidence and determine the best driver mutation therapy option based on patient's profile.

Keywords: TKI first line, EGFR mutation positive, comorbidities

P2.01-42 ALK-REARRANGEMENT MAY PROMOTE VTE BY INCREASING THE EXPRESSION OF TF IN ADVANCED LUNG ADENOCARCINOMA

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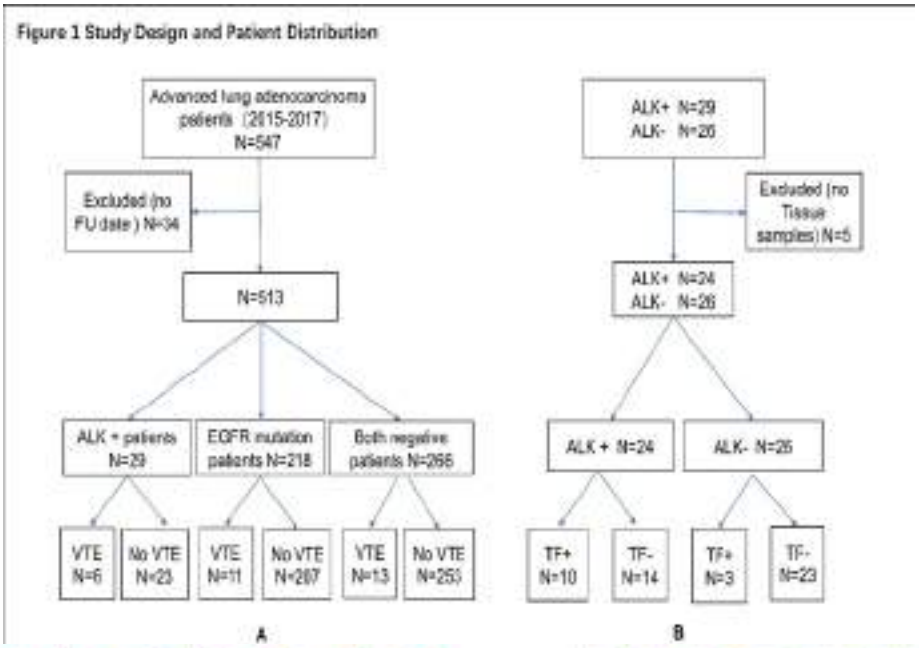
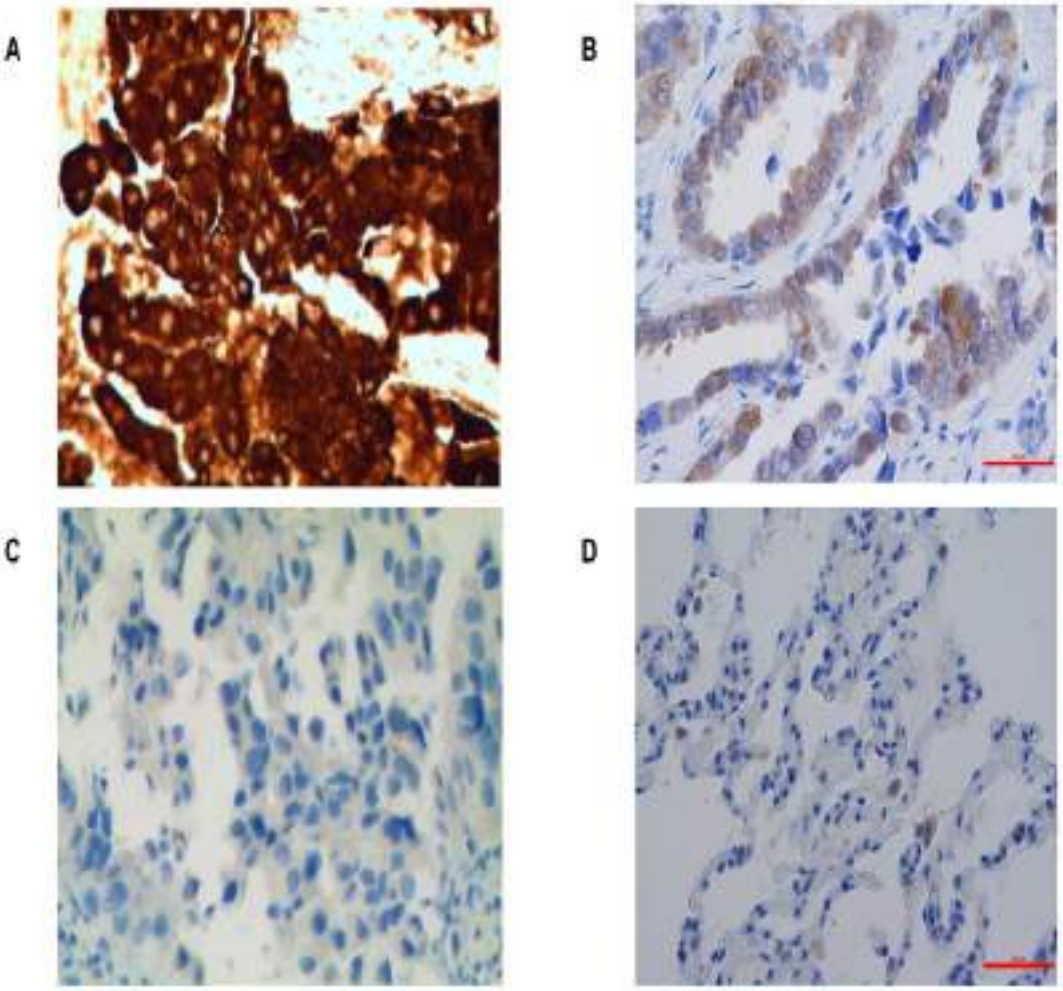
Background: Patients with lung cancer are at an increased risk for venous thromboembolism (VTE). About 8% to 15% of patients with advanced none small-cell lung cancer (NSCLC) experience a VTE throughout the course of the disease. However, the incidences of VTE in different molecular subtypes of NSCLC are rarely reported though they have big differentiation in clinical feature and prognosis. Tissue Factor (TF) expressed in many solid tumors could trigger the downstream coagulation cascade and lead to thrombin generation and clot formation. **Method:** Here we extracted retrospective data from electronic medical records at Henan Cancer Hospital

in China between January 2015 and January 2017. Advanced lung adenocarcinoma patients with ALK-rearranged, EGFR mutation and both negative were classified. The incidence of VTE of these patients were calculated. Then we randomly selected ALK-rearranged positive and negative lung adenocarcinoma tissues (N = 29, N = 26, respectively) and detected TF protein expression of the tissues with immunohistochemistry. **Result:** The present study work flow in shown in Figure 1. At a median follow-up of 2.5 years, 5.85% (30 in 513) patients with advanced lung adenocarcinoma experienced VTE. ALK-rearranged patients (Figure 2A) were more likely to occur VTE than EGFR mutation and both negative patients (Figure 2C) (6 in 29, 20.69%; 11 in 218, 5.05%; 13 in 266, 4.89%, respectively *P*=0.018). In ALK-rearranged positive tissues, 41.67% (10 in 24) of them had a high expression of TF protein (Figure 2B) – the incidence was significantly higher than that of ALK-negative tissues' TF protein expression (11.54%, 3 in 26, *P*=0.015) (Figure 2D).





Conclusion: ALK positive NSCLC patients are more likely to occur VTE and this might be due to higher expression of TF in tumor tissues.

Keywords: Non-Small Cell Lung Cancer, Venous thromboembolism, ALK

POSTERS

P2.01-43 PRE-THERAPEUTIC MARKERS AND SCORES PREDICT RESPONSE AND SURVIVAL IN STAGE IV LUNG CANCER PATIENTS INDEPENDENT OF HISTOLOGY

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Background: Lung cancer is the leading cause of death among all cancer entities. Identification of reliable and validated predictive and prognostic markers is important to estimate patients' prognosis. By doing this, planning of treatment and adequate patient guidance would improve. Many studies investigated several predictive and prognostic markers in lung cancer patients. Never the less, most of them describe very selective cohorts. This study aims at investigating histology independent predictive and prognostic markers in stage IV lung cancer patients. **Method:** We retrospectively analyzed 129 stage IV lung cancer patients who had been diagnosed and treated at a German tertiary care lung cancer center between 2015 and 2016. Patients' characteristics in terms of age, gender, performance status, histology, smoking status, treatment modalities and molecular pathological findings were collected from patients' charts. We extracted data sets from electronic patient records and compared anthropometric data, pre-therapeutic blood values as well as clinical scores and performed tests for prediction analysis **Result:** Eight markers and scores could be identified to significantly alter prognosis in univariate analysis. Over the normal cut off elevated values of CRP ($p < 0.001$), LDH ($p < 0.001$), Neutrophil to Lymphocyte ratio (NLR) ($p = 0.018$) and Systemic Inflammation Index (SII) ($p = 0.036$) as well as decreased levels of MCV ($p = 0.025$) and total protein ($p = 0.049$) were significantly associated with reduced overall survival (OS). Furthermore, the higher the Glasgow Prognostic Score (GPS) ($p < 0.001$) or the Lung Prognostic Index (PI-lung) ($p < 0.001$) were the worse was the OS. Failure of first line treatment was significantly predicted by low albumin (p=0.006), lymphocytes ($p = 0.032$) and PNI ($p = 0.001$) levels, whereas low values of CRP ($p < 0.001$), LDH ($p = 0.042$) and Thrombocyte to Lymphocyte ration (TLR) ($p = 0.017$) predict response to first line therapy. Multivariate analysis revealed CRP, PI-lung and GPS as independent prognostic factors regardless histology. **Conclusion:** Simply to obtain blood values and clinical scores provide histology independent markers for response to fist line treatment and survival in stage IV lung cancer patients.

Keywords: Lung cancer, stage IV, prognosis

P2.01-44 PROMOTER POLYMORPHISMS OF TOP2A AND ERCC1 GENES AS PREDICTIVE FACTORS FOR CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: TOP2A is an enzyme that control topologic changes in DNA during transcription and replication. ERCC1 is an enzyme takes part in DNA repair processes. Purpose of our studies was to assess predictive role of particular single nucleotide polymorphisms (SNPs) in promoter regions of *TOP2A* and *ERCC1* genes in non-small cell lung cancer patients (NSCLC) treated with chemotherapy. **Method:** We enrolled 116 NSCLC patients qualified to first line chemotherapy. Information on the chemotherapy regimens was available in 106 patients. All chemotherapy regimens were based on platinum compounds. 66 (62%) patients received additionally inhibitors of cell divisions (vinorelbine, taxanes). 40 (38%) patients were treated with nucleoside analogs or antimetabolites (gemcytabine, pemetrexed). DNA was isolated from whole blood with Qiamp DNA Blood Mini kit (Qiagen, Germany) according to the manufacture's instruction. We examined five SNPs: rs11615 (*ERCC1*), rs3212986 (*CD3EAP*), rs13695 (*TOP2A*), rs34300454 (*TOP2A*), rs11540720 (*TOP2A*). Quantitative PCR using TaqMan probe (ThermoFisher, USA) was performed on Eco Illumina Real-Time PCR system device (Illumina Inc., USA). Statistical analysis were performed with MedCalc and Statistica 13.1 softwares. **Result:** In whole group of patients, median of progression free survival (PFS) was 3 months. Patients with CC genotype in rs34300454 had significantly higher median PFS (8 months) compared to patients with CT genotype (4 months, p=0.0026; HR=0.36 with 95% CI: 0,19 to 0,7). We did not detect patients with TT genotype of this SNP. However, the differences in median PFS between patients with different genotypes of the *TOP2A* gene were significant only in the group receiving inhibitors of cell divisions (p=0.011). In second group of patients, we did not observed such significant relationship. Control of disease (response to chemotherapy or stable disease) were observed insignificantly more often in patients with AA genotype in rs11615 of *ERCC1* gene than in patients with AG genotype of this SNP (X^2=3.453, p=0.063). **Conclusion:** Polymorphism of *TOP2A* gene could influence PFS in NSCLC patients treated witch chemotherapy and CC genotype of this polymorphism may be a good predictive factor for chemotherapy regimens containing cell division inhibitors.

Keywords: NSCLC, TOP2A, ERCC1

P2.01-45 CLINICO-MOLECULAR CHARACTERISTICS AND PROGNOSTIC OUTCOMES OF TP53 MUTATED PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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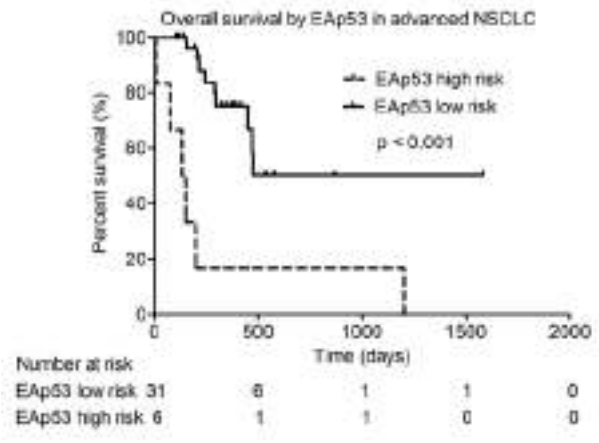
Background: *TP53* mutations are the most common molecular alterations in non-small cell lung cancer (NSCLC), but prognostic role of these mutations remains elusive. The aim of this study was to analyze the clinical and molecular characteristics of *TP53* mutated NSCLC patients and to evaluate a novel approach called evolutionary action (EAp53) to stratify them into high-risk or low-risk groups. **Method:** 85 advanced NSCLC patients were enrolled. Variations of *TP53* and other oncogenic drivers in NSCLC were identified by next-generation sequencing. EAp53 are available at http://mammoth.bcm.tmc.edu/EAp53/. **Result:** Overall, 77 patients (90.6%) exhibited at least one genetic alteration. *TP53* mutations were detected in 51 patients (60.0%) mainly in exons 4, 5, 6, 7, and 8. Notably, *TP53* mutations were not observed in exon 4 when they coexisted with *EGFR* mutations. Mutant allele frequencies (MAFs) of *EGFR* sensitizing mutations (exon 19 deletion or L858R) were significantly higher than those of other *EGFR* mutations in patients harboring *TP53* mutations ($p = 0.012$). Among *TP53* mutated patients, 39.2% of them carried *TP53* truncating mutations (nonsense, splice site, or frameshift), which were correlated with female gender and smokers ($p = 0.026$ and $p = 0.024$, respectively), and were potentially associated with young patients ($p = 0.078$), and were more common in non-DNA-binding domain of *TP53* ($p = 0.033$). Additionally, overall survival time of 37 patients were collected, and patients with high-risk mutations stratified by EAp53 had a significantly worse OS compared to others (HR 23.15; 95% CI 4.30-124.50; $p < 0.001$).



Conclusion: This study is of great significance in understanding the population characteristics of *TP53* mutated NSCLC patients. Furthermore, the data also indicates that evolutionary high risk *TP53* mutations can identify a subset of patients with poor prognosis, suggesting that EAp53 is a novel approach and may be useful in clinical prognosis of NSCLC patients with *TP53* mutations.

P2.01-46 THE EFFICACY AND SAFETY OF 2ND-LINE NIVOLUMAB FOR NON-SMALL CELL LUNG CANCER IN REAL-WORLD PRACTICE WITH EMPHASIS ON HYPERPROGESSION

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Background: The efficacy of nivolumab, a PD-1 immune checkpoint inhibitor, has been proven through many clinical trials. However, the data about whether it can be generalized to real-world patients are limited. We investigated the outcomes of non-small cell lung cancer (NSCLC) patients who received nivolumab with emphasis on hyper-progressive disease (HPD). **Method:** This retrospective study enrolled stage IV NSCLC patients who received nivolumab following the progression after previous chemotherapy between July 2016 and June 2018 in single center. HPD was defined as the progression by RECIST at the first evaluation with ≥2-fold increase of the tumor growth rate between the prior and the upon nivolumab period. **Result:** A total of 83 patients with a median age of 60 years were included (Squamous vs non-squamous; 25[30%] vs 58[70%]). Among 59 patients with available PD-L1 level, 17% of patients showed the negative expression of PD-L1 while 20% of them had more than 50% of expression. The response and disease control rate were 7% and 52% while the median PFS and OS were 2.6 (95% confidence interval [CI], 0.82 to 4.31) and 8.6 months (95% CI, 5.56 to 11.59), respectively. The PD-L1 level ≥ 50% group (n=12) showed the superior outcome with the median OS of 18.1 months. Treatment-related adverse events of grade 3 or 4 occurred in 8.4%. HPD developed in 16 (19.2%). The median OS of HPD group was 2.2 months (95% CI, 0.92 to 3.75) whereas that of other progression group was 4.1 months (95% CI, 1.54 to 6.67). Among patients with pleura or pericardium metastasis, increased effusion was seen in 90% of HPD group (n=9/10) whereas 28.6% of other progression group (n=4/14) (p=0.004). There was no other significant HPD-related factor. **Conclusion:** Although the efficacy and safety of nivolumab in real-world patients are comparable to those of clinical trials, clinicians should beware of HPD as it is not uncommon and represents the worst prognosis. The relationship with HPD and effusive metastasis should be further investigated.

Keywords: Non-Small Cell Lung Cancer, nivolumab, hyperprogression

P2.01-47 IPSILATERAL LUNG DOSE CONSTRAINTS PREDICT RADIATION PNEUMONITIS BETTER THAN CONVENTIONAL ONES IN NSCLC PATIENTS TREATED WITH RCT

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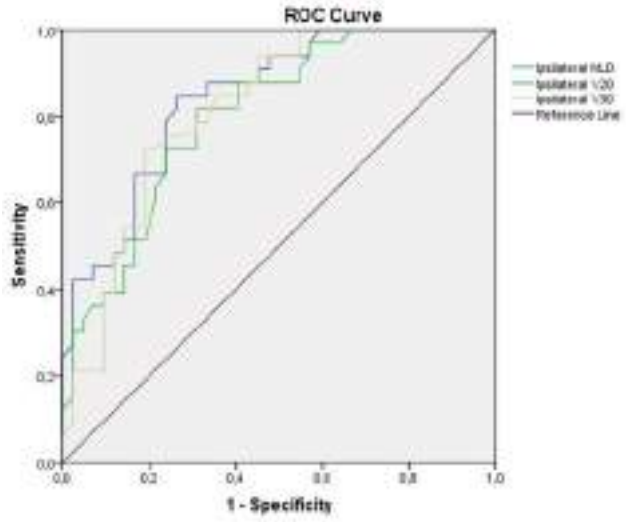
Background: Mean lung dose (MLD) and percent of total lung volume that receive a dose greater than 20 Gy (V_{20}) have been mostly validated parameters in prediction of radiation pneumonitis (RP). But these parameters present mean values of total lung parenchyme and predict the right and the left lung as a unique functional organ unit, not take into account the difference in function, dose density and radiosensitivity between the lungs. Also, there has been very limited data evaluating ipsilateral lung dosimetric constraints in addition to total lung parameters to predict RP in NSCLC-patients treated with radiochemotherapy (RCT). **Method:** Between 2010-2017, clinical-radiological findings of NSCLC-patients treated with RCT were evaluated in terms of RP, retrospectively. The right and the left lung were contoured separately.The total lung was created by extracting PTV. Ipsilateral lung was described as the lung containing more than 50% of PTV and was created by extracting PTV from ipsilateral lung. Pulmonary toxicity was graded according to RTOG/EORTC. Clinicaly important RP was defined as ≥ grade 2 lung morbidity. The primary end point was to asses the relation between ipsilateral lung dose constraints and RP risk.The secondary end-point was to evaluate the predictive value of ipsilateral dose constraints in case of a relationship. **Result:** There were 75 patients.There was ≥ grade 2 RP in 33 cases (%44).Median age at diagnosis was 59.The median follow-up was 21 months.The median RT dose was 63 Gy.There was ≥ grade 2 RP in 33 cases(%44).RP risk was 75% if the tumor was located in upper lobe(p:0.012). Univariate analysis was carried on clinical and dosimetric variables.The most significant ones were;ipsilateral MLD(p<0.001), ipsilateral V_{20}(p<0.001), ipsilateral V_{30}(p<0.001) and total lung V_{30}(p<0.001). Ipsilateral MLDp<0.001(OR:1.34)(%95CI:1.16-1.55) and PTV p:0.039(OR:1.002)(%95CI:1.000-1.004) were found to be the independent risk factors for RP. The diagram of ROC curve analysis is shown in Figure 1.AUC values for ipsilateral MLD, ipsilateralV20, ipsilateralV30, MLD, V20 and V30 were 0.84, 0.80, 0.81, 0.64, 0.69 and 0.77, respectively.Threshold values for ipsilateral MLD, ipsilateral V20 and ipsilateral V30 were selected by ROC curve analysis and was determined as 18 Gy. 35% and 28% respectively.



Conclusion: In NSCLC-patients treated with CRT, MLD, V_{20} and V_{30} values of ipsilateral lung parameters might increase the predictablity of RP risk in addition to total lung parameters or even better. RT plannings might be improved by simply adding ipsilateral dose volume constraints witthout any additional test or effort to the patient

Keywords: ipsilateral lung constraints, Nonsmall cell lung cancer, Radiation pneumonitis

P2.01-48 ENHANCED EXPRESSION OF MIR-204 REDUCES CISPLATIN RESISTANCE IN NSCLC

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Background: Non-small cell lung cancer (NSCLC) is the most common and lethal human malignant tumor worldwide. Platinum-based chemotherapy is still the mainstay treatment for NSCLC. However, long-term chemotherapy usually induces serious drug resistance. Accordingly, it is valuable to develop treatment strategies that could reduce the resistance against platinum-based drugsin NSCLC cells . **Method:** Cisplatin-resistant NSCLC models in A549 and PC9 cell lines (CR-A549 and CR-PC9) were established through long-term exposure to cisplatin. Expression levels of caveolin-1 (CAV-1) and miR-204 in A549, PC9, CR-A549, and CR-PC9 cell lines were detected by western blot and q-PCR, respectively. Regulation of CAV-1 by miR-204 was assessed by bioinformatic analysis, western blot and luciferase reporter assay. The role of the miR-204/CAV-1 axis in regulating cisplatin resistance in NSCLC cells was tested by MTT assay. Interactions with Bcl-2-associated agonist of cell apoptosis (Bad) and Bcl-xl (Bcl-2) were evaluated by co-immunoprecipitation assay. Flow cytometry was used to detect the apoptosis of NSCLC cell lines. **Result:** We observed significant upregulation of CAV-1 expression and a significant decrease of miR-204 expression in CR-A549 and CR-PC9 cells compared to their parental A549 and PC9 cells. Furthermore, we detected down regulation of miR cells. We then found that enforced expression of miR-204 can resensitize CR-A549 and CRPC9 cells to cisplatin treatment through the inhibition of CAV-1 expression. Thus, we declared that recovery of miR-204 expression was able to sensitize the cisplatin-induced mitochondrial apoptosis observed in CR-A549 and CR-PC9 cells through suppression of the caveolin-1/AKT/Bad pathway. **Conclusion:** This study suggested that enhanced expression of miR-204 could increase the sensitivity of cisplatin treatment by suppression of caveolin-1/AKT/Bad pathway, which concluded that overexpression of miR-204 could be a potential approach for enhancing the sensitivity in NSCLC cells with cisplatin resistance.

Keywords: miR-204, Caveolin-1, cisplatin

POSTERS

P2.01-49 TARGETING STAT3-POSITIVE REACTIVE ASTROCYTES WITH SILIBININ IN THE THERAPEUTIC LANDSCAPE OF NON-SMALL-CELL LUNG CANCER WITH BRAIN METASTASES

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Background: Silibinin is a bioactive flavonolignan extracted from milk thistle (*Silybum marianum*) and is a direct inhibitor of STAT3 – with high affinity to both the Src homology-2 domain and the DNA-binding domain of STAT3. Pre-clinical data indicate that blocking STAT3 signaling in reactive astrocytes, a major component of the brain metastasis microenvironment, can decrease the number and size of brain metastases (BM). **Method:** We present data on all patients diagnosed with BM from non-small cell lung cancer (NSCLC) from the Cancer Register of the Hospital Universitari Dr. Josep Trueta during 2013–2017. Age, gender, histology, and treatment in patients were recorded. During this period, some patients received compassionate use of Legasil®, a commercially available silibinin-based nutraceutical, in addition to standard oncologic treatment. The data cut-off for survival analysis was 28th March 2019. **Result:** We identified 221 patients with NSCLC and BM. Median age: 62 y (range: 32–88 y); male: 161 (72.9%). Synchronous BM were observed at the diagnosis of primary lung cancer in 133 (60.2%) patients. Differences in median overall survival (mOS) were detected by histology subtype: adenocarcinoma (66.1%)=4.6 m, squamous (17.6%)=1.8 m, not otherwise specified (16.3%)=2.2 m, p=0.000003. Treatment effects on mOS are summarized in Table 1. In the subgroup of patients that received brain radiotherapy in addition to systemic therapy for BM, differences were maintained between patients that received Legasil® (n=15) or not (n=64):28.5 months *vs* 6.3 months (p=0.000052).

Table 1

Treatment	%	mOS (without)	mOS (with treatment)	p-value
Brain radiotherapy	53.8%	1.9 m	5.1 m	< 0.000001
Systemic therapy	52%	1.6 m	6.9 m	< 0.000001
Brain surgery	5%	3.2 m	15.5 m	=0.000127
Silibinin supplementation	8.1%	3.5 m	22.8 m	=0.000001

Conclusion: Our data indicate that silibinin supplementation could contribute to the control of BM in patients with NSCLC. Further evaluation of silibinin, or other STAT3 inhibitors, in clinical trials is warranted in this setting.

Keywords: silibinin, NSCLC, brain metastasis

P2.01-50 CD 146 A POTENTIAL THERAPEUTIC TARGET FOR LUNG CANCER

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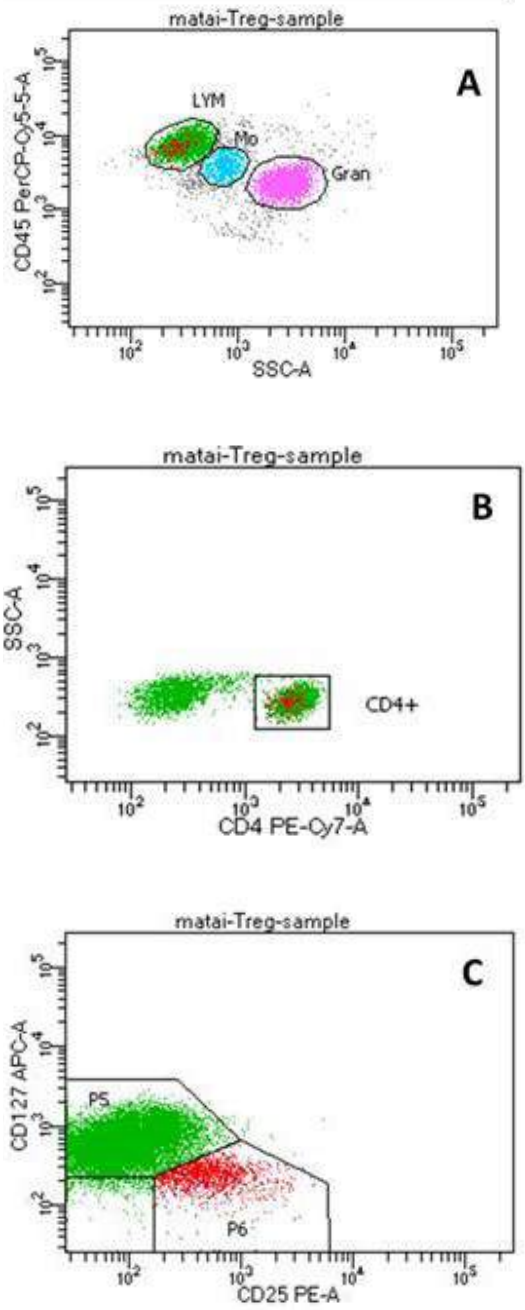
Background: Non-small-cell lung cancer (NSCLC) patients often exhibit lymphopenia, which has been associated with poor clinical outcomes. However, the mechanisms that lead to lymphopenia have not been fully established. CD 146 is an important glycoprotein found on the integral membrane of the cells. Its ectodomain contains five immunoglobulin-like domains and its cytoplasmic tail contains potential protein kinase C recognition sites and PDZ binding sites indicating possible involvements in cell signaling **Method:** Blood was collected from lung cancer patients and from healthy subjects. The frequency of CD146 cells and the expression of CD 4, CD45, CD 127, CD 25 were determined by flow cytometry. Lymphocytes apoptosis was determined by 7-amino-actinomycin D/Annexin V-APC staining. **Result:** The percentage of CD 146 was significantly higher in patients than in controls. CD 146 expression in whole-blood samples was higher in NSCLC patients than in controls



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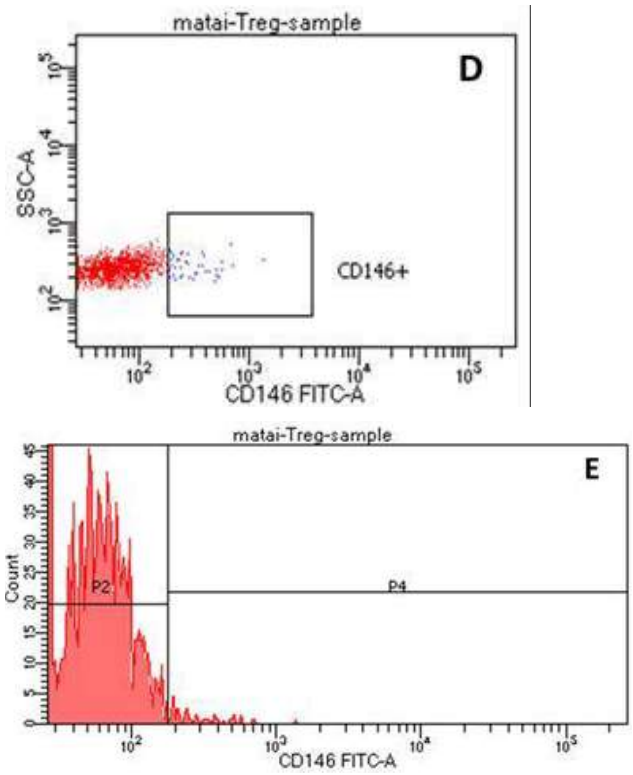

Conclusion: Increased CD 146 expression on the blood of lung cancer patients may be associated with the underlying mechanisms leading to lymphopenia in NSCLC patients

P2.01-51 NEXT-GENERATION SEQUNCING FOR EFFECTIVE DETECTION OF VARIOUS EGFR EXON 20 INSERTIONS (E20INS) IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Epidermal growth factor receptor (EGFR) E20ins are known as uncommon EGFR mutation and relatively insensitive to current EGFR tyrosine kinase inhibitors (TKIs). However, recent newer TKIs such as poziotinib show good clinical activity against them. Thus, we further explored the rate of EGFR E20ins and their clinical characteristics **Method:** Between March 2017 and October 2018, 488 NSCLC tumor specimens were examined with OncoPanel AMC version3 which is a Next-generation sequencing (NGS) based assay for the detection of single-nucleotide variants, insertions, deletions, copy number alterations and structural variants across 382 genes. Peptide Nucleic Acid (PNA) clamping method version2 is to detect EGFR mutations using allele specific polymerase chain reaction and 6 variants of E20ins could be detected by it. We analyzed those NGS results and they were compared with PNA clamping method results if examined previously. Clinical characteristics were also reviewed. **Result:** Among 488 patients, 143 showed EGFR mutations;16 patients showed wide variety of E20ins, while 59, 54 and 14 patients showing exon 19 deletion, L858R, and other rare EGFR mutations, respectively. Thus, the rate of E20ins was 11.2% of all EGFR mutations. For those 16 patients with E20ins, PNA clamping method failed to detect E20ins EGFR mutation in 8 patients (50%). Male/Female ratio was 7/9. Median age was 57 years (25-76 years). The rate of non-smoking was 68.8%. First-line platinum based regimen were given in 10 patients with 2.5 months of median progression free survival (PFS), while first-line EGFR TKIs were given in 5 patients with 2.3 months of median PFS. Poziotinib was provided to 2 patients later and they showed stable disease and partial remission. **Conclusion:** EGFR E20ins were detected in 11.2% of EGFR-mutant NSCLC by OncoPanel AMC version3, and it was twice the rate by PNA clamping method. Clinically those patients showed lack of response to current EGFR TKIs. Poziotinib is a new EGFR TKI and promising for E20ins EGFR mutation.

Keyword: Non-small cell lung cancer, EGFR mutation, Exon 20 insertion, PNA clamping

P2.01-52 CLINICAL CHARACTERISTICS AND OUTCOMES IN NSCLC PATIENTS ASSOCIATED WITH VERY HIGH PD-L1 EXPRESSION

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Background: Clinical characteristics and outcomes for patients with non-small cell lung cancer (NSCLC) and very high PD-L1 expression are unknown. We sought to better characterize this subset of patients with PD-L1 ≥90% to determine any differences in clinical presentation or survival. **Method:** We performed a retrospective analysis of patients treated at our institution between 2014 and 2018 with metastatic NSCLC and an available PD-L1 result (any assay). We assessed tumor size, location of metastasis, and presence of mediastinal invasion using continuous PD-L1 values (Wilcoxon Mann-Whitney test) and compared two subgroups based on a PD-L1 cut point of ≥90% (Fisher's exact test). Survival comparisons used Kaplan Meier log-rank methodology. **Result:** A total of 101 patients were included in the analysis; 16.8% had PD-L1 ≥90%. A summary of the patient demographics and clinical characteristics are summarized in Table 1. Higher PD-L1 values were associated with mediastinal invasion (median PD-L1 60% vs 5% without invasion, p=0.0268) and those with PD-L1 ≥90% were more likely to have adrenal metastasis (p=0.0266). There was no correlation between tumor size or other sites of metastasis and PD-L1 expression. OS was not significantly different when compared to those with PD-L1 50-89% or lower PD-L1 subgroups in either immunotherapy alone treatment group (p=0.6358) or for the combination chemotherapy/ immunotherapy group (p=0.2580). Patients receiving immunotherapy alone with PD-L1 expression ≥90% had a median OS of 38.0 months compared to 21.3 months for PD-L1 0-89% (p=0.8480). Table 1:

	PD-L1 status				
	Less than 90% n (% if applicable) n=84	Greater than 90% n (% if applicable) n=17	Total N (%) n=101	P-value (continuous)	P-value (≥90% vs. <90%)
Patient Demographics					
Age (median in years)	63	60	62.5		
Female	42 (50)	9 (53)	51 (51)		
History of Smoking	72 (86)	15 (88)	87 (86)		
Line of treatment with immunotherapy					
First Line	38 (45)	8 (47)	46 (46)		
Second Line or greater	46 (55)	9 (53)	55 (55)		
Immunotherapy alone	57 (68)	13 (77)	70 (69)		
Chemo + IO	27 (32)	4 (24)	31 (31)		
EGFR mutation	0	0	0		
Clinical Characteristics					
Tumor Size (median in cm)	3.6	4.10	3.7	0.0843	0.3598
Evidence of Mediastinal Invasion	13 (16)	4 (24)	17 (17)	0.0268	0.4932
Adrenal Metastasis	10 (12)	6 (35)	16 (16)	0.2067	0.0266
Bone Metastasis	18 (21)	5 (29)	23 (23)	0.8942	0.5316
Brain Metastasis	24 (29)	7 (41)	31 (31)	0.6064	0.3879
Liver Metastasis	15 (18)	2 (12)	15 (15)	0.7518	1.0

Conclusion: Higher PD-L1 expression was associated with mediastinal invasion, and adrenal metastasis were more common in patients with PD-L1 ≥90%. While there were no detectable survival differences in the very high PD-L1 group, differences in clinical characteristics highlight the heterogeneity of this group of patients and need for further characterization that may be predictive of treatment response and help tailor treatments for this group.

Keywords: Non-Small Cell Lung Cancer, metastatic

POSTERS

P2.01-53 SURGICAL RESECTION OF PRIMARY TUMOR IMPROVE THE PROGNOSIS OF LUNG CANCER PATIENTS WITH BONE METASTASIS

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Background: Most of the lung cancer patients are in advanced stage at the time of diagnosis due to occult onset. Bone metastasis is one of the most common sites of hematogenous metastasis of lung cancer. This study used the Surveillance, Epidemiology, and End Results (SEER) database to evaluate the impact of surgical resection of primary tumor on the prognosis of lung cancer patients with bone metastasis. **Method:** We identified 12578 lung patients with only bone metastasis from the Surveillance, Epidemiology, and End Results database. Propensity score matching was used to reduce the selection bias. Cancer–specific survival (CSS) were compared between patients with or without primary tumor resection. The Cox regression model was applied to evaluate multiple prognostic factors. The effects of different surgical extension and lymph node resection on prognosis were also analyzed. **Result:** After propensity matching, a total of 458 patients were selected into survival analysis. There were no statistical differences in age, gender, race, tumor location, histology, T stage and N stage between patients with or without surgical resection of primary tumor. The prognosis of patients undergoing surgical resection of primary tumor was significantly better than that of patients who had not undergone surgery (five-year CSS rate: 2.7% vs. 23.4%, respectively, P<0.001). Multivariable analysis revealed that surgical resection of primary tumor was an independent prognostic factor (HR=0.518, 95% confidence interval [CI] 0.414 to 0.648, P<0.001). In addition, the prognosis of patients undergoing lobectomy/bilobectomy was significantly better than that of others(P<0.001). Furthermore, regional lymph node resection during the operation could significantly improve the prognosis of the patients (P<0.001). **Conclusion:** For lung cancer patients with only bone metastasis, surgical resection of primary tumor could significantly improve the prognosis. Lobectomy/bilobectomy with regional lymph node resection was the best surgical strategy.

Keywords: Lung cancer, bone metastasis, Surgical resection of primary tumor

P2.01-54 REAL-WORLD PD-L1 TESTING PATTERNS FOR PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER IN GREECE

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Background: Programmed Cell Death Protein-1 (PD-1) and Programmed Death Ligand-1 (PD-L1) inhibitors are important immunotherapy targets for non-small cell lung cancer (NSCLC). This study sought to describe PD-L1 testing for patients with NSCLC in Greece. **Method:** This non-interventional study is based on Sotiria Lung Cancer Registry in Greece recording patients with histologically or cytologically confirmed stage IIIB/IV NSCLC diagnosis, who initiated systemic treatment between August, 15th 2016 and August, 14th 2018. **Result:** A total of 472 patients were included in the registry. Demographic and first-line treatment information are presented in Table 1, along with the respective comparison between patients tested and not tested for PD-L1. Patients with ECOG PS 0-1 are more likely to be tested for PD-L1 status. Among patients tested for PD-L1, Dako 22C3 was the most commonly used testing assay (87.8%). The number of patients tested for PD-L1 increased between the two consecutive time periods (from August, 15th 2016 to August, 14th 2018; Table 2).

Table 1 Demographic characteristics, PD-L1 testing, and first-line treatment patterns.

		Not tested for PD-L1 (N=332)	Tested for PD-L1 (N=140)
Age	≤65	108 (32.5)	45 (32.1)
	>65	224 (67.5)	95 (67.9)
	Mean (sd)	68.4 (8.8)	66.8 (10.0)
Gender	Female	62 (18.7)	36 (25.7)
	Male	270 (81.3)	104 (74.3)
Smoking status	Current	198 (59.6)	78 (55.7)
	Former	106 (31.9)	46 (32.9)
	Non Smoker	14 (4.2)	8 (5.7)
	Unknown	14 (4.2)	8 (5.7)
Stage	IIIB	83 (25.0)	31 (22.1)
	IV	249 (75.0)	109 (77.9)
EGOG PS (binary)*	0-1	190 (57.2)	99 (70.7)
	≥2	89 (26.8)	25 (17.9)
	Unknown	53 (16.0)	16 (11.4)
First-line Treatment [a,b]			
Chemotherapy (combination)		254 (76.5)	92 (65.7)
Chemotherapy (monotherapy)		60 (18.1)	11 (7.8)
TKI		12 (3.6)	9 (6.4)
PD-1 inhibitor (pembrolizumab)		0	18

*, p-value < 0.05; [a], statistical comparison not performed; values represent number of patients with percentages in parentheses, unless otherwise is mentioned; [b,] 16 patients initiated 1st line treatment but the regimen used was unavailable at the time of the database lock.

Table 2 Number of patients diagnosed with NSCLC stage IIIB or IV and PD-L1 testing by time period.

	Total number of patients diagnosed with NSCLC	PD-L1 Test	PD-L1 Test prior to 1st line initiation	PD-L1 TPS≥50%	PD-L1 TPS 1%-49%	PD-L1 TPS <1%	PD-L1 not-available TPS
Time period	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total (row%)	472	140 (29.7%)[a]	94 (67.1%)[b]	37(26.4%)[b,c]	47(33.6%)[b]	50(35.7%)[b]	6 (4.3%)[b]
15/Aug/2016-14/Aug/2017	254	43 (16.9%)[a]	21(48.8%)[b]	10 (23.3%)[b]	17 (39.5%)[b]	14 (32.5%)[b]	2 (4.6%)[b]
15/Aug/2017-14/Aug/2018	218	97 (44.5%)[a]	73 (75.3%)[b]	27 (27.8%)[b]	30 (30.9%)[b]	36 (37.1%)[b]	4 (4.1%)[b]

[a] The percentage of patients calculated over the number of patients diagnosed with stage IIIB or IV NSCLC in total and by each year; [b] The percentage of patients calculated over the number of patients tested in total and by year; [c] 30 out of 37 patients with TPS ≥50% were tested prior to 1st line treatment initiation

Conclusion: The percentage of newly diagnosed patients with advanced NSCLC in Greece tested for PD-L1 status doubled in a year (August, 15th 2016 – August, 14th 2018). Among those tested, 67% were tested prior to first-line treatment initiation and 26% of those tested had PD-L1 TPS ≥50%.

Keyword: advnaced NSCLC, PD-L1 biomarker, immunotherapy

P2.01-55 IMMUNOTHERAPY FIRST OR AFTER NINTEDANIB?: A SPANISH EXPERIENCE

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Background: Anti PD-1 and PD-L1 immunotherapies have demonstrated improved survival as second line treatment of patients with advanced lung cancer, and actually, this is a standard of care. In addition, Nintedanib-docetaxel is an option for few patients, and have demonstrated efficacy in second line treatment after platinum-based chemotherapy. The doubt is if immunotherapy could be change efficacy of nintedanib-docetaxel treatment. **Method:** We conducted a retrospective multicenter study, which included all patients with non-small cell lung cancer who received nintedanib with docetaxel in second o third line of treatment. The objective of this study was to determine the efficacy of the nintedanib-docetaxel combination before and after immune checkpoint inhibitors. **Result:** We enrolled 120 patients from 10 different Spanish centers. 72.4% had not received previous immunotherapy, while 27.6% had received it. Of those who had received previous immunotherapy: 10.6% received pembrolizumab, 10.6% received nivolumab and 3,3% received atezolizumab. Receiving previous immunotherapy had no impact on the PFS (4.5 months vs 3.2 months) or on the OS of the patients (25 months vs 20 months). Best response was partial

response in 11 patients, stable disease in 11 patients and progressive disease in 10 patients. After the progression to nintedanib/docetaxel, 21.9% received immunotherapy. 15 patients received nivolumab, 10 patients atezolizumab and 2 patients pembrolizumab. Best response was partial response in 13 patients, stable disease in 5 patients, complete response in 1 patient and progressive disease in 8 patients. Subsequent treatment with immunotherapy was not associated with increased SLP or OS in our study. **Conclusion:** Our experience suggests that the efficacy of nintedanib-docetaxel treatment is not modified by the treatment of previous or subsequent with immunotherapy.

Keyword: non-small cell lung cancer, nintedanib, immunotherapy.

P2.01-56 COPY NUMBER GAINS (CNGS) OF CLINICALLY RELEVANT GENES IN ADVANCED NSCLC PATIENTS

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Background: Somatic copy number variations (CNV; i.e. amplifications and deletions) have been implicated in the origin and development of multiple cancers and some of these aberrations are designated targets for therapies, such as amplified ERBB2 in breast cancer. In the case of NSCLC patients, MET alterations are receiving increasing attention as targets in precision medicine, and several clinical trials of anti-MET agents are ongoing. Routine testing for these potential targets on formalin-fixed paraffin embedded (FFPE) samples is mainly carried out by in-situ hybridization (FISH) approaches covering only a single gene of interest. Although this methodology is still the gold standard of CNV detection, it presents several drawbacks. Here we aimed to determine the potential of next generation sequencing (NGS) to simultaneously determine CNGs across many in FFPE samples **Method:** FFPE biopsies from 140 stage IIIb-IV NSCLC patients (p) of our institution were prospective tested. Of them, 110 corresponded to samples at diagnostic and 30 after progression to targeted therapies. DNA was purified submitted to NGS using the 16-gene QIAact Lung Panel (Genereader®, Qiagen). Coverages for the genes analyzed were normalized using the total coverage of the panel. Cut-off values for CNVs were established as the average normalized coverage for each gene plus two times the standard deviation. Representative samples were analyzed by FISH **Result:** Validation analyses in 8 cell lines showed 100% concordance between FISH and NGS for detection of EGFR, MET and ERBB2 amplifications. Among the 140 NSCLC p, MET was the gene showing a higher frequency of CNGs, followed by PIK3CA, NRAS, EGFR and KRAS (Table 1). In contrast, only one p was found to harbor a ROS1 CNG. Among the 17 samples with MET CNG (12%), 6 corresponded to p progressing to targeted therapies. In addition, 8 of the 17 samples with MET CNGs were submitted to FISH, 6 of them were positive and the remaining 2 samples had copy numbers higher than 3.5 by this technique. In the case of EGFR, CNGs were associated with sensitizing mutations, with 5 samples showing both alterations concomitantly. In contrast, PIK3CA, NRAS, ALK, BRAF, HER2, PDGFRA, KIT and MET CNGs were not associated with mutations (Table 1).

	n CNG	%	n MUTANT
MET	17	12.1	0
PIK3CA	12	8.6	0
NRAS	10	7.1	0
EGFR	10	7.1	5
KRAS	10	7.1	2
ALK	8	5.7	0
BRAF	8	5.7	0
ERBB2	8	5.7	0
PDGFRA	6	4.3	0
KIT	6	4.3	0
ROS1	1	0.7	0

Conclusion: CNGs in clinically relevant genes are present in a significant percentage of advanced NSCLC patients and, except in the case of EGFR, are not associated with driver mutations. Further research is warranted to determine the clinical implications of this finding.

Keywords: NGS, NSCLC, Copy number gains

P2.01-57 NEW PROGNOSTIC MARKERS IN PATIENTS WITH LUNG CANCER TREATED WITH IMMUNOTERAPY: NLR AND PLR

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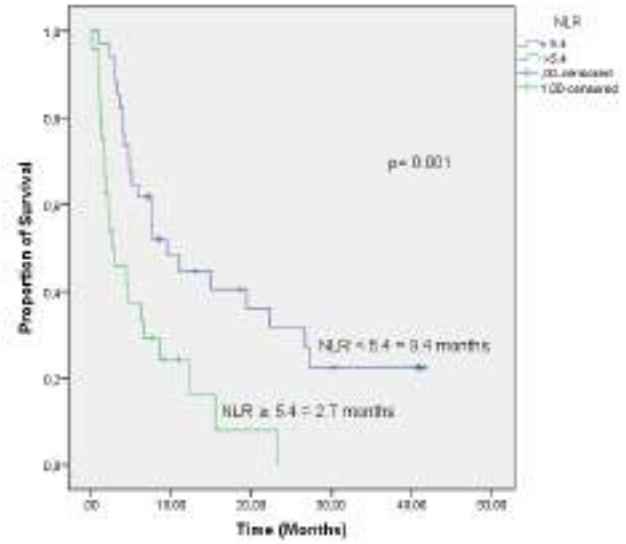
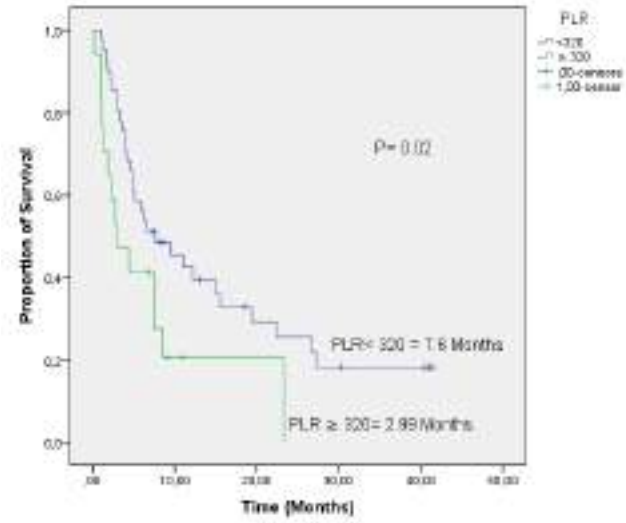
Background: Immunotherapy has become standard therapy in metastatic lung cancer. The problem for these agents is lack of prognostic and predictive markers which is feasible in clinical practice. On the otherhand up to 30% of patients accelerated progression of tumor early after immune checkpoint blockade(Hyperprogression). Predictive biomarkers of Hyperprogression(HP) have not been emerged. NLR and PLR are established strong prognostic markers associated with worse OS in several tumor types. The aim of our study was to analyse the prognostic impact of NLR and PLR in lung cancer patients treated with immunotherapy. And is there any relationship between these biomarkers and HP. **Method:** NLR was calculated by division of absolute neutrophil and lymphocyte counts measured in peripheral blood before start of immunotherapy. PLR was calculated by division of thrombocytes and lymphocytes accordingly. **Result:** The study included 63 patients who were treated with immunotherapy on metastatic setting. Most of patients (63.4%) had been given at least two line chemotherapy. The after-immunotherapy radiological response; three patients(4.8%) had a complete response, 13 patients(20.6%) had a partial response. Hyperprogression was detected 7(11.1%)patients. Median PFS was 3.2 months (95% CI 2.78 to 3.72), and median OS was 6.5 months (95%CI 4.04 to 9.04) with immunotherapy. Median OS was 9.4 vs 2.7 months in patients with NLR<5.4 vs NLR≥5.4(Log rank p= 0.001). Median OS was 7.6 vs 2.99 months in patients with PLR<320 vs NLR≥320(Log rank p= 0.02). Grade 1-2 hypothroidi was detected in six patients, Grade 3 pneumonia in two patients. No other complications are observed in any other patients.





Conclusion: NLR and PLR are standardized tests and easily used in daily routine. Elevated pre-treatment NLR and PLR are associated with shorter OS in patients with metastatic lung cancer. During the treatment of immunotherapy might be correlated with treatment response and we need larger studies.

Keywords: Immunotherapy, NLR, PLR

P2.01-58 DETECTION OF KRAS MUTATION FROM URINE OF INDONESIAN LUNG CANCER PATIENTS

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Background: KRAS is one of the most frequently mutated genes in Lung adenocarcinomas and has correlation with smoking history. The prevalence of KRAS mutated genes in Indonesian Lung cancer patients may be very high, because Indonesia is one of country with highest cigarettes consumption in the world. Urine is a potential source of biomarker analysis. In this study we identified KRAS mutation in urine sample from lung adenocarcinoma patients. **Method:** Seventy four urine samples from naive Lung adenocarcinoma patients were collected and extracted to get DNA as material of biomarker analysis. Analysis of KRAS mutation exon 2 was focused on codon 12 and 13 using Restriction Fragment Length Polymorphism (RFLP) and Sanger Sequencing methods. Analytical sensitivity of those methods was evaluated using dilution of DNA from mutant and normal KRAS cell lines. Gender and smoking history of the patients in correspondence with KRAS mutation were also evaluated. **Result:** The analytical sensitivity of the methods was at least 3.125% of mutant DNA using RFLP and at least 25% of mutant DNA by Sanger sequencing. KRAS mutation was detected in 15 of 74 urine patients. Eighty percent (12/15) of them are codon 12 mutation and twenty percent (3/15) are codon 13 mutation. In comparison between man and woman, we found that 7 male patients and 5 female patients have KRAS mutation in codon 12. We also found that 71.43% of KRAS mutation was in male patients with smoking history. **Conclusion:** It is concluded that KRAS mutation was found in urine samples of lung cancer patients and has correlation with smoking history. Urine is a great candidate to be an alternative of lung cancer samples. Comparison using cytological or biopsy samples must be evaluated to determine sensitivity and specificity of urine based KRAS mutation testing.

Keywords: Lung cancer, KRAS mutation, Urine

P2.01-59 PD-L1 VERY HIGH EXPRESSION ASSOCIATED WITH CLINICAL OUTCOME OF PEMBROLIZUMAB MONOTHERAPY OF ADVANCED NSCLC WITH PD-L1 TPS OF 50% OR GREATER

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Background: Programmed cell death ligand 1(PD-L1) pathway-targeted immunotherapy is emerging as a promising therapeutic strategy for non-small-cell lung cancer (NSCLC). Especially, pembrolizumab monotherapy is a standard-of-care regimen for first-line treatment of advanced NSCLC with PD-L1 tumor proportion score(TPS) of 50% or greater. However, progressive disease rate of pembolizumab monotherapy for first-line treatment is 20-30%, and therefore we still need biomarkers in this clinical setting. **Method:** We analyzed data of 41 patients with NSCLC with PD-L1 TPS of 50% or greater treated in Japanese Red Cross Ise Hospital,between March 2017 and January 2019. All patients received pembrolizumab monotherapy. We collected data of patient characteristics, histology, performance status (PS), stage, metastatic sites, smoking history, driver mutation, PD-L1 expression, treatment line from medical records.Progression-free survival(PFS) of pembrolizumab and Overall survival(OS) was calculated using Kaplan-Meier method. We compared PFS according to PD-L1 expression using log rank test and Cox model was used to assess the effect of PD-L1 expression on PFS. Patients were stratified into 2 PD-L1 groups based on PD-L1 expression: medium-high expression(TPS 50-74%), and very high expression(TPS 75-100%). **Result:** The median age was 74 years (range: 43-86) and 15% of patients were women. The metastatic sites were brain(17%), pleural effusion(27%), bone(39%), liver(7%). The 22% of patients previously treated with chemotherapy and 78% of patients was treatment-naive. Median PFS of all patients was 7.0 months (CI95%. 4.2-16 months) and, median OS of all patients was not reached, respectively. In log-lank test, sex, smoking history, brain metastasis, pleural effusion, driver mutation, and PD-L1 expression were associated with PFS. In multivariate analysis using Cox model, only PD-L1 very high expression was associated with good prognosis (HR: 0.37, CI95%: 0.14-1.00). **Conclusion:** Even in cohort of PD-L1 TPS of 50% or greater, PD-L1 very high expression was predictive marker of pembrolizumab monotherapy.

Keywords: PD-L1, NSCLC, Pembrolizumab

P2.01-60 ANALYSIS OF PROGNOSTIC FACTORS ACCORDING TO PERFORMANCE STATUS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH NIVOLUMAB

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Background: Nivolumab has a promising efficacy for patients with non-small cell lung cancer (NSCLC) as second or later line treatment. Various prognostic factors have been reported in many articles.

Among them, performance status (PS) is often reported as a strong prognostic factor. The aim of this study is to clarify the prognostic factors of good PS group and poor PS group. **Method:** The medical records of 296 patients with NSCLC who were treated with nivolumab at Kinki-chuo Chest Medical Center between December 17, 2015 and December 31, 2018 were collected. We collected clinical data at the time of nivolumab treatment commencement. We investigated the relationship between progression free survival (PFS) and patient characteristics. Furthermore, we analyzed a prognostic value factor according to PS (PS 0-1 or PS 2-4). **Result:** The median age was 70 (range, 40-90) years. 206 patients were male and 224 patients were good PS group (PS 0-1). The median PFS was 3.0 months, 4.6 months, 1.2 months in all patients, good PS group, poor PS group, respectively. Multivariate analysis showed smoking history correlated with longer PFS in both good PS group (Hazard ratio (HR), 0.452; 95% confidence interval (CI), 0.264-0.774; P = .00382) and poor PS group (HR, 0.248; 95% CI, 0.0946-0.6476; P = .00444). Furthermore, steroid use at baseline (HR, 2.341; 95% CI, 1.230-4.457; P = .00962), pleural effusion (HR, 1.516; 95% CI, 1.097-2.222; P = .01343), and liver metastases (HR, 1.732; 95% CI, 1.014-2.958; P = .00444) correlated with shorter PFS in good PS group. On the other hands, high level of advanced lung cancer inflammation index (ALI) (HR, 0.280; 95% CI, 0.109-0.724; P = .00861) and adenocarcinoma (HR, 0.464; 95% CI, 0.219-0.984; P = .0451) correlated with longer PFS in poor PS group. **Conclusion:** Smoking history is independent predictors of nivolumab efficacy in both good PS group and poor PS group. Steroid use at baseline, pleural effusion, and liver metastases are independent prognostic factors in good PS group and ALI and histology are independent prognostic factors in poor PS group.

Keywords: nivolumab, prognostic factors, performance status

P2.01-61 MULTIPLE PRIMARY CARCINOMAS (MPC) IN PATIENTS WITH NON SMALL CELL LUNG CANCER (NSCLC)

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Background: The improving survival of NSCLC patients, due to: 1. the initial diagnosis in early stages using the newer modern diagnostic tools, 2. the treatment of the disease with new effective antineoplastic drugs, and 3. the remarkable suspicion of the physicians, leads to registry of high incidence ratio of MPC in NSCLC patients. **Method:** The aim of the study was the registration of the number and clinical characteristics of MPC in NSCLC patients. Between 4/1986-3/2019, 1756 patients, 1123 (64%)men, 633 (36%)women, median age 64(33-87)years and ECOG 2(0-3) were consequently admitted in our Unit. Stage <IIIA had 304(17%) and ≥IIIA 1452(83%)patients (groups A, B respectively). Median follow-up was 20+(1+-240+)months. Survival ≥5years observed in 351(20%)patients. According to our protocols, patients stage <IIIA, underwent only follow-up after radical surgery, while patients stage IIIA treated with platinum-based chemotherapy(PBC) adjuvantly or neoadjuvantly±locoregionally radiotherapy. Patients stage ≥IIIB received therapeutically PBC±radiotherapy. **Result:** Eighty-six patients, 78/1123(7%)men, 8/633(1%)women (p<0.001), developed 102 MPC. The median interval time between NSCLC diagnosis and MPC detection, was 58(0-220)months. Two men experienced by four (all metachronous) MPC. One with lung adenocarcinoma(LADC), developed non-AIDS Kaposi-sarcoma of the leg, MDS and squamous-cell lung cancer(SqCLC). The second, with LADC, developed transitional-cell bladder carcinoma(TCBC), prostate adenocarcinoma(PrC), and colon cancer(CC). Five patients(3 men, 2 women) had by three, metachronous, MPC. One had LADC, NHL, CC, the second LADC, TCBC, PrC, and the third SqCLC, CLL and CC. One woman experienced LADC, lymphopenic HL and breast cancer(BC) and the other LADC, CLL, and small-cell lung carcinoma. Other 79 patients developed 79 MPC, 11(14%)median age 63(51-77)years, synchronous and 68(86%)median age 63.5(34-75)years, metachronous The synchronous were LADC/SqCLC in 2, LADC/PrC in 2, LADC/TCBC in 2, SqCLC/head-neck squamous-cell carcinoma(HNSqCC) in 2, and SqCLC/CC in 3 cases. The metachronous MPC were LADC, CLL, TCBC, SqCLC, PrC, CC, HNSqCC, BC, NHL, HL, in 12, 10, 8, 8, 8, 8, 6, 3, 3, 2, cases respectively. Among 351 patients surviving ≥5years, 40(11%) experienced MPC versus 46/1405(3%) with survival <5years(p <0.001). Seventy-five patients diagnosed with metachronous MPC: 10/304(3%) versus 65/1452(4.5%) of group A and B, (p=NS). There was no statistically significance in the location of non-haematological MPC related to the diaphragm (37 upper, 39 lower the diaphragm). **Conclusion:** According to our findings in NSCLC patients: 1. MPC detection is not uncommon, mainly in men. 2. The longer survival enhances the possibility of MPC. This must be considered during the follow-up of those patients. 3. Previous chemoradiotherapy doesn't increase the risk of MPC.

Keywords: Multiple primary carcinomas, synchronous, NSCLC

P2.01-62 CIRCULATING TUMOR DNA ASSAY AND SURVIVAL IN PATIENTS WITH METASTATIC, NON-SMALL CELL LUNG CANCER

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Background: Circulating tumor DNA (ctDNA) sampling has emerged as a non-invasive approach to characterizing genomic alterations in blood of patients (pts) with metastatic, non-small cell lung cancer (mNSCLC). ctDNA or 'liquid biopsy' may be used to guide treatment and prognosis. **Method:** This was a prospective pilot study of pts with histologically confirmed mNSCLC. Pts were enrolled prior to initiating a new line of therapy. Tumor and ctDNA specimens were collected prior to treatment and radiology scans were performed at standard intervals; ctDNA collections continued until progression. ctDNA was assessed by Inivata (InvisionFirst) using amplicon-based targeted next generation sequencing with 36-gene panel to detect single nucleotide variants, short insertions/deletions, copy number variations and structural variants. ctDNA features were calculated for each pt and included number of genomic alterations (numGA), number of mutations (numMUT), number of amplifications/fusions (numAMPFUS), sum mutant allele frequency (sumMAF), and maximum mutant allele frequency (maxMAF). Univariate and multivariable Cox proportional hazards models were used to identify ctDNA features associated with progression-free survival (PFS). ctDNA from baseline (T0) to the blood collection closest to progression or censor date (T1) was used to assess change in sumMAF and maxMAF. All models included ctDNA features as continuous variables. **Result:** 27 pts were evaluable. 85.19% were white; 37.04% were male. 85.19% were adenocarcinoma histology; remaining were squamous. 45.83% received prior systemic therapy. Average number of lines of prior therapy was 1.81. 44.44% had prior radiation therapy. 81.48% of pts had at least one genomic alteration detected in ctDNA at baseline. The median numGA, numMUT, and numAMPFUS, maxMAF, sumMAF was 2.00, 2.00, 0.00, 1.61, and 2.34 respectively. TP53, KRAS, and EGFR were the most frequently identified genomic alterations (59.26%, 25.93%, and 22.22%, respectively). EGFR alterations were the most commonly identified genomic alteration in ctDNA. 86.00% of EGFR alterations were actionable. Univariate Cox regression analysis identified numAMPFUS (HR=3.12, p=0.01), sumMAF (HR=1.02, p=0.02), and maxMAF (HR=1.05, p=0.00) to be significantly associated with PFS. Only maxMAF was retained in the final multivariable Cox model. Each percentage point increase in maxMAF from T0 to T1 resulted in a 4% decrease in the risk of progression/death (HR=0.96, p=0.08). **Conclusion:** In this pilot study, pts with higher levels of baseline maxMAF detected in ctDNA were associated with increased risk of progression/death. Following initiation of treatment, results suggest increased change in maxMAF may be associated with a decreased risk of progression/death.

Keywords: Non-Small Cell Lung Cancer, ctDNA, Survival

P2.01-63 RADIOSURGERY FOLLOWED BY TUMOR TREATING FIELDS (TTFIELDS) FOR BRAIN METASTASES (1-10) FROM NSCLC IN THE PHASE 3 METIS TRIAL

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Background: Tumor Treating Fields (TTFields) are non-invasive, loco-regional, anti-mitotic treatment modality comprising alternating electric fields. TTFields have demonstrated efficacy in preclinical non-small cell lung cancer (NSCLC) models. TTFields

treatment to the brain was safe and extended overall survival in newly-diagnosed glioblastoma. The METIS study [NCT02831959] investigates the efficacy and safety of TTFields in NSCLC patients with brain metastases. **Method:** NSCLC patients (N=270) with 1-10 brain metastases are randomized 1:1 to stereotactic radio surgery (SRS) followed by continuous TTFields ((150 kHz, > 18 hours/day) within 7 days of SRS or supportive care. The TTFields portable device delivers TTFields to the brain using 4 transducer arrays, while patients receive the best standard-of-care for their systemic disease. Patients are followed every two months until second intracranial progression. Key inclusion criteria: KPS ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial brain metastases from NSCLC amenable to SRS; KPS ≥70; and optimal therapy for extracranial disease. Prior WBRT or surgical resection of metastases, a single resectable lesion or recurrent brain metastases were exclusionary. Primary endpoint was time to 1st intracranial progression. Secondary endpoints included time to neurocognitive failure (HVLT, COWAT and TMT), overall survival, radiological response rate (RANO-BM and RECIST V1.1); quality-of-life; adverse events; time to first/second intracranial progression for patients with 1–4 and 5–10 brain metastases; bi-monthly intracranial progression rate from 2–12 months; and time to second intracranial and distant progression. The sample size (N=270) was calculated using a log-rank test (Lakatos 1988 and 2002) with 80% power at a two sided alpha of 0.05 to detect a hazard ratio of 0.57. In August 2018, an independent Data Monitoring Committee (DMC) performed a review of the METIS trial data collected to that point. The DMC concluded that no unexpected safety issues have emerged on the study, and recommended to continue the METIS study as planned. **Result:** "Section not applicable" **Conclusion:** "Section not applicable"

Keywords: Radiosurgery plus Tumor Treating Fields (TTFields), TTFields for brain metastases from NSCLC

P2.01-64 SYSTEMIC INFLAMMATORY MARKERS AS A PREDICTORS OF RESPONSE TO CRIZOTINIB IN PATIENTS WITH ALK-POSITIVE NON-SMALL-CELL LUNG CANCER

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Background: The significance of the presence of a systemic inflammatory response (SIR) in predicting survival has been demonstrated in patients with cancer. Moreover, neutrophil-to-lymphocyte ratio (NLR),lymphocyteratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been also investegated in patients with both early and advanced non-small-cell lung cancer (NSCLC). However, determination of SIR predicting outcomes of patients who are likely to response to crizotinib in ALK-positive NSCLC patients has not been clearly demonstrated. The aim of this study was to investigate the prognostic and predictive value of NLR, LMR and PLR in patients with ALK-positive NSCLC treated with crizotinib. **Method:** Eighty-two patients with ALK-positive NSCLC who were treated with crizotinib were retrospectively analyzed. The cutoff values for NLR, LMR and PLR were defined by the receiver operating characteristic (ROC) curve analysis.Univariate and multivariate analyses were used to evaluate the prognostic significance of NLR, LMR and PLR. Logistic regression analysis was also performed to determine predictive indicators of response to crizotinib. **Result:** Among 82 patients, 35 (42.7%) were male and 47 (57.3%) were female, with a median age of 52.5 years (range; 20–77 years). Crizotinib treatment was administered as a first-line in 26.8% of patients, second-line in 56.1%, third-line in 12.2% and forth-line and later in 4.9%. The objective response rate was 77.2% (CR+PR) and stable disease was obtained in 7.6% of patients. According to the ROC curve, the recommended cutoff values of NLR, LMR and PLR were 3.14, 2.31 and 185,5 respectively. The median follow-up time was 19.3 months. ECOG performance status (PS) (p=0.014) and response to crizotinib (p=0.001) for progression-free survival (PFS) and ECOG PS (p<0.001), response to crizotinib (p<0.001), NLR (p=0.029) and LMR (p=0.028) for overall survival (OS) were found to be prognostic factors by univariate analysis. On the other hand, multivariate analysis showed that only ECOG PS and response to crizotinib were independent prognostic indicators for both PFS and OS.A logistic regression analysis indicated that NLR and LMR was found to bean independent factor for predicting response to crizotinib (p=0.007, OR:0.10 and p=0.044, OR: 0.20, respectively). **Conclusion:** Our findings showed that NLR and LMR are readily feasible and simple and also inexpensive biomarkers predicting response of crizotinib for patients with ALK-positive advanced NSCLC.

P2.01-65 TEMPORAL CHANGES OF RADIATION-INDUCED LUNG INJURY FOLLOWING PROTON THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Proton therapy (PT) is increasingly being used in locally advanced non-small cell lung cancer (NSCLC), but is there currently a limited understanding of its radiation-induced lung injury pattern that can cofound radiologic interpretation. Here we characterize imaging of radiation-induced lung injury on CT (computed tomography) and FDG-PET (^{18}F-deoxy-glucose-positon emission tomography) following PT. **Method:** After institutional IRB approval, longitudinal imaging from adult NSCLC patients undergoing PT over a 5-year period at our institution were retrospectively analyzed by two thoracic radiologists. Tumor size and FDG standard uptake value max (SUV_{max}) were recorded. In addition, early (<12 months after PT) and late (>12 months) radiation-induced lung injuries were quantified (0-3 Likert score), including consolidation, ground glass, interlobular septal thickening, bronchiectasis and pleural effusion, on all serial imaging. **Result:**

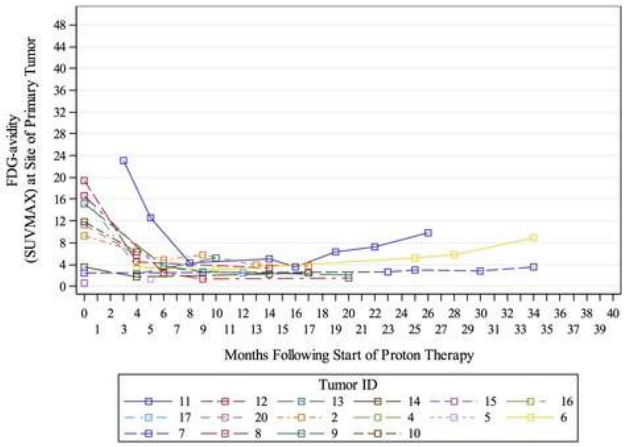

Figure: Temporal changes in FDG avidity in NSCLC following proton therapy. FDG (SUVmax) on PET/CT NSCLC treated with proton therapy exhibits a steady decrease glucose avidity over the first year following therapy.

19 consecutive locally advanced NSCLC patients (mean age 69.3 yrs) had PT during the study period and had serial images available for review. The mean imaging follow-up period from PT start was 30 months. Five patients developed local failure. In the remaining 14 patients, tumor size and FDG avidity steadily decreased over time (mean SUVmax = 10.8 at baseline and 2.5 at 12 months). Ground glass and interlobular septal thickening presented as early changes, increasing through months 6-12 and 9-12 respectively but generally resolved by 24 months. 68% of patients developed a pleural effusion (< 2 years), increasing in severity over the 1st 18 months. Consolidation consistently increased in severity throughout the observation period (max >48 months) Among 11 tumors, 8 achieved maximum severity in late changes of band-like or mass-like consolidation within 24 months and then typically plateaued. Late development of a pleural effusion, mass-like fibrosis, increased tumor caliber and increased FDG avidity were associated with local tumor recurrence. **Conclusion:** Radiation-induced lung injury follows a predictable temporal pattern on CT. Knowledge of expected timeline of the imaging findings may

prevent unnecessary imaging and/or biopsies. We are currently analyzing a larger cohort of 100 NSCLC patients to compare post radiation changes in local recurrence and local control.

Keywords: proton therapy, Non-Small Cell Lung Cancer, computed tomorgraphy

P2.01-66 GENOMIC LANDSCAPES OF DNA COPY NUMBER ALTERATIONS IN PRIMARY LUNG CANCERS AND MATCHED BRAIN METASTASES

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Background: Lung cancer (LC) is the leading cause of cancer mortality worldwide. The majority of LC patients will develop distant metastases at some point during their disease, and brain is among the most common sites of relapse. However, little is known about the mutational landscape of brain metastases (BM) and their potential inter-tumor heterogeneity. Better knowledge on this subject may pave the way to new therapeutic strategies. Here, we map the DNA copy number alterations (CNAs) by sequencing a cohort of primary LC samples and matched BM. **Method:** The study group included 57 patients (21 females and 36 males, median age 61±8 years; 35 adenocarcinomas, 18 squamous-cell carcinomas, 2 large-cell carcinomas, 1 adenosquamous carcinoma and 1 small-cell lung cancer). From all patients pair-matched tissue samples from primary tumor and corresponding BM were collected, fixed in formalin and embedded in paraffin. All patients were therapy-naïve at the time of primary tumor collection. Genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen, Germany), followed by NGS library preparation using the NEBNext Ultra II DNA kit (NEB, USA). Samples were sequenced shallowly (average depth 26 Mreads) on the NextSeq 500 system (Illumina, USA). The R package QDNAseq was used to call and visualize DNA copy number levels. The P value of <0.05 (Wilcoxon paired test) was considered statistically significant. **Result:** The median time between primary LC diagnosis and BM occurrence was 13 months range, 0 to 91 months), and synchronous BM were diagnosed in 12% of patients. Overall survival in the entire group was 22.5 months. The number of CNA was significantly higher in BM than in primary tumor, regardless of clinical/demographic data or type of aneuploidy (gains/losses). Primary tumors harbored significantly more gains and almost no losses. In both tumor sites, the most frequent gains affected 1q, 5p, 7p, 8q and 20q, whereas gains of 17q and 19q, and losses of 4p, 4q, 5q, 8p, 9p, 16q, 17p, 18q, 22q were identified only in BM. The fraction of the genome affected by mutational events in BM correlated positively with time to BM development. Three the top altered genes (*IL7R, MLT11, SETDB1*) were identical in both primary lesions and BM. **Conclusion:** Our results indicate that while primary LC lesions harbor frequent amplifications, the CNA landscape of BM is dominated by deletion events. Higher number of CNA harbored by late compared to synchronous BM suggests high levels of genomic instability.

Keywords: Corresponding brain metastases of lung cancer, DNA copy number alterations, Next generation sequencing

P2.01-67 ARE KRAS MUTATIONS PREDICTIVE OF RESPONSE TO IMMUNOTHERAPY IN NON SMALL-CELL LUNG CANCER? A SINGLE CENTER EXPERIENCE

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Background: Lung cancer is the leading cause of cancer-related mortality. In the last decade, the treatment landscape has evolved for non-small-cell lung cancer (NSCLC), in large part thanks to two therapeutic advances: targeted therapy for oncogene driven tumours and immune checkpoint-inhibitors (ICI). The latter can lead to very long survival, but only in a limited number of patients. Post-hoc analyses and preclinical data suggest KRAS mutated NSCLC may respond better to ICI. **Method:** We retrospectively analysed all stage IV NSCLC patients treated in our center with immunotherapy from January 2016 to December 2017 and compared KRAS mutated to wildtype patients. The clinical outcomes analysed were disease control rate (DCR), partial response (PR), progression free survival (PFS) and overall survival (OS). We performed an exploratory analysis on the impact of KRAS mutation type and concurrent mutations. **Result:** 45 patients treated with ICI. 7 were excluded due to insufficient data. 38 were included. 27 patients (71%) with nivolumab, 9 patients (24%) with pembrolizumab and 2 patients (5%) with atezolizumab. 22 patients (58%) were male and 16 (42%) female. The median age was 63. 21 patients (55%) presented KRAS mutations, of which 4 (19%) had concurrent p53 mutations and 1 (5%) an EGFR mutation. 17 patients (45%) were KRAS wild-type, of which 4 (24%) had EGFR mutations and 1 (6%) had a BRAF V600E mutation. In the KRAS mutated subgroup 59% were male and 41% were female, the median age was 61 years and all patients had PS 0-1. All patients received second line immunotherapy except for 2, one in third line, one fifth line. In the intention to treat population (ITT) the DCR was 71% with 55% PR, PFS was 11.3 months, and OS 17.7 month. In the KRAS wild-type subgroup DCR was 59% with 49% PR, the PFS was 8.4 months and OS 16.8 months. In the KRAS mutated subgroup, DCR was 81%, with 62% PR, PFS was 13.6 months and OS 18.5 months. An exploratory analysis based on KRAS mutation types or co-mutations was performed. The average PFS for G12C, G13C, G12V, G61H and other mutations was 19.1, 7.8, 9.4, 2.2, 13.9 months respectively. PFS for p53 co-mutated KRAS NSCLC was 23.5 months. Further analyses for STK11 co-mutations are ongoing, as these confer resistance to ICI. At the time of analysis 7 patients were still receiving immunotherapy. . **Conclusion:** In our retrospective study, KRAS mutations in NSCLC were predictive of numerically superior response to ICI compared to wildtype patients. Currently, the data is conflicting and larger clinical trials are needed to clarify this hypothesis and ascertain whether and how KRAS should be part of the treatment algorithm for the selection of ICI patients. Furthermore, more research is needed to confirm the potential role of mutation types and clinical impact of co-mutations in KRAS.

Keywords: NSCLC, KRAS, Immunotherapy

P2.01-68 HIGH NLR IS POOR PREDICTIVE BIOMARKER FOR NSCLC TREATED WITH PD-1 INHIBITOR IN REAL WORLD PRACTICE

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Background: PD-1 inhibitor in NSCLC is effective treatment option. PD-L1 expression and tumor mutation burden (TMB) is suggested as predictive biomarker for drug efficacy, but especially in the real-world, predictive factors have not been established. Therefore, we evaluated predictive biomarker for NSCLC treated with PD-1 inhibitor in real world practice. **Method:** This study evaluated 73 NSCLC patients treated with PD-1 inhibitor at St. Vincent hospital from April 2016 to January 2019. Following baseline data were recorded at the time of PD-1 inhibitor treatment: Age, Sex, ECOG performance status, PD-1 inhibitor type, line of treatment, lymphopenia, NLR (neutrophil-lymphocyte ratio), hyponatremia, presence of brain, liver and bone metastasis, EGFR status, PD-L1 expression. Progression free survival (PFS) and overall survival (OS) was evaluated and Cox survival analysis was used for these analyses. **Result:** Median age was 66 years old and male was predominant (67.1%). Nivolumab and pembrolizumab was treated in 34 (46.6%) and 39 (53.4%) patients, respectively. Lymphopenia (<1,000/microleter) was 20 (27.4%) and high NLR (≥ 3) was 41 (56.2%). Hyponatremia (135 mEq/L) was noted in 18 (24.7%) and metastasis of brain, liver and bone were 19 (26%), 12 (16.4%) and 28 (38.4%). Median PFS and OS were 84 days and 180 days, respectively. For PFS, ECOG performance status, presence of brain, liver, bone metastasis, PD-L1 (22C3), presence of EGFR mutation, lymphopenia and NLR was significant predictive factors in univariate analysis. As independent factors, presence of liver (Hazard ratio (HR): 3.32, 95% confidence interval (CI): 1.13-9.75, P-value: 0.029), bone metastasis (HR: 2.90, 95% CI: 1.25-6.75, P-value: 0.013), high PD-L1 expression (≥50%) (HR: 0.32, 95% CI: 0.14-0.72, P-value: 0.006) and high NLR (≥ 3) (HR: 2.58, 95% CI: 1.16-5.77, P-value: 0.021) were remained in multivariate analysis. Regarding OS, ECOG performance status, presence of bone metastasis, hyponatremia, lymphopenia and NLR were significant

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predictive factor for PD-1 inhibitor. In multivariate analysis, poor ECOG status (2 or 3 compared to 0 or 1) (HR: 2.95, 95% CI 1.54-5.64, P-value: 0.001) and high NLR (≥ 3) (HR: 3.29, 95% CI: 1.68-6.47, P-value: 0.001) were significant predictive factors. **Conclusion:** High NLR is significant predictive biomarker for both PFS and OS in this real world study. Further studies are needed to evaluate these findings.

Keywords: PD-1 inhibitor, NSCLC, NLR

P2.01-69 NSCLC MUTATION FREQUENCY IN THE CENTRAL AMERICAN AND CARIBBEAN REGION

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Background: Lung Cancer (LC) constitutes a leading cause of death in the World. Non-small cell lung cancer subtype adenocarcinoma (NSCLC-A) has been associated with epidermal growth factor receptor (EGFR) mutations, which is essential for treatment decisions. The EGFR mutation frequency has been proven to have regional variability in this NSCLC-A population . The current study presents the EGFR mutation incidence and T790M frequency in NSCLC-A cases diagnosed in Central American and Caribbean(CA&C) region. **Method:** A cross-sectional evaluation was performed in patients diagnosed with NSCLC-A between 2016 and 2018 in five CA&C countries. Patients were obtained from Reference Centers in Dominican Republic, Nicaragua, Panama, Honduras and Costa Rica through the AstraZeneca testing program. EGFR mutations were evaluated through Real-Time PCR. **Result:** The research included 972 cases. Mean of age at the diagnosis was 62.79(28.12-90.46) years. Overall distribution of cases by gender was female in 52.37% (509/972) and male in 47.64% (463/972). For the group of antiEGFR TKI naïve patients, tissue samples were processed in 67.83% (601/886). The group of post antiEGFR TKI, patient's plasma samples were processed in 90.70% (78/86). AntiEGFR TKI naïve group, EGFR mutations were present in 26.64% (236 / 886), the mean of age was 63.17 years (28.12-90.46). The frequency of Exon 19 was 53.38% (126/236) and Exon 21 was 27.54%(65/236) and 11.01% (26/236) were complex mutations. T790M mutations in this treatment naïve population was 2.14%(19/886). For the group of post antiEGFR TKI patients the frequency of T790M mutation was 50.00% (43/86) where 78.57% were obtain from plasma samples. **Conclusion:** The frequency of NSCLC EGFR mutation positive patients in the CA&C region was similar to that previously described in other Latin American (LA) countries. In the treatment naïve population, tissue samples remain the most important sample to analyze for EGFR mutations. T790M mutations can be seen in treatment naïve population. For patients that progressed to an antiEGFR TKI, T790M mutations were seen in a similar frequency as describe in previous LA countries. For post antiEGFR TKI patients, plasma samples were the preferred method to evaluate T790M mutations with an adequate sensibility.

Keywords: Non-Small-Cell Lung, epidermal growth factor, mutation

P2.01-70 THERAPY WITH OSIMERTINIB IN PATIENTS WITH T790M MUTATION: EXPERIENCE OF A PORTUGUESE ONCOLOGY CENTER

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Background: Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), was initially approved to treat locally advanced or metastatic non-small cell lung cancer (NSCLC) with T790M acquired resistance and recently for first-line treatment in those with EGFR activating mutations. The aim of the authors was to evaluate the efficacy of osimertinib in a sample of patients followed at a portuguese cancer center who progressed during prior therapy with EGFR-TKI. **Method:** We treated 26 patients with metastatic NSCLC with osimertinib between January 2017 and June 2018. Data was collected from clinical files. Statistical analysis was performed using SPSS software. **Result:** 18 women and 8 men with a median age of 68 (range, 41-81) were included. Median time of follow-up was 13.5 months. The majority (23) were non-smokers and 84.6% had ECOG-PS ≤1. Brain metastasis (BM) was present and stable in 6 patients at the start of therapy. The T790M mutation was diagnosed by liquid biopsy in 61.5%. The disease control rate was 88.5%. Median progression free survival (PFS) was 15 months and was significantly lower in the subgroup with BM (6 months vs. not reached, p = 0.033). The most frequent adverse events were fatigue (46.2%) and thrombocytopenia (38.5%) and one patient had to discontinue treatment for pancytopenia grade ≥3. **Conclusion:** This study revealed similar results to those observed in clinial trials, although with higher PFS. Despite the small sample and limited follow-up time, osimertinib has been shown to be safe and effective in our clinical practice.

Keywords: NSCLC, T790M, Osimertinib

P2.01-71 COMPREHENSIVE ANALYSIS OF EGFR T790M-MUTANT ABUNDANCE OF DIFFERENT TECHNOLOGIES AND ITS EFFECT ON EFFICACY OF OSIMERTINIB IN ADVANCED NSCLC

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Background: Osimertinib has been adopted as the standard of care for T790M-mediated acquired epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance. And detecting EGFR T790M mutation can be challenging in routine care, low abundance of the mutation and difficulty for re-biopsy in patients with advanced disease. We aim to compare droplet digital PCR (ddPCR) and next generation sequencing (NGS) in T790M mutation testing, and analyze whether the abundance of T790M mutation is associated with the efficacy of osimertinib in advanced Non–small cell lung cancer (NSCLC). **Method:** We retrospectively studied 132 T790M-positive advanced NSCLC patients who have received osimertinib after acquired TKI resistance from April 2017 to August 2018 at our institution. Treatment response was evaluated and survival data were collected and analyzed. **Result:** Among the 132 patients, 18(13.6%) had adopted amplifcation refractory mutation system (ARMS), 58(43.9%) adopted ddPCR, 43(32.6%) used NGS in T790M testing, and the detection methods of 13(9.9%) patients were unknown. Data of T790M-mutatnt abundance were obtained in 64 patients, 57 of whom were tested by ddPCR in plasma and the other 7 by NGS. The median progression free survival (PFS) was 15 months, median OS was not reached, objective response rate (ORR) was 88%. We found that ARMS, ddPCR, NGS have no difference in T790M testing (p=0.114). Among the 57 ddPCR testing patients with the abundance of T790M, there was no difference in PFS of T790M abundance in the cutoff value of 0.5 (p=0.303). **Conclusion:** Our results suggest that ARMS, ddPCR and NGS are all useful and reliable methods in EGFR T790M mutation detection. And the association between the abundance of T790M mutation using ddPCR in plasma and the efficacy of osimertinib seemed not strong and remained to be explored.

Keywords: Non-Small Cell Lung Cancer, T790M-Mutant Abundance, Osimertinib

P2.01-72 SAFETY OF PALLIATIVE RADIOTHERAPY AND IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (ICIs) are now widely used as standard of care treatments for metastatic non-small cell lung cancer (m-NSCLC) alongside palliative radiotherapy (RT). Commonly used ICIs have long half-lives, typically between 3-4 weeks, and with reported effect even months after discontinuation. The safety of RT based on timing and biologically effective dose (BED) with respect to ICIs is not yet elucidated. This study

hypothesized that RT use within 3 months interval prior and after ICI does not increase grade ≥2 toxicities from either ICIs or RT. **Method:** This retrospective analysis includes m-NSCLC patients treated with both RT and ICIs at the Sunnybrook Odette Cancer Centre, Toronto from June 2014 to January 2019. Patients were identified by both our chemotherapy computerized physician order entry system, OPIS and radiation database. ICIs and RT-related toxicities after first ICIs dose were graded as per CTCAE v4.0. Based on timing and location, toxicities attributed to either ICIs or RT by clinicians. **Result:** Forty-four m-NSCLC patients treated with ICIs (nivolumab, pembrolizumab, or atezolizumab) and RT were identified. Twenty one (47.7%) were females, median age 67.5 (33.4- 83.2) years, 36 (81.8%) Caucasian, 42 (95.5%) non-squamous histology, 34 (77.3%) previous or current smokers, PD-L1 1-49% in 7 (15.9%) patients and ≥50% in 15 (34.1%), 9 (20.5%) EGFR/ALK positive, 40 (90.9%) ECOG 0-1. Median follow-up was 10.6 (0.7- 54.6) months. Twenty-five patients (group 1) received RT within 3 months prior and after ICIs (60 courses total, 32 (53.3%) extracranial), with median biologically effective dose with α/β= 10 (BED_{10}) 59.5 (14.4-72.0) Gy_{10}, while 19 had no RT in that interval (group 2). Overall, group 1 had 142 RTs (82 outside interval), with median BED_{10} 52.7 (14.4-120) Gy_{10}, while group 2 had 51 RTs, with median BED_{10} 52.8 (10.1-105.6) Gy_{10}. Grade ≥2 toxicities (8 total, 7 ICIs-related, 1 RT-related) occurred in 7 (28.0%) patients from group 1, and in 4 patients (26.3%) in group 2 (6 total all ICIs-related); this was not statistically significant (χ^2 p= 0.60). Five grade 3 toxicities were: pneumonitis (2), hepatitis (1), colitis (1), and nausea (1). No grade 4 or 5 toxicity was reported. **Conclusion:** Palliative RT within 3 months of ICIs did not increase ICIs and RT-induced grade ≥2 toxicities. Proceeding with ICIs while receiving palliative RT for m-NSCLC is likely safe. Further research incorporating larger cohort is planned to verify these safety results.

Keywords: radiotherapy, toxicity, Immunotherapy

P2.01-73 OUTCOME DISPARITIES IN AMERICAN INDIAN/ ALASKAN NATIVES WITH ADVANCED STAGE LUNG CANCER

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Background: Although there have been many advances in the treatment of lung cancer, outcomes for American Indian/Alaskan Natives (AI/AN) have remained poor. AI/AN patients present at a younger age, more advanced stage and have higher lung-cancer attributed mortality rates. While disparities in treatment of early stage lung cancer are well described, the pattern of treatment in advanced stage disease and cancer guideline concordance is incompletely understood. **Method:** Data was obtained from the National Cancer Institute SEER database from 2000-2013, which was linked with Medicare enrollment and claims data from the Centers for Medicare and Medicaid Services. Patients were included if they were characterized as AI/AN by either SEER or Medicare databases and diagnosed with stage IIIB/IV lung cancer. Demographic data and clinical characteristics were abstracted. Metrics were developed to assess adherence with lung cancer treatment guidelines. **Result:** Out of 238,439 lung cancer patients, 404 patients had advanced stage disease and were coded as AI/AN in SEER. They were propensity matched by age at diagnosis, year of diagnosis and number of lung cancers to a cohort of white advanced stage patients (N=404). The comparison of the patient characteristics across the two race groups shows that AI/AN patients were more likely to have squamous cell histology, live in smaller urban communities, less likely to be married, and less likely to receive surgery or radiation. Only 20.5% of the advanced lung cancer AI/AN population received appropriate therapy within 90 days of diagnosis compared with 29.5% of the propensity matched white cohort (*p = 0.004*). **Conclusion:** AI/AN patients are less likely to receive cancer-directed care such as surgery or radiation than the matched white cohort and less likely to receive appropriate therapy within 90 days of diagnosis. Work is ongoing to evaluate adherence to other metrics such as receipt of appropriate diagnostics and treatment as well as trends in survival.

Keyword: SEER, AI/AN, disparities

P2.01-74 CLINICAL-PATHOLOGICAL FEATURES AND OUTCOME OF PATIENTS WITH ORAL METASTASES FROM LUNG CANCER: A MULTICENTER RETROSPECTIVE STUDY

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Background: Oral metastases are a rare event, accounting to less than 1% of all oral malignancies, sometimes being the first manifestation of a wide-spread disease. Regardless of the site of the primary tumor, patients with oral metastases have a poor prognosis, with a reported median overall survival (mOS) of 6 months. Lung cancer, particularly small cell lung cancer (SCLC) and poorly differentiated carcinoma, represents the main source of oral metastases, even if large datasets still lack. We conducted a multicenter retrospective study investigating incidence, clinical-pathological features and outcome of patients with oral metastases from lung cancer. **Method:** Between January 2014 and December 2018 we collected data from all consecutive patients diagnosed with lung cancer in four oncological Italian centers. Clinical-pathological features of those patients with oral metastases involving jaw or/and soft tissues were described. **Result:** Among 4,082 consecutive lung cancer patients, the incidence of oral cavity metastases was 0.15% (6 out of 4,082 patients,). Patients were more frequently male (5 out of 6, 83%), current or former smokers (5 out of 6, 83%), with a median age at diagnosis of 61 years (range 53-69) [table 1]. Four different histotypes of lung cancer were detected. Five patients (83%) were stage IV *ab initio*, with synchronous histologically confirmed oral metastases. All these patients had distant metastases other than in the oral cavity (median of 5 different metastatic sites). The mOS since the diagnosis of oral metastases was 67 days (range 36-166). Table 1. Patient characteristics

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Gender	Age (years)	Smoke	Histotype	N° metastatic sites	Site of oral lesion	Time between stage IV diagnosis and oral lesion occurrence	Local radio-therapy	Median OS from oral lesion occurrence (days)
M	69	Current	Poorly differentiated	4	Jaw	Syncronous	Yes	57
M	61	Current	Sarcomatoid	5	Jaw	Syncronous	Yes	107
M	61	Former	Adenocarcinoma	3	Gum	11 months	Yes	77
M	53	Former	Poorly differentiated	4	Gum	Syncronous	No	44
M	59	Current	SCLC	5	Gum	Syncronous	No	36
F	66	Unknown	Squamous (mut ex 19 EGFR)	5	Gum	Syncronous	No	166

Conclusion: To our knowledge, this is the largest study assessing the incidence of oral metastases in lung cancer patients. Oral involvement, usually diagnosed at an advanced stage, seems to be associated with a very poor prognosis, with a mOS of about 2 months. Further confirmatory datasets are warranted.

Keywords: Lung cancer, oral metastases

P2.01-75 TEMPORAL TRENDS IN TREATMENT PATTERNS FOR ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER (ANSCLC) IN ROUTINE CLINICAL PRACTICE

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Background: For aNSCLC patients lacking actionable molecular markers, guideline recommendations for first-line treatment include platinum-based chemotherapy or immune checkpoint inhibitors (ICIs) as single agents or in combination with platinum-based chemotherapy (platinum-based chemoimmunotherapy) based on recent clinical trials and FDA approvals. When initial therapy fails, recommendations are for second-line treatment with ICIs (if not given in first-line), single-agent chemotherapy, or ramucirumab+ docetaxel. The objective of this study was to understand the evolution of aNSCLC treatment patterns following the May 2017 FDA approval of platinum-based chemoimmunotherapy in frontline. **Method:** This retrospective observational study analyzed electronic health record data from the Flatiron Health database for adult patients who initiated first-line therapy for aNSCLC between 01/01/2015-12/31/2018. Eligible patients were stratified by first-line treatment initiation time period (before and after May 2017). **Result:** Of the 22,342 eligible patients receiving first-line treatment, 9,482 (42%) initiated second-line systemic therapy, and of those, 3,260 (34%) initiated third-line therapy during the study period. Patient characteristics were generally consistent over time. Overall, there was considerable heterogeneity in the treatment landscape for aNSCLC, with over 200 unique regimens used in each of the three treatment lines evaluated. After May 2017, platinum-based regimens continued to be the standard treatment in first-line (Table), with increasing usage of ICIs as single agents (mostly pembrolizumab) or in combination with platinum-based chemotherapy (mostly pembrolizumab+pemetrexed+platinum), and decreasing use of platinum-based regimens that do not contain an ICI. In second-line, use of ICI monotherapy was consistent and usage of single-agent chemotherapy decreased slightly after May 2017. The use of platinum-based chemotherapy in second-line increased after May 2017, consistent with increased usage among patients receiving first-line ICI monotherapy. Overall, second-line ramucirumab+docetaxel usage increased as ramucirumab+docetaxel has become the most commonly used regimen following first-line platinum-based chemoimmunotherapy. In third-line, the use of ICI monotherapy decreased after May 2017 while usage of single-agent chemotherapy remained consistent over time. Third-line ramucirumab+docetaxel usage also increased after May 2017, in line with increased use of third-line ramucirumab+docetaxel among patients previously treated with sequential platinum-based chemotherapy and ICI monotherapy in first- and second-line.

Table. Trends in Use of Standard Systemic Treatment for aNSCLC

Treatment	Before May 2017	After May 2017	*P*-value[a]
1L Regimen, %[b]			
Any therapy	100 (n = 13,656)	100 (n = 8,686)	
Platinum-based therapy without ICI	66.5	40.3	< 0.001
Platinum + ICI combination therapy	0.1	20.1	< 0.001
ICI monotherapy	12.0	23.5	< 0.001
2L Regimen, %[b]			
Any therapy	100 (n = 6,832)	100 (n = 2,650)	
ICI monotherapy	50.7	49.6	0.318
Platinum-based therapy	17.7	23.5	< 0.001
Single-agent chemotherapy	11.3	8.3	< 0.001
Ramucirumab + docetaxel	1.5	3.7	< 0.001
3L Regimen, %[b]			
Any therapy	100 (n = 2,694)	100 (n = 566)	
ICI monotherapy	32.7	23.3	< 0.001
Single-agent chemotherapy	22.5	24.9	0.227
Platinum-based therapy	16.9	22.3	0.003
Ramucirumab + docetaxel	6.6	10.4	0.002
Most common 2L regimen following above 1L regimens, %[c]			
1L platinum-based therapy without ICI, 2L nivolumab	50.8	32.5	< 0.001
1L platinum + ICI combination therapy, 2L ramucirumab + docetaxel	0.0	21.0	< 0.001
1L ICI monotherapy, 2L carboplatin + pemetrexed	7.4	10.4	< 0.001
Most common 3L regimen following above 1L regimens and common sequences, %[d]			
1L platinum-based therapy without ICI, 2L ICI monotherapy, 3L ramucirumab + docetaxel	13.5	16.7	0.148
1L platinum + ICI combination therapy, 2L ramucirumab + docetaxel, 3L gemcitabine	0.0	44.4	NA[e]
1L ICI monotherapy, 2L platinum-based therapy, 3L ramucirumab + docetaxel	6.5	10.8	NA[e]

Data are presented as %.
Abbreviations: 1L = first-line, 2L = second-line, 3L = third-line, ICI = immune checkpoint inhibitor, platinum = carboplatin or cisplatin.
[a]All p-values are from Pearson's Chi Squared Test.
[b]Percents may not add up to 100% as treatment groups are not mutually exclusive.
[c]Denominator (not shown) is total number of patients treated with 1L regimen of interest.
[d]Denominator (not shown) is total number of patients treated with 1L and 2L sequence of interest.
[e]P-value not computed due to small sample size.

Conclusion: This study illustrates the changing treatment landscape for aNSCLC in real-world clinical practice since May 2017. While usage of aNSCLC treatments continues to be highly variable, the approval and rapid uptake of ICIs in frontline appears to have altered how available post-progression treatment options are prescribed and sequenced. Future studies should evaluate the impact of these changes and treatment heterogeneity on patient outcomes.

Keywords: treatment trends, Non-Small Cell Lung Cancer, immune checkpoint inhibitor

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P2.01-76 BONE METASTASIS AND PLEURAL DISSEMINATION AS A POTENTIAL MARKER FOR PREDICTING OF T790M MUTATION IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Acquired resistance in epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC)-patients after tyrosine kinase inhibitor (TKI)-treatment is a major clinical problem. In the majority of these patients, the T790M-mutation is detected at time of acquired TKI-resistance. However, it is less clear if the location of metastatic site may influence the ability to identify T790M mutation in NSCLC patients. **Method:** We retrospectively screened patients with NSCLC harboring EGFR mutations with progressive disease who were rebiopsied between January 2016 and December 2018. EGFR T790M mutation status after EGFR-TKIs failure was assessed using liquid biopsy or tissue rebiopsy sample. Clinical factors influencing T790M status were evaluated by univariate and multivariate analysis. **Result:** Among 39 rebiopsied patients for whom EGFR mutation status was available, 21 (53.8%) had T790M mutations. Patient characteristics at rebiopsy were not significantly different between T790M-positive and -negative groups, except for bone metastasis. Total duration of EGFR-TKI treatment before rebiopsy, EGFR-TKI treatment history immediately before rebiopsy, progression-free survival after initial TKI treatment, and rebiopsy site (other than fluid samples) significantly influenced T790M status. The incidence of T790M mutation was shown by multivariate analysis to be significantly higher in patients with bone metastasis and pleural dissemination (odds ratio, 26.4; 95% confidence interval (CI), 3.80-184 and odds ratio, 12.1; 95% CI, 1.57-92.4, respectively). **Conclusion:** Bone metastasis and pleural dissemination may represent useful predictive markers for T790M detection. In patients with these clinical factors, rebiopsies may be more recommended to detect T790M mutation.

Keywords: Metastatic site, EGFR, T790M

P2.01-77 PET CT RADIOGENOMIC DEPICTION WITH EGFR AND ALK MOLECULAR ALTERATIONS IN LUNG CANCER AMONG INDIAN POPULATION

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Background: Non small cell lung cancer (NSCLC) represents an area of paramount importance wherein patients undergo testing for targetable genetic alterations. Association between the imaging and molecular phenotypes is vital highlighting the growing importance and unmet need of classifications based on radio genomic characterization. This study was conducted to evaluate the correlations between the radiologic and molecular phenotypes in patients with NSCLC. **Method:** 211 patients with lung cancers during the study period of one year from October 2017 till November 2018 in our institution and undergoing both radiologic (PET-CT) and molecular investigations [Epidermal Growth Factor Receptor (EGFR), Anaplastic lymphoma kinase (ALK)] were included in the study. Both quantitative and qualitative CT findings were evaluated and correlated with the molecular findings. Quantitative data included SUV max obtained from PET component of CT and maximum diameter of lesion according to the RECIST criteria. Qualitative data recorded included location, pleural tail, pleural effusion, pericardial effusion, opacity, margins, calcifications, obstructive changes, pleural nodules, lung nodules, invasion, air bronchogram, emphysema, pulmonary fibrosis, mediastinal lymph nodes and distant metastasis. Statistical analysis was performed to evaluate the association of the qualitative features with the molecular expression. Receiver operating characteristic curves (ROC) were drawn and the corresponding area under curve (AUC) was calculated. *P*-values <0.05 were considered significant. **Result:** Overall, EGFR mutation positivity and ALK rearrangement was observed in 114 and 37 patients, respectively whereas 60 patients had neither of these. SUV max was comparable between the groups with EGFR mutation (11.3±3.9) and ALK rearrangement (12.3±4.0). Correlations were observed between EGFR mutation and ALK rearrangement and location (p-value <0.0001), pleural tail (p-value <0.0001), pleural effusion (p-value <0.0001), obstructive changes (p-value <0.025), pleural nodule (p-value <0.002), lung nodules (p-value <0.002), air bronchogram (p-value <0.002), emphysema (p-value <0.002), mediastinal nodes (p-value <0.002) and distant metastasis (p-value <0.002). EGFR mutation also correlated with invasion (p-value 0.022). In ROC curves, for EGFR mutation and ALK rearrangement prediction based on mediastinal lymph nodes, the AUC was 0.661 and 0.588, respectively. **Conclusion:** The correlation between CT findings and molecular findings highlights the importance of newer radio genomic based characterization for patients with NSCLC for better diagnostic and prognostic approaches.

Keywords: Non small cell lung cancer, radio genomic, SUV max

P2.01-78 A METAANALYSIS AND BIOINFORMATICS EXPLORATION OF THE PROGNOSTIC VALUE OF TP53 CO-MUTATIONS IN EGFR MUTATED NSCLC

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Background: As the leading cancer type for the estimated new cancer cases, lung cancer represents the major cause of cancer related worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of primary bronchogenic carcinomas and leads the ranking of cancer-related mortality in the western world. TP53 mutations were recently reported as a useful index in predicting the prognosis of lung cancer. However, the prognostic role of TP53 co-mutations in epidermal growth factor receptor (EGFR)mutated NSCLC remains controversial. **Method:** Relevant literatures were retrieved from PubMed, Embase and Web of Science databases. Meta-analysis was performed using hazard ratio (HR) and 95% confidence intervals (CIs) as effect measures. A total of 1146 patients from 7 studies were finally enrolled in the meta-analysis. Information regarding TP53 and EGFR alterations and patients' survival time in NSCLC was downloaded from the Cancer Genome Atlas Database and The Clinical Lung Cancer Genome Project (CLCGP). Patients were further subdivided into subgroups based on different mutation exons. The distribution of different mutation exon as well as the prognostic value were evaluated. 2660 pieces of data from 2241 NSCLC patient were collected. **Result:** The summary results showed that dual TP53/EGFR mutations predicted poorer overall survival (OS) (HR: 1.38, 95%CI: 1.06–1.81, p < 0.05). Subgroup analysis revealed that dual TP53/EGFR mutations was also associated with poor OS in NSCLC treated by EGFR-TKIs (HR:1.47, 95%CI: 0.88-2.46, P < 0.05). Patients with TP53 mutations in exons 6 and 8 had worse OS compared with patients with TP53 mutations in other exons(HR: 1.22, 95%CI: 0.89–4.33, p < 0.05), especially coexisting with EGFR mutations in exons 20(HR: 1.78, 95%CI:1.13–2.52, p < 0.05). **Conclusion:** In EGFR mutated NSCLC, dual TP53/EGFR mutations suggest poor prognosis, especially in patients treated by EGFR-TKIs. The presence of TP53 mutations in exons 6 and 8 correlated with inferior OS. Larger datasets are required to validate these observations.

Keywords: NSCLC, TP53, EGFR

P2.01-79 AFATINIB IN EGFR MUTATION-POSITIVE (EGFRM+) NSCLC HARBOURING UNCOMMON MUTATIONS: EXPERIENCE IN 'REAL-WORLD' CLINICAL PRACTICE

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Background: Approximately 10–12% of patients with *EGFR*m+ NSCLC have tumors harboring uncommon *EGFR* mutations. Preclinical data indicate that the ErbB family blocker, afatinib, has broader inhibitory activity against uncommon mutations, including compound mutations, compared with first-generation EGFR TKIs.[1,2] Post-hoc analysis of the LUX-Lung 2, 3, and 6 trials[3] demonstrated that afatinib is active against certain uncommon *EGFR* mutations. The objective response rate (ORR) with afatinib against G719X (n=18), L861Q (n=16), and S768I (n=8) single/compound mutations was 78%, 56%, and 100%, respectively. Patients with exon 18–21 uncommon mutations had progression-free survival (PFS) and overall survival of 10.7 and 19.4 months, respectively. The aim of this analysis was to explore the sensitivity of uncommon *EGFR* mutations to afatinib in a broader 'real-world' patient population. **Method:** We undertook a pooled analysis of data from an Asian phase IIIB trial (NCT01953913) and a German non-interventional study (NCT02047903) that assessed afatinib in patients with EGFR TKI-naïve *EGFR*m+ NSCLC. Tumour response was based on investigator review, and PFS was calculated by Kaplan–Meier methodology. **Result:** Fifty-four patients were identified with tumours harbouring uncommon mutations, including L861Q (n=13), S768I (n=3), G719X (n=23), and other (n=8); 21 patients had compound mutations. Baseline characteristics were: male, 59%; median age (range), 63.5 (35-79) years; Eastern Cooperative Oncology group performance status 0 or 1/>1, 93%/6%. The combined ORR for evaluable patients with L861Q, S768I, or G719X was 59% (20/34), and the disease control rate was 91% (30/34); ORR and DCR in patients with compound mutations was 47% (9/19) and 89% (17/19), respectively. Overall, median PFS in patients with L861Q, S768I, or G719X was 10.7 months; median PFS in patients with compound mutations was 7.3 months. **Conclusion:** In this 'real-world' cohort of patients with *EGFR*m+ NSCLC, afatinib was active against uncommon mutations known to be less responsive to reversible EGFR TKIs. These data are in line with the LUX-Lung trials and support the use of afatinib in patients with non-resistant *EGFR* mutations.

Keywords: EGFR mutation, Afatinib, Uncommon

P2.01-80 CLINICAL OUTCOMES IN ADVANCED EGFR-MUTANT NSCLC PATIENTS TREATED WITH FIRST-GENERATION EGFR TKIS FOLLOWED BY SUBSEQUENT OSIMERTINIB

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Background: Treatment with first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) plus subsequent osimertinib is standard of care for advanced (*EGFR*)-mutant non-small cell lung cancer (NSCLC) harboring T790M mutation. However, few data are available that have assessed the cumulative survival benefit of sequential EGFR TKIs in patients with *EGFR*-mutant NSCLC with T790M mutations in 'real-world' clinical practice. **Method:** We retrospectively identified advanced *EGFR*-mutant NSCLC patients treated with first-line EGFR TKIs plus subsequent osimertinib between January 27th, 2015 and December 1st, 2018 at our institute. Clinical outcomes were analyzed. Subsequent genetic profiling was performed at the time of progression by next-generation sequencing (NGS). The primary endpoint was overall survival (OS) calculated from first-line treatment start to death or the last follow-up, and the secondary endpoint was progression-free survival (PFS) with osimertinib defined as the time from the first dose of osimertinib to disease progression or death. Primary resistance to osimertinib was defined as PFS≤4 months for T790M-mutant patients treated with osimertinib. The last follow-up time was January 27th, 2019. Median follow-up time was 52.0 months (range, 9.0-108.0 months). **Result:** Among 117 eligible patients treated with first-line EGFR TKIs plus subsequent osimertinib, 96 had T790M mutation and 21 showed negative T790M mutation or unknown status at the baseline of osimertinib treatment,. Median OS was significantly prolonged in T790M-mutant patients than those with negative/unknown T790M mutation (58.0 vs. 28.3 months, p<0.001). However, there was no significant difference in median PFS with osimertinib between the two groups. Furthermore, there was no significant difference in both median OS and PFS with osimertinib between the non-brain metastatic and brain metastatic groups (median OS, 58.0 vs. 54.8 months, p=0.840; median PFS, 11.8 vs. 9.1 months, p=0.145). Median OS was significantly shortened in patients (N=20) with primary resistance to osimertinib than those (N=72) with PFS>4 months (38.2 vs 54.8 months, p=0.027). **Conclusion:** In real-world clinical practice, treatment with first-generation EGFR TKIs plus subsequent osimertinib for T790M-mutant patients can significantly prolong OS than those with negative/unknown T790M mutation. However, survivals are similar between the patients with and without brain metastases at the baseline of osimertinib. OS is significantly shorter in those with primary resistance to osimertinib.

	Non-brain metastasis at the baseline (n=55)	Brain metastasis at the baseline (n=41)	P-value	Osimertinib PFS≤4m (n=20)	Osimertinib PFS>4m (n=72)	P-value
Sex						
Male	21 (38.2%)	20 (48.8%)	0.299	7 (35.0%)	32 (44.4%)	0.450
Femal Age,years ≤55 >55	34 (61.8%) 19(34.5%) 36(65.5%)	21 (51.2%) 18(43.9%) 23(56.1%)	0.357	13 (65.0%) 9 (45.0%) 11(55.0%)	40 (55.6%) 27(37.5%) 45(62.5%)	0.543
ECOG PS						
0-1	54(98,2%)	38(92.7%)	0.000	20(100%)	68(94.4%)	0.281
2-4	1(1.8%)	3(7.3%)		0(0%)	4(5.6%)	
Histology						
adenocarcinoma	53 (96.4%)	41 (100%)	0.217	18 (90.0%)	72 (100%)	0.007
non-adenocarcinoma	2 (3.6%)	0 (0%)		2 (10.0%)	0 (0%)	

Keywords: Osimertinib, advanced NSCLC, EGFR TKIs

P2.01-81 PREDICTIVE FACTORS OF SURVIVAL IN PATIENTS TREATED WITH NINTEDANIB: A MULTICENTER RETROSPECTIVE SPANISH STUDY

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Background: Nintedanib is a triple angiokinase inhibitor that blocks the proangiogenic pathways mediated by vascular endothelial growth factor receptors, platelet-derived growth factor receptors and fibroblast growth factor receptors. Nintedanib in combination with docetaxel is indicated for adults with adenocarcinoma metastatic lung cancer after chemotherapy. Although, as in other antiangiogenic therapies, we do not have a predictive response marker. The aim of this study is to analyze probably factors that influence in the response to the nintedanib-docetaxel scheme. **Method:** We conducted a retrospective multicenter study, which included all patients with non-small cell lung cancer who received nintedanib with docetaxel in second or third line of treatment. Explorative analyses were conducted according to therapy antiangiogenic previous, status PDL1, nintedanib or docetaxel dose adjustment and time to treatment fail in previous line (> 9 months or < 9 months), age, sex and smoking. **Result:** We enrolled 124 patients from 10 different Spanish centers. Progression free-survival was 4,1 months and the overall survival was 26,9 months. Of the factors studied, only the dose adjustment of docetaxel during treatment (5,7 months vs 2,7 months, p<0,05) and the dose adjustment of nintedanib (7,2 months vs 4,7 months, p<0,05) were associated with an increase in PFS. The dose adjustment level of nintedanib (100 mg vs 150 mg twice) did not reach statistical significance. The only factors that achieved statistical significance in overall survival were progression to the first line> 9 month (36,5 months vs 19,3 months, p <0.05) and the dose adjustment of nintedanib (37 months vs 22 months, p < 0.05). Therapy antiangiogenic previous, status PDL1, age, sex and smoking did not increase survival. **Conclusion:** In our study, nintedanib- docetaxel concluded significant OS benefits in adenocarcinoma lung cancer patients with time to relapse to first line >9 months and in patients with dose adjustment during treatment. Further studies are needed to verify this data.

Keyword: non-small cell lung cancer, nintedanib, predictive factors of survival

P2.01-82 LUNG CANCER IN LUNG TRANSPLANT RECIPIENTS

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Background: Long-term immunosuppression is considered to increase the chance of developing malignancy, which is one of the leading causes of death after organ transplantation. Lung cancer in lung transplant recipients can originate from de-novo occurrence, transplanted donor's lung and progression/recurrence of the recipient's lung cancer. We conducted a survey of lung cancer in lung transplant recipients in our institution and report the case series. **Method:** All 189 recipients who underwent lung transplantation (97 brain-dead donor lung transplantation, 90 living donor lobar lung transplantation, 2 hybrid lung transplantation) since October 1998 until December 2018 at Okayama University Hospital were retrospectively reviewed. **Result:** Lung cancer was diagnosed in 4/189 (2.1%) of 16/189 (8.5%) all malignant diseases, in lung transplant recipients with a median follow-up of 4.5 years. Whereas de novo lung cancer occurred in one patient, patient-baring lung cancer was histologically detected in resected lung in three patients, leading to progression after transplantation in the two recipients. One recipient who had a previous history of lung cancer with over 5-year disease free period, experienced no recurrence afterword. All three recipients who had advanced lung cancer died relatively early from the diagnosis of lung cancer, regardless of cancer treatment. Lung cancer in lung transplant recipients could be difficult to detect by radiological screening and biopsy due to severely deteriorated lung condition, especially in idiopathic interstitial pneumonitis. Additionally, recipients with advanced lung cancer seem to have poor prognosis.

Case	Underlying disease	Occurrence	LTx - Lung cancer	Degree of progression	Treatment/Prognosis
#1	LAM	De novo	10 years	Chest wall invasion	Right pneumonectomy (10 months)→chemotherapy (9 months)→death
#2	IIP	Resected recipient's lung	15 months	Mediastinal lymph-nodes	Lymph-node resection (10 months) →death
#3	IIP	Resected recipient's lung	3 months	Pleural Dissemination	chemotherapy (6 months)→death
#4	BO	Resected recipient's lung	nil	nil	nil

LAM: lymphoangioleiomyomatosis IIP: idiopathic interstitial pneumonitis BO: bronchiolitis obliterans LTx: lung transplant

Conclusion: Lung cancer in lung recipients should be screened carefully ever since listing for transplantation.

Keywords: Lung transplantation, Lung cancer

P2.01-83 ROLE OF EXOSOMAL MICRORNAS (MIRNAS) AS PREDICTORS OF RESPONSE TO TREATMENT AND PROGNOSIS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Exosomes are 30 - 100 nm cellular entities secreted from cells. Exosome contain messenger RNA, miRNAs, DNA and active peptides . Cancer derived exosomes have distinct miRNA profiles. Signature profile of miRNAs can be utilized for disease characterization including response . We are evaluating exosomal miRNAs from urine of NSCLC patients. **Method:** Urine (30-50ml) was collected, before and after treatments in 5 advanced NSCLCs. Exosomes were isolated by differential ultracentrifugation method, miRNA libraries were constructed using 100 ng of total RNA isolated from exosomes and sequenced on the Illumina MiSeq platform. A minimum of 20 million 50base pair sequencing reads were collected and data analyzed using CLC Genomics Workbench Software. miRNAs that was significantly changed (up- or down-regulated) in the matched samples were identified as candidate biomarkers. Target mi RNAs were analyzed with bioinformatics tools. **Result:** miRNA sequencing (RNAseq) showed 111,416 sequence hits for small non-coding RNAs and after aligning with miRBase21, 548 mature miRNAs were identified. The differentially expressed miRNAs clustered separately in pre- and post-treatment samples in all five-patients. Two miRNAs (hsa-miR-6842 and hsa-miR-143) showed marked reduction in post-treatment samples compared to pre-treatment samples. Validation studies by quantitative (q)PCR using miRNA specific primers confirmed the RNAseq results. *In silico* target analysis identified RAS oncogenic family as a prominent target for these miRNAs. Table 1; characteristics of patients, miRNAs changes (fold reduction), response and long term outcomes

Patients	1	2	3	4	5
Age/Sex	42/male	74/female	59/male	81/male	68/male
Stage	4	4	4	4	3 (T1N3)
Pathology	Adenocarcinoma	Squamous cell		Adenocarcinoma	Squamous cell
Tissue Molecular Abnormalities	KRAS G12V, STK11 K62fs*99, NFKBIA amplification, NKX2-1 amplification, TP53 R249W	Not tested	STK11 Y156fs*5, CDKN2A p16IN-K4a E69fs*77 and p14ARF G83fs*51+, MYST3 S1496L, TP53 splice site 919+1G>	Met exon 14 splicing	Not tested
Treatment	Carbo, Permetrexed, Bev X2, f/b carbo/ etoposide with radiation	Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel	Carboplatin/ Paclitaxel with radiation
Change in mir-143	-4.371	-1.25	-1.27	-1.139	-15.7
Change in mir-6842	-21.37	-6.27	-4.21	-3.41	-4.57
Treatment Response	PR	PR	SD	SD	CR
Current Status	Alive, 38 months since diagnosis	Died 18 months after diagnosis	Died 6 months after diagnosis	Alive, 38 months since diagnosis	Alive, 32 months since diagnosis

Out of all mi RNAs, miR-143 and miR 6842 showed maximum reduction in value and changes were more pronounced in patients1 and 5. Both patients received radiation with chemo and had very good response and prolonged control of disease with longer survival. Interestingly both of miRNAs are targeting KRAS mRNA. Patient#1 had K ras mutation while Patient#5 was not tested **Conclusion:** Based on our initial experiments we conclude that upon receiving chemo+ radiation combination therapy the miRNA 143 and miRNA 6842 are packaged at lower levels in exosomes by the tumor cells i.e. cells are trying to retain miRNAs within themselves. Since retention of miRNAs will decrease the levels of target miRNA which is KRAS which will result in better treatment outcome. Our study suggests that urine derived exosomal miRNAs 143 and 6842 can be used as prognostic markers to assess treatment response. This is a preliminary data and study is ongoing.

Keyword: NSCLC, Exosomes, Micro RNAs

P2.01-84 SERUMAL SERPINE2 AS A POTENTIAL BIOMARKER FOR RADIORESISTANCE IN NSCLC

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Background: Radioresistance is the main reason for the failure of clinical radiotherapy in lung cancer. Among the different tumors, SERPINE2 is a protein with anticoagulant properties which could promote or inhibit solid tumor growth. However, its role in the pathogenesis of lung cancer has not been determined. **Method:** To get radioresistant cell lines A549R and PC9R, A549 and PC9 cells were treated with fractionated irradiation by high energy X-ray. Cell survival fractions were measured by colony formation assay. Furthermore, we performed RNA-SEQ and protein profiling to screen genes differentially expressed in the A549/A549R and PC9/PC9R cells. To elucidate the biological role of SERPINE2 in radioresistance of NSCLC, we conducted SERPINE2 gene overexpression/knockdown experiments using NSCLC cell lines. The aim of this study was to assess serum SERPINE2 concentrations in a group of 26 NSCLC patients with radiation therapy alone in one course of treatment. Blood samples were collected before treatment. Serum SERPINE2 concentration was measured using specific ELISA methods. We analyzed its prognostic significance regarding outcome analysis, as well as its potential biomarker for radiotherapy. **Result:** Two radioresistant lung adenocarcinoma sublines A549R and PC9R were successfully established through dose fractionated irradiation after six months. Results of RNA-SEQ and protein profiling showed the SERPINE2 was higher in A549R and PC9R compared to that in parental cells A549/PC9. We also demonstrated that knockdown of SERPINE2 expression inhibit cell migration and invasion in A549/PC9 cell lines. And the overexpression of SERPINE2 promote cell migration and invasion in H1975/HCC827 cell lines. Knockdown of SERPINE2 expression in the A549R/PC9R by shRNA also reduced significantly cell radiation resistance.The radiobiology parameters, which including SF_2, D_0, D_q and α/β, were significant differences compared with non-silencing shRNA cells. According to response evaluation criteria in solid tumors, the concentrations of SERPINE2 were significantly higher in PD patients compared with SD and PR. **Conclusion:** The preliminary study indicates the SERPINE2 play an important role in the radioresistance of NSCLC and implies the evaluation of SERPINE2 expression in serum may be considered as a potential biomarker in radiotherapy of NSCLC patients. Further research must be explored to clarify the function and mechanism of SERPINE2 in the radioresistance of lung cancer.

Keywords: SERPINE2, NSCLC, Radioresistance

P2.01-85 SCHWANN CELLS ARE OVEREXPRESSED AND INVERSELY CORRELATED WITH SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS

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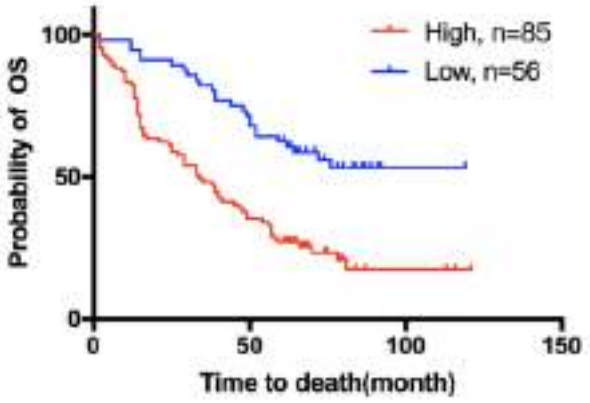
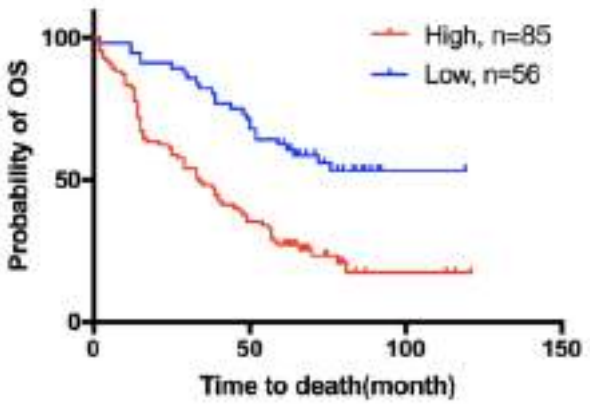
Background: The lungs are densely innervated by the peripheral nervous system (PNS). We have recently reported the presence of schwann cells(SCs), the principal glial cells of the PNS, in the murine and human lungs and the mechanisms by which tumor–neuroglia interaction affect lung cancer growth and metastasis(Cancer Research. 2018;78(20):5927-39). Nevertheless, the clinical epidemiological characters of the innervation of lung cancer has not been intensively investigated.This study aimed to complement this vacancy by determining the prevalence of SCs expression in NSCLC and analyzing its associations with clinical pathologic parameters and outcome. **Method:** Totally, 141 operated patients at stage I-III NSCLC were enrolled. Formalin-fixed and paraffin-embedded (FFPE) tumour sections were reviewed and stained with glia-specific antibodies S100b, GFAP and P75NTR. The correlations between expression of SCs and clinical pathologic features, overall survival (OS) and recurrence free survival(RFS) were analyzed. **Result:** No significant relationship were found between SCs expression and patients'gender, age, smoking history, subtype or EGFR status. Interestingly, SCs expression was markedly increased in cancer tissues compared with in adjacent tissues. Furthermore, SCs were significantly overexpressed in tumors of stage II-III than in stage I(P<0.01). Kaplan-Meier curve analysis revealed that high expression of SCs was negatively associated with longer RFS (P<0.001) and OS(P<0.001).5 year-RFS were 18.8%(High) and 51.8%(Low) respectively.



P<0.01,HR=2.706,95%CI:1.794 to 4.082



P<0.01,HR=2.706,95%CI:1.794 to 4.082

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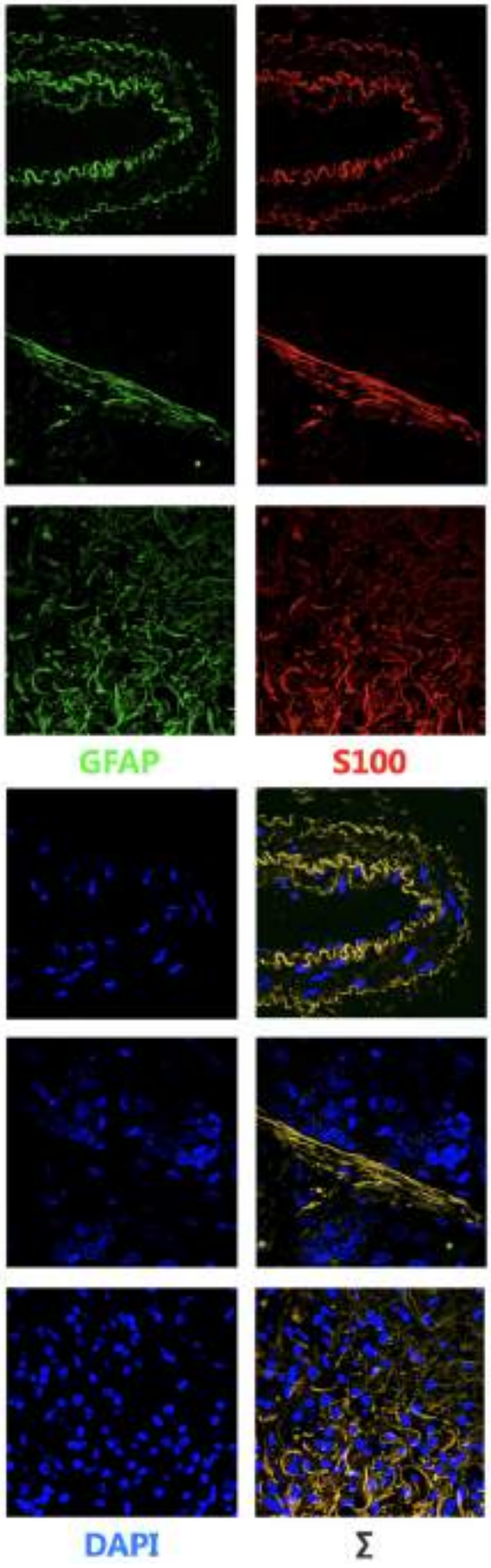

Conclusion: High expression of SCs is negatively correlated with tumor stage and survival, indicating its potential diagnostic and therapeutic value for operated NSCLC patients.

Keywords: Schwann cells, Non-Small Cell Lung Cancer, prognosis

P2.01-86 HIGHLY IMMUNOGENIC NEOANTIGENS ENHANCE TUMOR RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Immune checkpoint inhibitors have revolutionized the treatment of metastatic non-small cell lung cancer (NSCLC) as significantly extending survival in patients relative to chemotherapy. However evidence to support the role of immune checkpoint inhibitors in *EGFR*-mutant lung cancers remains conflicting. In recent years, neoantigens become promising targets for cancer immunotherapy. Immunogenic neoantigens generated by somatic mutations can be recognized by the host immune system and then tumor clones presenting such neoantigens will be eliminated. **Method:** We report two advanced NSCLC patients with *EGFR* mutations who have both exhibited durable response to PD-1 blockade. We comprehensively analyzed predictive biomarkers and experimentally validated immunogenicity of peptides generated by driver mutations. **Result:** Patient 1 is a 34-year-old male diagnosed with lung adenocarcinoma (IV, cT4N2M1b). *EGFR* exon 19 deletion and *TP53* point mutation (A161T) were identified by next generation sequencing in February 2017 and first line treatment was initiated with Icotinib. He obtained PD within 5 months. After 5 cycles of chemotherapy, brain metastasis was confirmed and *EGFR* T790M mutation was identified by lung biopsy in June 2018. The patient was enrolled in a phase III clinical trial of Nivolumab in July 2018. Patient 2 is a 61-year-old female diagnosed with stage IV lung adenocarcinoma harboring *EGFR* exon 19 deletion identified by next generation sequencing in March 2018. After multilines treatment including TKI therapy, chemotherapy and anti-angiogenic therapy, Nivolumab was given alone to the patient from November 2018. Both patients achieved partial response (PR) to Nivolumab based on imRECIST criteria. The PD-L1 expression level was > 50% and ≥ 5%, respectively in Patient 1 and Patient 2. We performed a target region sequencing which covered 811 cancer genes to determine tumor mutation burden (TMB) and tumor neoantigen burden (TNB). Both patients had moderate level of TMB and TNB. TMB was 6.00 muts/Mb and 4.69 muts/Mb while TNB was 2.67 neos/Mb and 2.68 neos/Mb, respectively in Patient 1 and Patient 2. In order to evaluate the immunogenicity of neoantigens, peptides representing top 7 putative neoantigens were synthesized and tested against PBMC in an IFNγ ELISpot assay. The results revealed tumor-specific T cell immunity targeting neoantigens derived from *EGFR* exon 19 deletion and *TP53* point mutation and the latter exhibited the highest immunogenicity. Strikingly, the patient harboring these mutations achieved partial response for more than 9 months. Additionally, the dynamic changes of TCR profiling during Nivolumab treatment were examined to assess T cell immunity responses. Data shown the maintenance of a majority of high-frequency clonotypes, suggesting the preexisting high-avidity T cells may contribute to antitumor immune response. **Conclusion:** Our study suggests that *EGFR*-mutant NSCLC may still respond to PD-1 blockade. This is the first report on experimentally verifying the highly immunogenic neoantigens derived from *EGFR* driver mutation in patients receiving immunotherapy, which supports potential value of such neoantigens as therapeutic agents. Our study also shows the dynamic monitoring of TCR profiling could help predict T cell immune response.

Keywords: neoantigen, EGFR-mutant lung cancer, immune checkpoint inhibitor

P2.01-87 β-ADRENERGIC ANTAGONISTS SENSITIZES CHEMORADIATION THERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Locally advanced non-small cell lung cancer (NSCLC) is highly resistant to chemoradiotherapy, and many cancer patients experience chronic stress. Studies suggest stimulation of β-adrenergic receptor (β-AR) promotes tumor invasion and therapy resistance. We investigated whether β-AR inhibition with beta-blockers acts as a chemotherapy and radiation sensitizer *in vitro* and in patients treated with chemoradiation followed by surgery for locally advanced NSCLC. **Method:** We investigated the effects of the non-selective beta-blocker propranolol on two human lung adenocarcinoma cell lines (PC9, A549) treated with radiation or cisplatin. We retrospectively evaluated 77 patients with Stage IIIA NSCLC who received induction chemoradiation followed by surgery. Pathological and imaging response, metastatic rate and survival were analyzed using SPSSv20 and PrismGraphpad6. **Result:** Propranolol combined with radiation or cisplatin decreased clonogenic survival of PC9 and A549 cells *in vitro* ($p<0.05$). Furthermore, propranolol decreased expression of p-PKA, a β-adrenergic pathway downstream activation target, in both cell lines compared to irradiation or cisplatin alone ($p<0.05$). In patients treated for Stage IIIA NSCLC, 16 took beta-blockers, 61 did not. Beta-blockade is associated with a trend to improved overall survival (OS) at 1 year (81.3% vs 57.4%, p=0.08) and distant metastasis-free survival (DMFS) (2.6 years vs 1.3 years, p=0.16). Although beta-blocker use was associated with decreased distant metastases (risk ratio [RR] 0.19; p=0.03), it did not affect primary tumor pathological response (p=0.40) or imaging response (p=0.36). **Conclusion:** β-AR blockade enhanced radiation and cisplatin sensitivity of human non-small cell lung cancer cells *in vitro*. Beta-blockers use is associated with decreased distant metastases and potentially improved OS and DMFS. Additional studies are warranted to evaluate the role of beta-blockers as a chemoradiation sensitizer in locally advanced NSCLC.

Keywords: Beta-blocker, Non-Small Cell Lung Cancer, chemoradiation

P2.01-88 MOLECULAR ALTERATIONS IN CEREBROSPINAL FLUID PREDICT CLINICAL OUTCOMES OF CENTRAL NERVOUS SYSTEM METASTASES IN LUNG CANCER

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Background: Cerebrospinal fluid (CSF) has been proven as good media for genetic profiling of central nervous system (CNS) metastases. However, the association of genetic alterations in CSF and clinical outcomes remains elusive. **Method:** A total of 94 lung cancer patients with CNS metastases underwent lumbar puncture. Circulating tumor DNA were extracted from CSF and profiled by next-generation sequencing. The effect of genetic alterations in CSF on survival and treatment outcomes were evaluated. **Result:** The most common genes seen in CSF were *EGFR*, *TP53*, *MET*, *CDKN2A*, *MYC*, *NTRK1* and *CDK6*. Kaplan-Meier survival analysis indicated that *CDK4*, *CDK6*, *FGFR1*, *MET* and *MYC* alterations, which were also characterized by more copy number changes, were associated with poor survival. Multivariate analysis found only *MET* (HR, 2.01; 95% CI, 1.15 to 3.52) and *MYC* alterations (HR, 2.31; 95% CI, 1.27 to 4.21) were correlated to poor OS. Forty-two patients harbored high n-CNVs (defined as the number of genes with copy number variations >2) while 50 patients carried low n-CNVs (defined as the number of genes with copy number variations <=2). Median overall survival (OS) of patients with high n-CNVs in CSF was 14.9 months (95% CI, 9.2 to 25.8 months), significantly shorter than those with low n-CNVs (21.6 months, 95% CI, 17.9 months to not reached (NR); HR, 1.9; 95% CI, 1.11 to 3.24; *P*=0.016). Patients with high n-CNVs and *MET* and *MYC* CNVs (copy number variations) were associated with the poorest OS. Osimertinib significantly prolonged OS only among patients with high n-CNVs (with vs. without osimertinib, 25.8 vs. 9.2 months; *P*=0.004). Among *T790M* negative patients, high n-CNVs seemed to positively associate with better response to osimertinib (OS with vs. without osimertinib, 23 vs. 7.8 months; *P*=0.058). Further analysis indicated that *EGFR* and *FGFR1* CNV were the most significant factors associated with OS benefit from osimertinib among the high n-CNVs group (*P*=0.014; *P*=0.02). *TP53*_LOH and Wnt pathway alterations were significantly more prevalent in the high n-CNVs group than in the low n-CNVs group (*P*=0.016, *P*=0.006). With regard to clinical characteristics, higher performance status score (HR, 2.06; 95% CI, 1.38 to 3.07; *P*=0.0004) and occurrence of extracranial metastases (HR, 3.21; 95% CI, 1.25 to 8.24; *P*=0.015) suggested poor OS.

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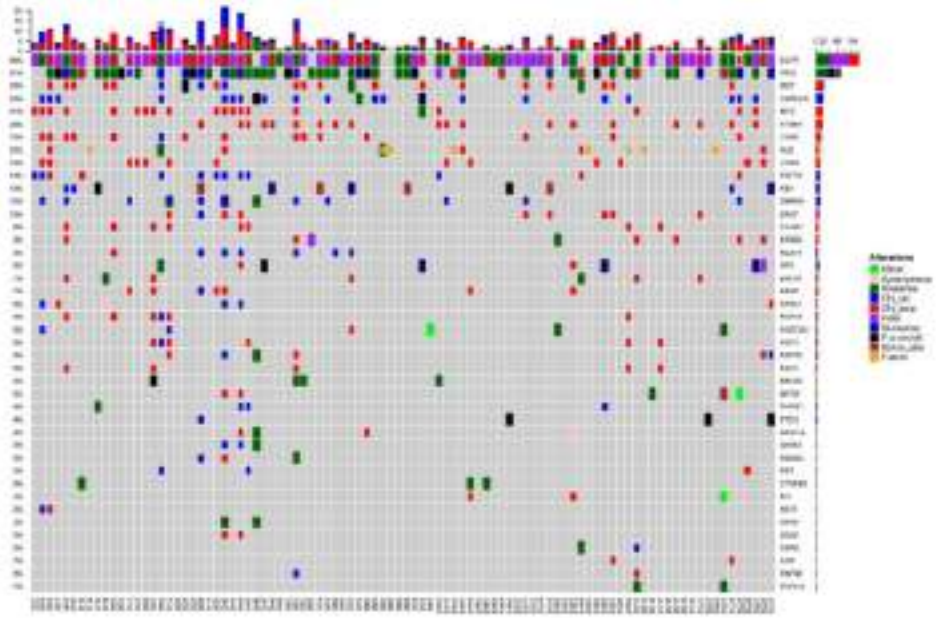

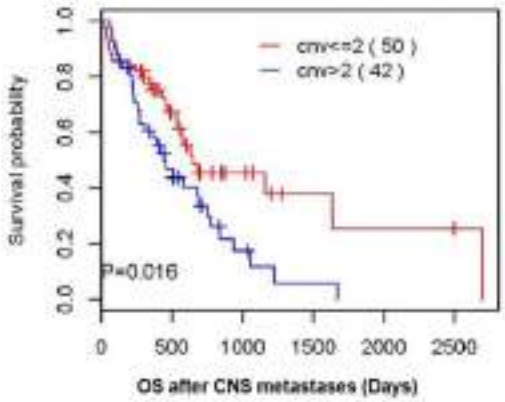

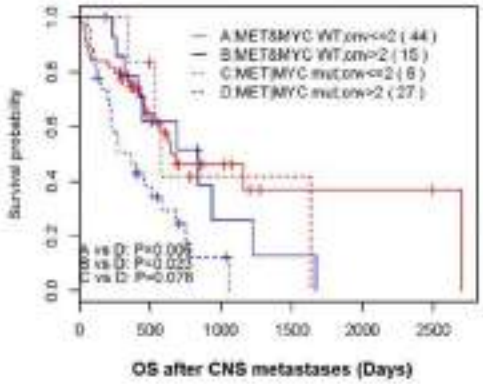

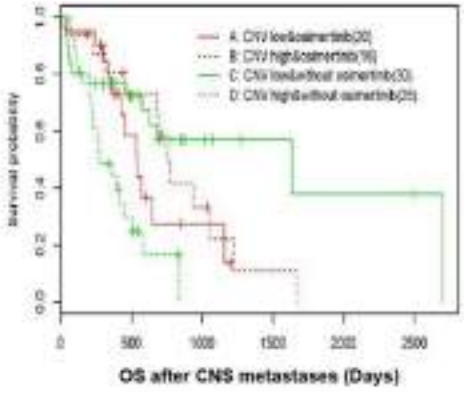

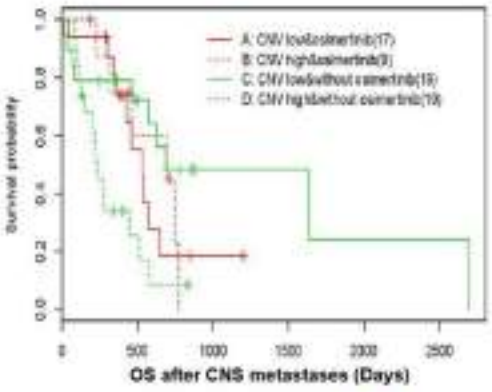

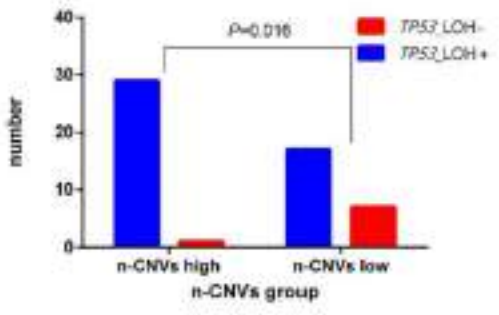

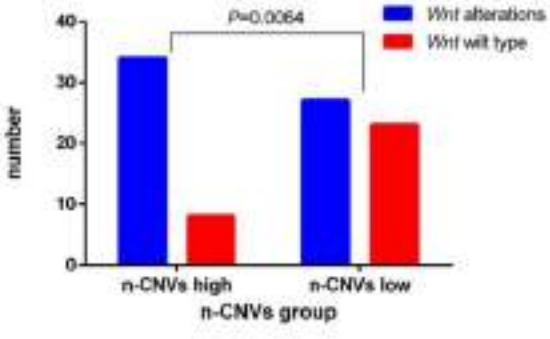

Conclusion: While genetic profiles in CSF, like high n-CNVs as well as *MET* and *MYC* CNV were related to poor prognosis, patients with high n-CNVs, especially those with *EGFR* or *FGFR1* CNV might benefit more from osimertinib, further supporting CSF as liquid biopsy of CNS metastases in lung cancer.

Keywords: central nervous system metastases, cerebrospinal fluid, Lung cancer

POSTERS

P2.01-89 FEASIBILITY OF INDIVIDUALIZED MULTIDISCIPLINARY TREATMENT FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER BASED ON THE TREATMENT PLANNING

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Background: In the individualized multidisciplinary treatment of patients with locally advanced non-small cell lung cancer (LANSCLC), the feasibility of dose escalation to the patients with sequential chemoradiotherapy for increasing tumor control and dose reduction to the patients with concurrent chemoradiotherapy for mitigating the side effects of radiotherapy was analyzed in the aspect of treatment plan optimization. **Method:** Fifty patients with LANSCLC were randomly chosen from Shanghai Pulmonary Hospital and treatment plans were replanned. These patients' PTV was defined as CTV+0.4cm, and CTV was the extravasation of 0.6-0.8cm of GTV, at least 95% volume of the PTV receive 60Gy/30fx, and these plans were called control group. The initial GTV was taken as GTV1, and GTV2 was obtained after GTV irradiated 40Gy; PTV1 was defined as GTV1+0.4cm, and PTV2 was defined as GTV2+0.4cm. With PTV2 dose escalated, the plans with lung remaining the same dose as control group were the Test1 group, and the plans with PTV1 receiving 60Gy and PTV receiving 45Gy were the Test2 group. The feasibility of the treatment regimen for Test1 Group and Test2 Group was analyzed from the perspective of dose drop gradient and the sparing of OARs, respectively. **Result:** By comparing Test1 group with control group, it is found that the dose PTV2 received is affected greatly by the volume ratio, $V_{PTV\text{-}PTV1}/V_{PTV}$, which will escalate when $V_{PTV\text{-}PTV1}/V_{PTV}$ increases. When $V_{PTV\text{-}PTV1}/V_{PTV}$ is in these range, 0.2~0.3, 0.3~0.35, 0.35~0.4, 0.4~0.45, then the dose escalated for PTV2 will be 63Gy, 66Gy, 69Gy and 72Gy. And by comparing Test2 group with control group, it is found that the dose received by OARs will be reduced in Test2 group, for example, V5, V20, V30 and MLD for lung will decrease 2.17%±1.2792%, 1.7148%±1.04733%, 1.9982%±1.165%, 1.299Gy±0.564Gy, respectively; V50 and MHD for heart will decrease 1.9128%±2.1184%, 1.229Gy±0.921Gy, respectively; V60, Dmax and MED for esophagus will decrease 5.41%±5.91%, 4.6296Gy±4.4479Gy, 2.3491Gy±1.3411Gy, respectively, and all the p values are far less than 0.05. **Conclusion:** Individualized radiotherapy can be performed on LANSCLC, and $V_{PTV\text{-}PTV1}/V_{PTV}$ can be used to predict the dose drop gradient. In Test1 group, considering not add additional dose to lung, the larger $V_{PTV\text{-}PTV1}/V_{PTV}$, the higher the PTV2 can escalate. In test2 group, reducing the initial irradiation-field dose significantly decreases the dose OARs received, and it is meaningful that more locally advanced patients can receive concurrent chemoradiotherapy. This study will facilitate the individualized multidisciplinary treatment of patients with LANSCLC, which needs further prospective studies to confirm.

Keywords: individualized multidisciplinary treatment, treatment plan optimization, locally advanced non-small cell lung cancer

P2.01-90 DOSIMETRY PREDICTION OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER BASED ON THE TUMOR LOCATION AND THE VOLUME RATIO OF TUMOR TO LUNG

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Background: Based on the tumor location and the volume ratio of tumor to lung, we give a method to predict the lowest dose-volume histogram (DVH) curve for the locally advanced non-small cell lung cancer patients. **Method:** Fifty locally advanced non-small cell lung cancer patients were randomly chosen from Shanghai Pulmonary Hospital, who were treated with radical radiotherapy by intensity modulated radiotherapy(IMRT) technique. The volume of the PTV for these 50 patients range from 44.65cc to 935.36cc, and they were located in different position of the lung. All of the patients received 60Gy total dose in 30 fractions, and at least 95% of the PTV were covered by the prescription dose. All the treatment plans were required to have their optimal results based on the lowest DVH curve of the lung, and the final DVH of the lung were analyzed according to the tumor location and its volume ratio relative to the lung. **Result:** By analyzing the tumor location in lung and the volume ratio of tumor to lung, it is found that the DVH for the lung cancer can be predicted. When the tumors are in the same position, as the volume ratio of tumor to lung increases, the dose volume of the lung will increase proportionally; when the tumors are located in different positions, even if the volume ratio of tumor to lung is the same, the DVH of the lung appears differently; and moreover, it is found that the volume of the lung affects the DVH of the lung much more than the volume ratio of tumor to lung, ie, even though the volume ratio of tumor to lung has a larger value, if the lung has a larger volume, a lower DVH curve of the lung can be obtained. At last, we found that, in any case, if the volume between the 10Gy and 65Gy is in an inverse proportional relationship and the dose received by the other OAR(organ-at-risk) is inside its safe range, then the treatment plan for the patient will be the best. The inflection point (around 6~7 Gy) of the DVH curve for the lung will be obtained, which is the extreme value of the DVH curve. **Conclusion:** By analyzing these 50 patients' treatment plans, the DVH of lung can be predicted for any locally advanced non-small cell lung cancer patient based on the tumor location and the volume ratio of tumor to lung. The lowest DVH curve of the lung can be assessed by its obtained inflection point.

Keywords: volume ratio of tumor to lung, dose-volume histogram (DVH), dosimetry prediction

P2.01-91 EXOSOMAL ANALYSIS OF ALK REARRANGEMENTS BY SPIN COLUMN WITH POROUS GLASS FILTER

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Background: ALK rearrangements account for about 3-5% of non-small cell lung cancer (NSCLC). ALK-tyrosin kinase inhibitors (TKI) demonstrated robust efficacy compared with cytotoxic chemotherapy in patients with ALK alterations detected in the tumor tissues. Identifying ALK rearrangement was performed using tissue samples, which are not always available. The spin column with porous glass filter has been developed by Nagoya university and AGC Inc, resulting in highly efficient and easy to use exosome isolation. The exosomes contain various molecules of their cell of origin, including proteins and RNA. The purpose of this study was to explore the spin column to capture exosome and detect ALK alterations in exosomal RNA from blood. **Method:** The supernatant of cell culture medium (H3122, H2228) and plasma samples from 3 patients with ALK-positive NSCLC were passed through the filter using a conventional centrifugation. Exosome captured in the filter was lysed with reagent for RNA extraction. The total RNA was retrotranscripted by random primers. The ALK rearrangement in the exosome were determined by RT-qPCR and DNA sequencing. **Result:** EML4-ALK variant 1 and 3 were detected in exosome from 500μL of culture supernatant of H3122 and H2228, respectively. In the analysis of exosome in plasma from patients with EML4-ALK determined by fluorescence *in situ* hybridization and immunohistochemistry, EML4-ALK variant 1 was successfully detected in all cases. **Conclusion:** Exosome remains relatively stable in the blood, making it an attractive target for liquid biopsy. Our preliminary results showed potential capability in the detection of ALK alteration in exosomes from blood. These findings require confirmation in further studies with a larger number of patients with ALK-positive NSCLC.

Keywords: exosome, ALK, Non-Small Cell Lung Cancer

P2.01-92 CIMAVAX-EGF IN COMBINATION WITH FIRST-LINE CHEMOTHERAPY IN III STAGE NSCLC

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Background: A Cuban therapeutic cancer vaccine composed by human recombinant Epidermal Growth Factor (EGF) conjugated to a carrier protein, P64K from Neisseria Meningitides (CimaVax-EGF) induces antibodies against self EGF that decrease its concentration and affect EGF-EGFR interaction. Cimavax EGF was registered in Cuba as switch maintenance therapy for advanced

stage NSCLC. Objective: Evaluate the safety an immunogenicity of the combination of cimavax and first-line chemotherapy in patients with inoperable stage IIIa non-small cell lung cancer **Method:** A phase I clinical trial was conducted in two hospitals in Cuba, with the approval of Ethic Committee of each one. Cimavax EGF was administered by intramuscular injection in four sites of administration (4 subdoses of 0.25 ml), every 2 weeks the first 4 doses and after this induction phase monthly reinmunizations were given. First-line platinum-based chemotherapy was administered concomitantly, four to six cycles platinum-based ChT every 21 days. **Result:** Thirty patients entered the study. Most frequently adverse events registered with the combined treatment were: injection-site reaction (7.8 %), cough (7.3%), anemia (6.1%), fever (5.3%), asthenia (4.9%) and anorexia (4.9%). Most of them were classified as grade1 -2 according CTCAE version 3. There were no deaths related to the combined treatment. Antibody response against EGF was repeatedly measured in 24 patients. More than 90% of patients (n = 23; 95,8%) were classified as good antibody responders (GAR). It was observed an inverse correlation between EGF concentrations and anti-EGF antibody titers, as previously Cimavax EGF trials have reported. Anti-EGF antibody titers continue increasing until day 76 during the chemotherapy course and was maintained until the end of the treatment. In fact, there were high anti-EGF antibodies post-chemotherapy than before. The median overall survival (mOS) time for all included patients was 9.4 months. **Conclusion:** Cimavax EGF vaccine in combination with first-line platinum-based chemotherapy was a safe treatment option for NSCLC patients with IIIa stage NSCLC. Immune response was not affected with the administration of chemotherapy. This was the first combined study of Cimavax in locally advanced NSCLC.

Keywords: IIIa NSCLC, immunogenicity, Cimavax Egf vaccine

P2.01-93 DETECTION OF GIANT CANCER-ASSOCIATED MACROPHAGE-LIKE CELLS AFTER CONCURRENT CHEMOIMMUNORADIATION IS ASSOCIATED WITH POOR SURVIVAL IN NSCLC

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Background: Circulating cancer-associated macrophage-like cells (CAMLs) are a recently described stromal cell found in the peripheral blood of cancer patients that have been shown to be associated with disease progression. The presence of giant CAMLs (≥50 μm) was previously reported to be predictive of disease progression in multiple tumor types. In this phase II DETERRED trial of patients with unresectable locally advanced non-small cell lung cancer (NSCLC) treated with atezolizumab (atezo) combined with concurrent chemoradiation, we explored the utility of CAMLs in predicting progression based on blood samples collected throughout treatment and follow up. **Method:** Patients were enrolled between February 2016 and April 2018. Patients were treated with carboplatin/paclitaxel (CP) and conventionally fractionated radiation therapy (60 – 66 Gy) with atezo, followed by CP-atezo, followed by maintenance atezo. Median follow up after the completion of concurrent chemoimmunoradiation (cCIRT) was 13.5 months. CAMLs were collected by obtaining peripheral blood from patients at baseline at the beginning, during, at the end, at first follow up, and final follow up after cCIRT. Blood was filtered using CellSieve™ filtration and CAMLs quantified. CAML size ≤49 μm or ≥50 μm was quantified with the observer blinded to clinical information. Relapse free survival (RFS), distant metastasis free survival (DMFS), progression free survival (PFS), and overall survival (OS) were analyzed at each time point. **Result:** We evaluated 40 patients with unresectable locally advanced NSCLC and obtained a total of 375 samples. CAMLs were identified in 80.5% of samples, averaging 2.5 CAMLs per 7.5 mL sample. Patients with giant CAMLs (≥50 μm) compared to those with smaller CAMLs (≤49 μm) exhibited no difference in RFS, PFS, DMFS, or OS at baseline, during, or immediately after completion of cCIRT. Patients with detectable giant CAMLs at the first follow up (median time 29 days from completion of cCIRT) demonstrated significantly worse RFS (HR=11.79, 95% CI 4.27-32.56, p=0.0021), DMFS (HR=6.48, 95% CI 2.15-19.54, p=0.0009), and PFS (HR=12.47, 95% CI 4.66-33.37, p=0.0014) while OS trended towards statistical significance (HR=5.39 95% CI 1.33-21.81, p=0.071). Long term evaluation of patients with CAML ≥50 μm at first follow up (N=16) revealed 3 patients who converted to CAML<49 μm at last follow up. Patients who converted did not experience any relapses, while all 13 patients who continued to have CAML ≥50 μm experienced progression or death. **Conclusion:** Giant CAMLs at first follow up after completion of concurrent chemoimmunoradiation is predictive of disease progression and death. This may represent an immediate surrogate marker for poor response at the completion of definitive therapy. Long term follow up with maintenance immunotherapy indicates that a subset of patients convert from giant CAMLs to smaller CAMLs, with better outcomes than those that do not, suggesting that these patients may have derived benefit from maintenance immunotherapy. Continued prospective validation of CAMLs as a peripheral blood-based biomarker is needed to validate these findings.

Keywords: NSCLC, Immunotherapy, biomarkers

P2.01-94 ADVANCED AGE AND HIGH MODIFIED GLASGOW PROGNOSTIC SCORE ARE ASSOCIATED WITH INCREASED COMPLICATIONS AFTER PNEUMONECTOMY

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Background: Pneumonectomy is associated with increased morbidity and mortality compared to parenchyma sparing anatomic lung resections. The aim of this study was to identify risk factors in lung cancer patients undergoing curative intent pneumonectomy. **Method:** All newly diagnosed non-small cell lung cancer patients undergoing pneumonectomy in curative intent as the primary surgical procedure between 1/2013 and 12/2018 were retrospectively analyzed. We reviewed demographic, clinical, functional and surgical variables. Postoperative complications and 30- as well as 90- day mortality were analyzed to identify risk factors for postoperative morbidity and mortality . **Result:** 103 lung cancer patients (67% male; mean age 62.3 ± 8.5) who underwent pneumonectomy with a curative intent have been identified. 62 patients (60%) received neoadjuvant treatment with chemotherapy (n=20) chemoradiation (n=42). Postoperative complications were registered in 35 (34%) patients (34%), with a major complication rate of 12%. Patients older than 65 years had a significantly higher risk for complications (p=0.0039). There was a strong trend in patients with modified Glasgow Prognostic Score >1 for higher postoperative complications (p=0.0715). There was no increase in postoperative morbidity in patients who underwent neoadjuvant treatment. 30- and 90-day mortality was 2.9% and 2.9%, respectively. **Conclusion:** Pneumonectomy for lung cancer can be done with low postoperative morbidity and mortality. Elderly patients should receive a careful preoperative evaluation. Modified Glasgow Prognostic Score can be considered for risk stratification for this procedure.

Keyword: Lung cancer, pneumonectomy, complications

P2.01-95 UPDATED DATA OF KRSG 1302 STUDY: NEDAPLATIN AND NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED SQUAMOUS CELL LUNG CANCER

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Background: Nedaplatin (N) and nab-paclitaxel (nab-P) are efficacious for the treatment of non-small cell lung cancer, especially advanced squamous cell lung cancer. Although a combination of N and nab-P is expected to result in the treatment of squamous cell lung cancer, no sufficient and reliable data have been reported yet. **Method:** Patients and methods: The inclusion criteria were no prior chemotherapy; stage IIIB or stage IV squamous cell lung cancer; a performance status (PS) of 0–1; 75 > patients' age > 20 years; and adequate major organ function. Patients received escalating doses of nab-P under a fixed dose of N (100 mg/m^2, 1st day) every 3 weeks in phase I. The initial dose of nab-P was 100 mg/m^2 on the 1st and 8th

day (level 1), and the next dose was 100 mg/m^2 on the 1st, 8th, and 15th day (level 2). In phase II, the patients received the recommended dose of N/nab-P. The primary endpoint was tumor response, which was measured according to the revised version of response evaluation criteria in solid tumors. **Result:** In this study, 5 patients were enrolled in the phase I. Three patients in level 1 experienced no dose-limiting toxicities (DLTs); whereas, 2 patients in level 2 experienced DLTs. Therefore, level 1 was named the recommended dose. In addition, 23 patients were enrolled in phase II. Three and 23 patients in level 1 and phase II were evaluated, respectively. However, among them, 2 of 26 patients were not assessed due to pneumonia, and 1 of 26 patients was excluded from analysis due to patients' refusal. Partial response, stable disease, and progressive disease were noted in 21, 0, and 2 patients, respectively, yielding a response rate of 91.3% [95% confidence interval (CI): 72.0–98.9]. The median progression-free survival (PFS) was 223 days (95%CI: 144–330), and the median overall survival (OS) was 358 days (95% CI: 255–950). The 1- and 2-year PFS rate were 17.8% and 12.0%. The 1- and 2-year OS rate were 50.0% and 43.8%, respectively. The grade 3 and grade 4 toxicities were manageable and there was no treatment-related death. These data were published in 2018 ESMO. We will report updated efficacy and safety of N/nab-P in KRSG 1302 study. **Conclusion:** Conclusions: A combination of N (100 mg/m^2, 1st day) with nab-P (100 mg/m^2, 1st and 8th day) every 3 weeks demonstrated an effective therapeutic approach. Therefore, N/nab-P administration is to be safe and efficacious for patients with advanced squamous cell lung cancer.

Keywords: Nedaplatin, nab-Paclitaxel, Squamous Cell Lung Cancer

P2.01-96 RESPONSE TO ANTI-HER2 AFATINIB IN A CASE OF INVASIVE PULMONARY MUCINOUS ADENOCARCINOMA WITH A SLC3A2-NRG1 FUSION

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Background: Neuregulin 1 gene (*NRG1*) fusions such as *SLC3A2-NRG1* have been identified in 6,7% of invasive pulmonary mucinous adenocarcinoma (IMA). This fusion leads to ErbB2 and ErbB3 pathway activation. Theoretically a matched targeted therapy may be afatinib, an oral irreversible ErbB-family inhibitor. **Method:** We present the case of a 80 year-old non smoker caucasian female with breathless at rest, bronchorrhea, fever, bilateral ground glass opacities and right lower lobe atelectasia. Body CT scan and PET-scanner revealed hypermetabolic multifocal lung involvement. Cytologic examination of bronchioloalveolar lavage revealed adenocarcinomatous cells compatible with IMA. She received first-line gefitinib 250mg per day, antibiotics and solumedrol. After a clinical improvement of 15 days, cough and hypoxemia worsened and CT scan showed pulmonary opacities progression. A *SLC3A2(e5)-NRG1(e6)* gene fusion was identified with a targeted RNA sequencing performed on cytologic samples (Panel « FusionPlex CTL Kit », ArcherDx). The sample was negative for *EGFR* ex18 to 21, *KRAS, BRAF, PIK3CA, ERBB2, MET* mutations. Afatinib 30mg orally once daily was started. At 8-week follow-up, the patient reported resolution of cough, bronchorrhea, hypoxemia and chest CT showed significant improvement of ground glass opacities in the left lower lobe. The clinical response was sustained to week 16, when her bronchorrea and hypoxemia worsened and CT scan showed progression despite an increasing dosage of afatinib at 40mg once daily. She subsequently received carboplatine- paclitaxel- bevacizumab. A progression eventually occurred after 4 months. We rechallenge afatinib 30mg orally once daily and a clinical and imaging response is still ongoing after 8 weeks. **Result:** The clinical efficacy of afatinib in this case was suggestive of an on target effect of afatinib, with rapid clinical improvement and radiographic response despite a disease control shorter than 16 weeks. **Conclusion:** This report offers some evidence of the activity of afatinib in *NRG1* gene fusion-positive lung cancer.

Keywords: NSCLC, Targeted therapy, SLC3A2-NRG1 FUSION

P2.01-97 ANGIOTENSIN-CONVERTING ENZYME INHIBITOR IS ASSOCIATED WITH DECREASED SURVIVAL IN NSCLC PATIENTS TREATED WITH PD-1 CHECKPOINT BLOCKERS

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Background: Angiotensin-converting enzyme (ACE) inhibitors are frequently used to treat hypertension and congestive heart failure. Preclinical evidence shows that ACE plays a role on both innate and adaptive immune responses by promoting macrophages and neutrophils function and the stimulation of antigen presentation, thus suggesting the possibility of anti-tumor immunity through an ACE inhibitor-mediated mechanism. Interactions between ACE inhibitors and immune checkpoint blockers (ICB) have not been currently investigated in cancer patients (pts). Our study evaluated the effect of ACE inhibitors on non-small cell lung cancer (NSCLC) pts treated with PD-1/PD-L1 inhibitors. **Method:** We conducted a retrospective multicohort retrospective analysis of pts treated with PD-1/PD-L1 inhibitors for NSCLC at Dijon Cancer Center, and at the University of Montreal Hospital. Clinical data and co-medications were collected. Groups were defined as pts treated with ACE inhibitor or not with at the time of ICB initiation. PFS and OS were compared between both groups. Statistical analyses were performed using the Kaplan-Meier method. Cox regression analyses were performed separately to adjust for standard prognostic factors. RNA sequencing of several tumors were performed and analyzed using CIBERSORT to determine immune cells infiltration. **Result:** Among 283 pts included (177 pts from Dijon, and 106 pts from Montreal), 27 (10%) received ACE inhibitors. Baseline characteristics were equally balanced in both groups. However, the ACE inhibitor group was more frequently treated with statins, beta blockers and metformin. The ACE inhibitor group had shorter median PFS compared to the control group: 2.5 vs. 3.8 months, p= 0.02 (HR=1.7 CI95% 1.1-2.5). The negative impact of ACE inhibitor group was maintained after multivariate analyses adjusting for known risk factors (HR=1.9 CI95% 1.1-3.5 p=0.02 for PFS and HR=2.3 CI95% 1.2-4.4 p=0.01 for OS). RNA sequencing suggested that ACE inhibitor group tumors had lower M1 macrophages, activated mast cells, NK cells and memory activated T cells thus suggesting an immunosuppressed state. **Conclusion:** ACE inhibitor prescription concomitant to the PD-1/PD-L1 inhibitors treatment is associated with impaired outcome in pts with advanced NSCLC pts. This reduction is independent of standard prognostic factors. Biological correlative analyses suggest a tumor immunosuppressed state in ACE inhibitor group. These results should be validated in larger prospective cohorts.

Keywords: Angiotensin-converting enzyme inhibitor, immune checkpoint inhibitor, NSCLC

P2.01-98 NEUTROPHIL-PLATELET SCORE (NPS), A PREDICTIVE SYSTEMIC INFLAMMATION SCORE FOR PEMBROLIZUMAB IN FIRST LINE OF ADVANCED NSCLC PATIENTS

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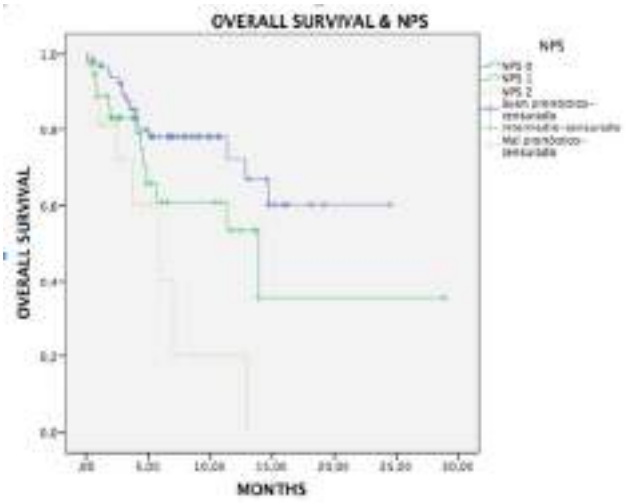
Background: Systemic inflammation response can be characterized by changes of peripheral blood cell amounts. Several blood cell-based scores have been found to have prognostic value in some tumors treated with ICI. Neutrophil-platelet score (NPS) is a systemic

inflammation-based score characterizing 3 prognostic groups: good (0), neutrophils <=7500 and platelets <=400000; intermediate (1), neutrophils >7500 or platelets >400000; poor (2), neutrophils >7500 and platelets >400000). It has never been evaluated as prognostic biomarker in first line treatment setting of non-small-cell lung cancer (NSCLC) patients treated with pembrolizumab. **Method:** This is a multicenter retrospective study with the aim to evaluate prognostic value of NPS in patients with advanced NSCLC and high PD-L1 expression treated with pembrolizumab monotherapy between September 2016 and March 2019. Clinical data were contributed by 12 medical centers in Spain. Primary endpoint was association of NPS with overall survival (OS). **Result:** 121 patients were evaluated. Median age was 68 years (38-88). 90 (74,4%) were male and 90 (74,4%) had PS1. Predominant histologies were adenocarcinoma (68,6%) and squamous-cell carcinoma (23,1%). Median number of cycles was 7 (1-33). Median follow-up: 6,5 months. Most were current or former smokers (95,9%). Only 1 patient had driver mutation (ALK rearrangement). 66,9% had 2 or more metastatic locations, 18,2% had central nervous system (CNS) disease, 17,4% liver metastasis, and 41,3% bone metastasis. Response rate was 40,4% according to RECISTv1.1 criteria. 11% had hyperprogression and 7,2% pseudoprogression. Estimated 12-month-OS was 62% (95%CI: 49.1%-72.5%) and estimated 12-month-PFS was 44.2% (95%CI: 31.1%-56.5%). Higher NPS was associated with poor PFS: NPS1 HR 1,23 (95%CI, 0,61-2,46), p=0,56; NPS2 HR 3,56 (95%CI, 1,61-7,86), p=0,002. NPS was not associated with disease control rate (DCR) or overall response rate (ORR).



Conclusion: NPS predicted OS and PFS in advanced NSCLC patients with high PD-L1 expression treated with first line pembrolizumab monotherapy. NPS2 subgroup has an especially bad prognosis in spite of high PD-L1 expression and frontline treatment with pembrolizumab. These results need to be validated in prospective studies.

Keyword: NPS, neutrophil-platelet score, immunotherapy, biomarkers, NSCLC, pembrolizumab

P2.01-99 A PHASE IIIB OPEN-LABEL STUDY OF AFATINIB IN EGFR TKI-NAÏVE PATIENTS WITH EGFR MUTATION-POSITIVE NSCLC: FINAL ANALYSIS

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Background: The safety and efficacy of afatinib, an orally administered irreversible EGFR TKI, have been demonstrated in patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC in several Phase III clinical trials. However, prospective evidence supporting the clinical benefit of afatinib in the real-world setting is limited. Here, we report final data from a Phase IIIb open-label, multicenter trial evaluating safety and efficacy of afatinib in EGFR TKI-naïve Asian patients with locally advanced/metastatic *EGFR*m+ NSCLC, in a setting similar to real-world practice. **Method:** EGFR TKI-naïve patients with locally advanced/metastatic *EGFR*m+ NSCLC were recruited from 34 sites in China, Hong Kong, India, Singapore, and Taiwan. Patients received 40 mg/day afatinib. Dose reduction to minimum 20 mg/day was permitted. Treatment continued until lack of clinical benefit as determined by the investigator. The primary and secondary safety endpoints were number of patients with serious adverse events (SAEs), and number of patients with drug-related AEs, respectively. The secondary efficacy endpoint was time to symptomatic progression (TTSP). Further endpoints included progression free survival (PFS), objective response, and duration of disease control. **Result:** In total, 541 patients received afatinib. Baseline characteristics were representative of patients with *EGFR*m+ NSCLC (median age, 59 years; female, 52.9%; never smoked, 69.3%; *EGFR* mutations, common [Del19/L858R]/uncommon: 88.2% [48.2%/40.5%]/11.8%; ECOG performance status 0/1, 18.3%/79.7%; brain metastases, 19%). SAEs were reported in 164 patients (30.3%). 34 patients (6.3%) had drug-related SAEs, most commonly (grouped terms): diarrhea (1.8%), stomatitis (0.7%), and vomiting (0.7%). Drug-related AEs (DRAEs) of any grade were reported in 528 patients (97.6%). AEs leading to dose reduction occurred in 154 patients (28.5%); TRAEs leading to treatment discontinuation were reported in 17 patients (3.1%). Three patients experienced DRAEs leading to death (decreased appetite, dyspnea, and respiratory failure). Median TTSP was 14.0 months (95% confidence interval [CI]: 12.9, 15.9) and median PFS was 12.1 months (95% CI: 11.0, 13.6). Objective responses were reported in 312 patients (57.7%) by week 52; the median duration of response was 12.2 months (95% CI: 11.0, 13.5). 483 patients (89.3%) achieved disease control of median duration 13.6 months (95% CI: 12.1, 14.4). **Conclusion:** Safety data for afatinib in this patient population were consistent with previously reported data, with no new safety signals. AEs were manageable and did not lead to discontinuation in most patients. This study also demonstrated the efficacy and clinical benefit of afatinib in Asian patients with locally advanced or metastatic *EGFRm+* NSCLC in a near real-world setting.

P2.01-100 SPECTRUM OF EGFR EXON 20 INSERTION MUTATIONS AND CO-OCCURRING GENETIC ALTERATIONS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Background: Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations are associated with a low response rate to approved EGFR tyrosine kinase inhibitors (EGFR-TKIs) and short progression-free survival. Pre-clinical studies have shown differences in the affinity of *EGFR* exon 20 insertion mutations for EGFR-TKIs, suggesting that the location of the insertion within the C-helix may play an important role in determining EGFR-TKI sensitivity. Several EGFR-TKIs designed to target *EGFR* exon 20 insertion mutations are in clinical development. Comprehensive genomic profiling has allowed for identification of co-occurring genomic alterations, which may help us identify additional pathways that may drive disease progression and

drug resistance. **Method:** Formalin-fixed paraffin-embedded (FFPE) samples from patients with non-small cell lung cancer (NSCLC) were profiled by targeted next-generation sequencing (NGS) using Caris Molecular Intelligence (Caris Life Sciences, Phoenix, AZ). Mutations and copy number variations (CNV) were assessed for each gene included in the NGS panel. Gene amplification (including low amplifications) was defined as gene copy number ≥ 4 and copy number loss as gene copy number < -1.4. **Result:** Among the 1,556 patients with *EGFR* mutations, 104 (6.7%) patients were found to harbor an *EGFR* exon 20 insertion mutation. There were 70 (67.3%) females and 34 (32.7%) males with a mean age 62 (± 11.5 years). 61 (58.7%) samples came from primary lung sites and 43 samples (41.3%) came from metastatic sites. The main histological types were: adenocarcinoma 89 (85.5%), acinar adenocarcinoma 6 (5.7%), papillary adenocarcinoma 5 (4.8%), adenocarcinoma with bronchoalveolar features 1 (1%), squamous cell carcinoma 1 (1%) and carcinoma not otherwise specified 2 (2%). The most common exon 20 insertion mutation was A767_V769dup (25%), followed by S768_D770dup (13%), H773_V774insAH (5%) and H773dup (5%). The most common pathogenic mutations (including presumed pathogenic) included *TP53* (51%), followed by *CTNNB1* (6%), *PIK3CA* (4%), *PTEN* (3%), *SMAD4* (3%), and *CHEK2* (2%). Of the 104 cases, CNVs were available from 54 patients. Among these patients, commonly amplified genes included *CDK4* (11%), *EGFR* (9%), *MDM2* (9%), *FOXA1* (7%), and *HMGA2* (6%). Copy number loss was observed with *CDKN2A* (7%), *CTNNB1* (2%), *ATR* (2%), *BRCA2* (2%), and *FANCL* (2%). **Conclusion:** The diverse spectrum of *EGFR* exon 20 insertion mutations shows molecular heterogeneity of this rare type of *EGFR* mutations. The presence of co-occurring genomic alterations that may promote tumor progression and drug resistance suggests that combination approaches may be necessary to overcome resistance to EGFR-TKI therapy in some patients with an *EGFR* exon 20 insertion mutation.

Keywords: exon 20 insertion mutation, NSCLC, co-occurring genomic alterations

P2.01-101 MULTIPLE CHEMOTHERAPY-BASED COMBINATION THERAPY STRATEGIES FOR ADVANCED LUNG CANCER PATIENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: The treatments for patients with advanced lung cancer focus on chemotherapy, targeted therapy and immunotherapy, or a combination of multiple treatments. This study compares various chemotherapy-based combination therapies to identify the best one for patients with advanced lung cancer. **Method:** A literature search was performed (PubMed, EMBASE and Medline) for randomized controlled trials of advanced lung cancer combination therapy from 2008 to 2018. Primary outcomes were overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), adverse as second outcome indicators. A Bayesian mesh meta-analysis for multiple treatment strategies was implemented. The results of four outcome variables were combined to find the best chemotherapy-based combination therapy strategy. **Result:** The analysis included 43 studies and five combination therapies: Chemotherapy/chemotherapy plus placebo (CT), CT plus one targeted therapy drug (CT+T), CT plus 2 targeted therapy drugs (CT+T+T), chemotherapy combined with immunotherapy (CT+IO) or chemotherapy combined with biotherapy (CT+B) (Figure 1 A-B). Hazard ratios for OS of CT+T, CT+T+T, CT+IO, CT+B compared to CT were 0.92 (CI 0.86, 0.97, p =0.0154), 0.90 (CI 0.74-1.1), 0.82 (CI 0.71-0.93, p =0.0069) and 1.1 (CI 0.77-1.5). And the HRs of CT+T+T, CT+IO compared to CT+T were 0.98 (CI 0.82-1.2), 0.89 (CI 0.77, 1.0). Finally, comparing with CT+T+T, CT+IO had longer survival 0.91 (CI 0.71-1.1). With the same tendency as PFS/ORR and OS (Figure 1 C-H), CT+IO showed the best therapeutic benefits, and its treatment-related adverse reaction rate was the lowest. Among immunotherapy drugs in these studies, pembrolizumab showed superior efficacy. **Conclusion:** Among multiple chemotherapy-based combination therapy strategies, chemotherapy combined with immunotherapy is the best choice for patients with advanced lung cancer. Moreover, the results also showed that the PD-1 inhibitor (pembrolizumab) is superior to the CTLA4 inhibitor (ipilimumab).

Keywords: Advanced lung cancer, network meta-analysis, combination therapy

P2.01-102 OUTCOME OF PATIENTS WITH EGFR EXON 19 MUTATION IN A PHASE III RANDOMIZED TRIAL COMPARING GEFITINIB TO GEFITINIB WITH CHEMOTHERAPY

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Background: In patients with EGFR sensitizing mutations, the subtype of the EGFR mutation impacts the clinical outcome and carries both prognostic and predictive value. **Method:** We had conducted a Phase III randomized trial in patients with advanced NSCLC harboring *EGFR* sensitizing mutation, ECOG PS 0 to 2 planned for first-line palliative therapy. The type of sensitizing *EGFR* mutation (exon 19 versus others) was a stratification factor. Randomization was 1:1 to gefitinib 250 mg orally daily (gef) or pemetrexed 500 mg/m^2 and carboplatin AUC 5 IV 3-weekly for 4 cycles, followed by maintenance pemetrexed with gefitinib from day 1 (gef+C). The primary end-point was progression-free survival (PFS); secondary end-points included overall survival (OS), response rate and toxicity. We present the subset analysis of the patients with exon 19 in-frame deletion. **Result:** Between 2016 and 2018, 216 patients with EGFR exon 19 mutation were randomly assigned to gef (n=109) and gef+C (n=107). The median age was 54 years, 51% were males, 20% were PS 2 and 21% had brain metastases. Median follow-up was 17 months (range, 7 to 30). Radiologic response rates were 81% and 75% in gef+C and gef arms respectively, P=0.29. Estimated median PFS was significantly longer with gef+C than gef [17 months, (95% CI, 12.4 to 21.6) versus 8 months (95% CI, 6.8 to 9.3); hazard ratio for disease progression or death, 0.49; 95% CI, 0.35 to 0.69; P<0.001]. Data for OS are immature. Clinically relevant ≥ grade 3 toxicities occurred in 55% and 23% of patients in gef+C and gef arms respectively, P<0.001. **Conclusion:** In patients with exon 19 in-frame deletion, combining pemetrexed and carboplatin chemotherapy with gefitinib led to a significant PFS prolongation, with an increase in clinically relevant severe toxicities.

Keywords: NSCLC, exon 19, EGFR

P2.01-103 REAL-WORLD TREATMENT PATTERNS AND SURVIVAL IN NON-SMALL CELL LUNG CANCER PATIENTS WITH EGFR EXON 20 INSERTION MUTATIONS

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Background: Mutations in the epidermal growth factor receptor (EGFR) gene have been identified in 10-50% of patients with non-small cell lung cancer (NSCLC), and 2-10% are exon 20 insertion mutations. This study describes real-world characteristics, treatment patterns, and overall survival (OS) of NSCLC patients with EGFR exon 20 insertions. **Method:** Flatiron Health electronic health record data from 1/2011-4/2018 were used for this retrospective study. Treatment-naïve (TN) and relapsed/refractory (RR) patients with advanced/metastatic NSCLC with EGFR exon 20 insertion mutation aged ≥18 years at treatment initiation were included. Patient characteristics were described, and Kaplan-Meier analyses were used to assess OS for TN and RR patients. **Result:** There were 128 TN and 71 RR patients identified. Median age was 66.5 and 65.0 years for TN and RR patients, respectively, and over half were female (TN: 59.4%, RR: 53.5%). Among 83 TN and 47 RR patients with known ECOG score at advanced diagnosis, most had score 0-1 (TN: 56.3%, RR: 62.0%). Central nervous system metastases were observed in 35.2% of TN and 33.8% of RR patients. 45.3% of TN patients and 23.9% of RR patients received chemotherapy only. Approximately 20% of TN and RR patient were treated with EGFR TKI only. Only 6.3% of TN patients received any immuno-oncologic therapy (IO) or combination, while this was higher in RR patients (29.6%). Overall, median OS was low at 16.2 months for TN patients, and 12.5 months for RR patients. Treatment with any IO was associated with poor survival in TN (6.1 months) and RR (8.0 months) patients.

	TN		RR	
	N (%)	OS Median (IQR), months	N (%)	OS Median (IQR), months
All	28 (100.0)	16.2 (16.9, 27.2)	71 (100.0)	12.5 (5.0, 21.1)
Chemotherapy only	58 (45.3)	18.2 (9.2, 26.5)	17 (23.9)	17.1 (8.7, 30.0)
EGFR TKI only	27 (21.1)	7.1 (2.5, 20.7)	18 (25.4)	15.3 (5.0, 23.5)
IO in any combination	8 (6.3)	6.1 (5.3, -)	21 (29.6)	8.0 (2.0, 10.1)

EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; IO = immuno-oncology therapy; IQR = interquartile range; OS = overall survival; RR = relapsed/refractory; TN = treatment naïve.

Conclusion: OS of patients with EGFR exon 20 NSCLC remains poor. In TN patients, chemotherapy was the most common treatment, followed by EGFR TKIs. Treatment patterns were more diverse in RR patients. This study demonstrated unmet medical need for patients with NSCLC with EGFR exon 20 insertion mutation.

Keywords: Non-Small Cell Lung Cancer, EGFR exon 20 insertion, overall survival

P2.02 ADVOCACY
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.02-01 ALKFUSION AND THE UNMET NEED OF PATIENT-CENTRIC RESEARCH

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Background: Approximately four (4) to seven (7) percent of non-small cell lung cancer (NSCLC) is driven by the ALK transfusion. In the United States, approximately 11,000 people are diagnosed with ALK-positive NSCLC every year. There are an array of treatment options for the ALK-positive patient, and these options have improved overall survival rates in this subset of NSCLC patients. Currently, there are five FDA approved tyrosine kinase inhibitors (TKIs) that treat ALK-positive NSCLC: crizotinib, ceritinib, alectinib, brigatinib and lorlatinib. There are other drugs and drug combinations that are currently in clinical trials. Invariably, patients develop acquired resistance to each of these drugs, but the mechanisms of resistance can vary. Better understanding these mechanisms of resistance will provide invaluable information and improve survival outcomes. The development of new drugs, drug combinations, and innovative treatments will significantly impact the survival rate for ALK-positive lung cancer. **Method:** ALKFusion was conceived by a group of seven lung cancer patient advocates with over 30 years of combined patient focused advocacy experience in the lung cancer community. A primary goal of the ALKFusion group is to improve survival for people with ALK-positive NSCLC by accelerating research. Patient collaboration with key shareholders in the lung cancer arena is critical. Further, patients must be educated about their disease in order to make the best treatment decisions. Often, patients lack access to doctors who specialize in ALK-positive lung cancer, as it is a rare subset of NSCLC, so there is a particular need for patients themselves to have the educational resources to discuss with their doctor. **Result:** As a patient-centric organization, ALKFusion is committed to accelerating research to improve the outcomes for ALK-positive lung cancer patients. ALKFusion's vision is twofold; to initiate and support patient-centric research with a focus on collaboration and disease management, and to provide tools to patients so that they can truly be a partner in their care decisions. As patients, the members of ALKFusion are on the frontline of this disease. To aid it in achieving this goal, the group has engaged with a wide range of researchers, clinicians, other lung cancer organizations, and the pharmaceutical industry, with the aim of advancing cutting-edge research and in the treatment of those living with ALK-positive NSCLC. Further, ALKFusion publishes a monthly newsletter titled The ALKFusion Reporter, which provides summaries and links to every recent scientific publication relating to ALK-positive lung cancer. **Conclusion:** ALKFusion is a crucial component of the "patient-first" movement that has been gaining momentum in several oncogene communities. It is a rapidly growing group of educated patient advocates who endeavour to be true partners with the medical community in order to accelerate research for ALK-positive lung cancer.

Keywords: ALK, patient, education

P2.03 BIOLOGY
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.03-01 MMP1 SECRETED BY CANCER CELLS INDUCES A PRO-TUMORIGENIC SENESCENT PHENOTYPE IN FIBROBLASTS IN LARGE CELL CARCINOMA OF THE LUNG

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Background: Tumor associated fibroblasts (TAFs) are key effector cells of cancer progression. Senescent TAFs have been reported in a growing list of aggressive cancer subtypes including the aggressive subtype large cell carcinoma (LCC) of the lung. We previously reported that LCC cells induce fibroblast senescence in normal fibroblasts after co-culture, revealing that paracrine signaling must be involved. Moreover, we found that senescent fibroblasts secrete factors that stimulate the growth and invasion of LCC cells beyond the stimulation elicited by non-senescent fibroblasts, supporting that fibroblast senescence may contribute to the aggressive nature of LCC. Whole-genome transcriptional profiling on a panel of non-small cell lung cancer (NSCLC) cell lines, including adenocarcinoma (ADC), squamous cell carcinoma (SCC) and LCC, identified MMP1 as highly overexpressed in LCC cells compared to non-LCC cells. Here we examined the role of MMP1 in LCC cells in the paracrine induction of fibroblast senescence. **Method:** We silenced MMP-1 expression in LCC cancer cell lines by shRNA and analyzed common senescence markers after co-culture with normal fibroblasts, including β-galactosidase staining as well as the expression of common factors of the senescence-associated secretory phenotype (SASP) by qRT-PCR. In addition, the growth and invasion pro-tumorigenic effects elicited by the conditioned medium of fibroblasts co-cultured with shMMP1 or shscramble LCC cells was analyzed. **Result:** Knocking-down MMP1 in LCC cells was sufficient to abrogate fibroblast senescence induction in co-cultures with LCC cells, as well as the growth and invasion enhancement of LCC cells elicited by the conditioned medium of fibroblasts. The addition of active recombinant MMP1 partially rescued the fibroblast senescent phenotype in co-culture, yet it was not sufficient to induce senescence when added to fibroblasts cultured alone. **Conclusion:** Our results unveil a process of "niche construction" by LCC cells that is driven by the overexpression of MMP1, which induces senescence in adjacent fibroblasts. Moreover, our results unveil a novel biological function of MMP1 (i.e. paracrine senescence induction in fibroblasts), that is strikingly different from its well-known collagenolytic function. Our results also show that MMP1 is necessary but not sufficient to induce fibroblast senescence. Moreover, our findings support that the aberrant carcinoma cell-fibroblast crosstalk mediated by MMP1 may be a suitable therapeutic target in LCC.

Keyword: Tumor associated fibroblasts, senescence, MMP1

P2.03-02 A SINGLE SAMPLE PREDICTOR OF TRANSCRIPTIONAL LUNG ADENOCARCINOMA SUBTYPES: PREDICTING BIOLOGY AND PROGNOSIS

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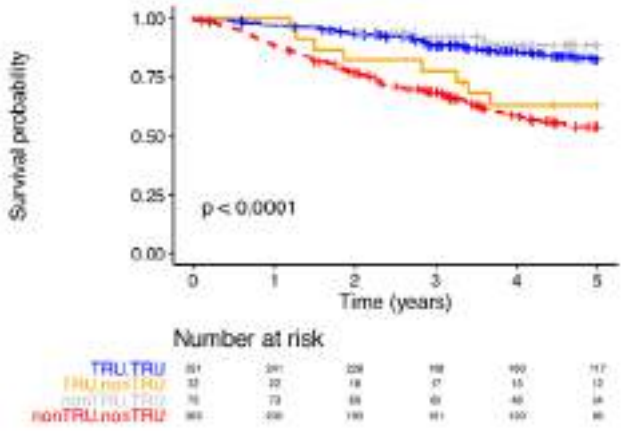
Background: Lung adenocarcinoma accounts for nearly 40% of all lung cancers, thereby representing the major histological subtype. Comprehensive molecular studies have proposed three molecular lung adenocarcinoma subtypes termed the terminal respiratory unit (TRU), proximal-inflammatory (PI), and the proximal-proliferative (PP) subtype based mainly on transcriptional patterns. These subtypes have been linked to molecular characteristics but also to

differences in prognosis, favoring the TRU subtype compared to the PI and PP (combined PI and PP = non-TRU) subtypes. However, the method used (nearest centroid classification=NCC) to classify samples into transcriptional subtypes depends on the cohort composition, consequently struggle with e.g. reproducibility and classification of single samples. In this study, we aimed to derive a single sample predictor (SSP) of these subtypes, capable of predicting single samples irrespective of technical platforms and cohort composition. **Method:** In this study, the gene expression based SSP called "Absolute assignment of breast cancer Intrinsic Molecular Subtype" (AIMS) were trained on a large combined dataset collection (n=1655, 17 datasets) with AC assignment obtained by the NCC method and tested in 5 publicly available gene expression datasets (n=977) with treatment data available. Survival analysis was performed to compare the two classification methods (AIMS vs. NCC) with overall survival (OS) as clinical endpoint. Survival curves were compared using Kaplan-Meier estimates and the log-rank test. **Result:** Using AIMS, a SSP of lung adenocarcinoma transcriptional biology and prognosis was successfully trained and tested in publicly available gene expression datasets. The majority of the samples were assigned equally by the two methods. However, a minor subset (n=97) of samples were given discordant labels. The derived SSP had an accuracy of 85.5% in 977 independent validation samples for TRU vs non-TRU cases, independent of gene expression platform. Interestingly, the patient group consisting of samples classified as TRU by the NCC method and nonTRU by AIMS (TRU.nonTRU, Fig.1, orange line), showed a survival outcome more similar to the nonTRU patient group. The reverse was observed for the nonTRU.TRU patient group (Fig.1, grey line) with a survival pattern resembling that of the TRU group. Thus, on a survival basis, the discordant samples seems to be more accurately classified by the AIMS method.



Conclusion: We present a SSP for proposed transcriptional adenocarcinoma subtypes capable of predicting single samples irrespective of technical platform and cohort composition, thereby overcoming critical limitations in the applicability of gene signatures. The classifier provides refined categorization of patients with respect to prognosis, representing a prognostic predictor in lung adenocarcinoma.

Keywords: adenocarcinoma, single sample predictor, classifier

P2.03-03 LANDSCAPE OF GENE FUSIONS IN LUNG ADENOCARCINOMA PATIENTS WITH MINIMAL CIGARETTE EXPOSURE IDENTIFIED ON MALIGNANT PLEURAL EFFUSIONS

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Background: Gene fusions in lung adenocarcinoma (LuAD) involving tyrosine kinase receptors such as *ROS1*, *ALK* or *RET* are recurrent oncogenic drivers (~10%), enriched in light or never-smokers. Some of them represent emerging and predictive biomarkers for targeted therapies. Here we report the fusions detected in a cohort of metastatic LuAD patients with low tobacco exposure (never or former-smokers). **Method:** Patient-derived cancer cell lines (PDC) were successfully established from malignant pleural effusions from 11 patients diagnosed with LuAD. We assessed the genetic and molecular profile by whole-exome sequencing (WES) and RNA sequencing (RNA-seq) in each cell line. **Result:** Patients' characteristics: median age, 58 (39-86); 9 were female. Eight of eleven were never-smokers and three, former-smokers. Seven patients were treatment naïve when pleural effusion samples were collected. A cytological examination of pleural fluid was performed by a lung pathologist and all samples were positive for malignant cells. Known driver mutations in lung primary tumours included one *ALK* translocation detected by FISH and three *EGFR* Del19 mutations by targeted sequencing. The three EGFR-mutant LuAD patients progressed to first or second-generation EGFR-TKI and we were able to stablish paired PDC after progressing to tyrosine kinase inhibitors (TKI) in two of them. We identified an acquired *FGFR3-TACC3* fusion in one paired PDC after gefitinib progression (T790M-negative), that led to overexpression of *FGFR3* concurrent with an enrichment of squamous cell lineage transcripts (e.g. *TP63, SOX2*) and MDM2 amplification. Among EGFR wild type (wt) patients, two RET rearrangements, *CCDC6-RET* and *KIF5B-RET*, and one *EML4-ALK* fusion -also detected in the primary tumour- were identified in PDC models. In addition, in two of the samples we discovered novel gene fusions that will be described in detail, involving proteins that are not kinases, and thus, their potential role in cancer is still unknown. **Conclusion:** In this cohort enriched with never-smoking LuAD patients presenting pleural effusions at diagnosis, the presence of known driver fusions during the disease's course detected by RNA-Seq was 36% (4/11), including a *FGFR3-TACC3* fusion as an acquired resistance mechanism to EGFR-TKI. Further study is ongoing in our PDC models to test the functional role of these fusions in order to facilitate precision medicine.

Keywords: Fusions, FGFR3-TACC3, lung adenocarcinoma

P2.03-04 THE PROGNOSTIC VALUE OF SEROLOGICAL TUMOR MARKERS IN LUNG CANCER – ANALYSIS OF 13,373 CASES

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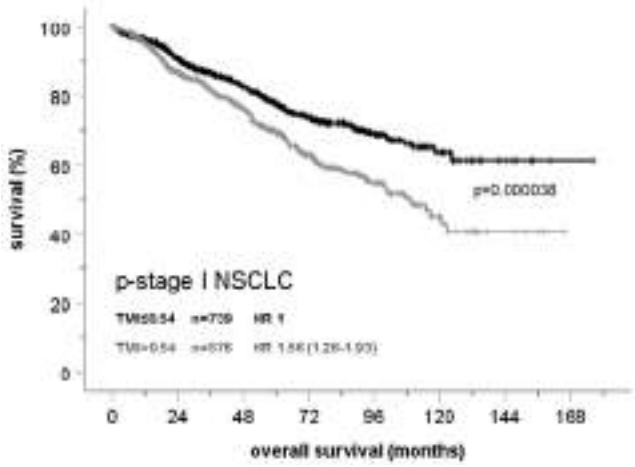
Background: Serological tumor markers such as Carcinoembryonic Antigen (CEA), Cytokeratin 19 Fragments (Cyfra 21-1) and Neuron Specific Enolase (NSE) have been shown to provide prognostic information in lung cancer. We have introduced an algorithm to combine two markers (CEA, Cyfra 21-1) into a new variable the so called tumor marker index (TMI). TMI is defined as the geometric mean of normalized marker values (Muley et al, Anticancer Res 24:1953-56, 2004). **Method:** We have uploaded available routine tumor marker data from various sources (excel sheets, extracts from laboratory IT-systems and from our clinical cancer registry) into the clinical research data warehouse based on i2b2/tranSMART using Talend Open Studio procedures. We extracted selected clinical parameters together with tumor marker data for further analyses with the statistical software package SPSS 25.0 (IBM Deutschland GmbH, Ehningen). Pretherapeutical tumor markers were measured with Roche Elecsys (Roche Diagnostics GmbH, Penzberg). A complete set of tumor marker data for the calculation of TMI1 (CEA, CYFRA21-1) and TMI2 (CEA, CYFRA21-1, NSE) was available in n=13373 and n=13174 cases, respectively. **Result:** The median value (range) for TMI1 and TMI2 was found to be 0.94 (0.01-1311.98) and 1.01 (0.01-201.67), respectively. Besides the validation of our originally published prognostic cut off value of 0.54 for TMI1 (Muley et al, Lung Cancer 2008, 60:408-415) in 1315 p-stage I NSCLC patients (figure), we found additional cut off values for the differentiation of prognostic groups in the data set of all patients. Up to 7 groups with patient number >1800 could be significantly differentiated by both indices (table).



TMI1 cutoff	Patients (n)	Median (mos)	HR	TMI2 cutoff	Patients (n)	Median (mos)	HR
0.42	2,014	62.4	1	0.55	1,989	82.1	1
0.58	1,837	35.3	1.33	0.70	1,774	40.8	1.39
0.79	1,891	26.3	1.61	0.89	1,913	23.5	1.92
1.11	1,913	17.2	2.12	1.15	1,868	16.5	2.49
1.76	1,916	13.3	2.70	1.64	1,871	13.7	3.09
3.54	1,891	10.2	3.44	2.73	1,883	9.4	4.34
>3.54	1,910	6.7	5.00	>2.73	1,871	6.6	5.97

Conclusion: The usefulness of our clinical data warehouse for assembling and structuring of clinical parameters and tumor marker data is warranted. The value of TMIs for the stratification of individual risk groups could be verified in one of the world wide largest series of tumor marker data in lung cancer.

Keywords: prognosis, CYFRA 21-1, CEA

P2.03-05 PHLPP1 EXPRESSION THROUGH AKT AND ERK DUAL SIGNALING PATHWAYS MAY SLOW DOWN THE RESISTANCE TO TKI IN EGFR-MUTATED LUNG ADENOCARCINOMA

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Background: The epidermal growth factor receptor (EGFR) kinase inhibitors are effective treatments for lung cancers with EGFR activating mutations, but the magnitude of tumor regression varies and drug resistance is unavoidable. Multiple mechanisms of resistance to EGFR-TKIs have been identified, including the occurrence of secondary mutations in the EGFR gene, MET amplification, acquired BRAF rearrangements and activation of bypass pathways. Central to these mechanisms of resistance is the re-activation of AKT and ERK signaling, which enables escape of tumor cells from EGFR inhibitor treatment. However, the mechanisms of reactivation of PI3K-AKT and ERK/MAPK pathway are unclear. Pleckstrin homology (PH) domain leucine-rich repeat protein phosphatase (PHLPP) acts as tumor suppressors in various types of human cancer by suppressing cell survival pathways and promoting apoptosis through inhibiting AKT and ERK pathway activation. Here, we hypothesize that PHLPP is a key regulator of EGFR-TKI resistance in lung cancer and a potential treatment target for overcoming resistance to EGFR-TKI treatment. **Method:** A transcriptomic of PHLPP1 in non-small lung cancer cell according to gefitinib sensitivity obtained from Gene Expression Omnibus (GEO) database under accession number GSE4342 were analysis. The lentivirus-mediated delivery of shRNA was used to generated stable knockdown of PHLPP1 expression lung cancer cells, and retrovirus-mediated delivery was used to generated stable overexpression of PHLPP1 lung cancer cells. Western blotting, real-time PCR (RT-PCR) and immunofluorescence were used to determined PHLPP expression *in vitro*. PHLPP1 expression in clinical sample was determined by Immunohistochemical (IHC) staining. MTT assay was conducted to determine the cell proliferation. Xenografts bearing PHLPP overexpression and control were evaluated EGFR-TKI induced tumor regression. **Result:** PHLPP1 gene expression was higher in gefitinib-sensitive NSCLC cell lines than gefitinib-resistant NSCLC cell lines from a GEO public database. *In vitro*, EGFR mutated NSCLC cell line HCC827 continuously exposing to gefitinib exhibited dramatically reduced expression of PHLPP1 and increased phosphorylation AKT and ERK. Knockdown of PHLPP1 decreased cell death induced by the EGFR-TKI in EGFR-mutant lung cancer cells, overexpression of PHLPP1 enhanced gefitinib-induced apoptosis in gefitinib-resistance EGFR-mutant lung cancer cells. In xenograft model, overexpression of PHLPP showed significantly more tumor regression after gefitinib treatment at 1-week time point compared to control group. In patients, PHLPP1 were highly expressed in tumors with EGFR common mutations pre- and post-development of resistance to EGFR TKIs. PHLPP1 expression were down regulated in the post-relapse tumor samples compared to that of pre-treatment, and patients with higher PHLPP1 expression in pre-treatment had significantly longer progression-free survival (PFS). **Conclusion:** PHLPP loss may be a key molecule contributing to the resistance of EGFR-TKI by activating PI3K-AKT and ERK/MAPK signaling pathway. PHLPP may serve as a potential predictor of EGFR-TKI treatment response in these patients. Up-regulating PHLPP expression may prevent or /and delay the emergence of EGFR-TKI resistance. Further study is warranted to prove PHLPP as an effective strategy.

Keywords: PH domain leucine-rich-repeats protein phosphatase (PHLPP), Drug resistance, Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

P2.03-06 DETECTION OF CTDNA AND CORRELATION WITH TUMOR MUTATION TESTING IN EARLY STAGE NSCLC

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Background: In advanced disease, circulating tumor (ctDNA) has proven a viable alternative to tissue based molecular testing to identify patients with lung adenocarcinoma (LUAD) eligible for targeted therapies. ctDNA is under investigation for utility in early cancer detection and non-invasive companion diagnostics to allow for identification of targetable biomarkers in patients who may benefit from neoadjuvant targeted therapy. However, in the early stage cancer setting, ctDNA has been limited by reliance on interrogation of genomic alterations alone resulting in low detection rates (13% stage I, 22% stage II, 40% stage III, Abbosh et al, Nature 2017). Herein, we test the ability of the novel ctDNA-based assay to detect ctDNA in patients with early stage LUAD, and secondarily, to identify targetable oncogenes in these patients. **Method:** Eligible patients had stage IA-IIIA LUAD deemed surgically resectable. Following consent, plasma samples were collected prior to surgery or neoadjuvant therapy. Circulating free DNA (cfDNA) was analyzed for ctDNA with the LUNAR assay (Guardant Health), which utilizes an integrated genomic and epigenomic ctDNA assessment at a tumor allelic fraction down to 0.01% to report "ctDNA detected" or "ctDNA not detected". This single blood sample cfDNA assay utilizes a variant filter to distinguish tumor from non-tumor derived cfDNA alterations in the absence of other genomic DNA (e.g. tissue sequencing or peripheral blood mononuclear cells). Molecular analysis of paired FFPE primary tumor specimens was performed using the Illumina TruSight Tumor 26 or ArcherDx VariantPlex Solid Tumor library preparation kits followed by next-generation sequencing (NGS) on the Illumina platform in a CLIA-certified laboratory. Sensitivity for tumor driver mutation detection is evaluated by comparing tumor drivers identified in ctDNA with those identified in corresponding paired primary tumor specimens. **Result:** We enrolled 31 patients with early stage LUAD who ultimately underwent surgical resection,

29 of whom completed LUNAR testing (19 with stage I, 4 with stage II and 6 with stage IIIA). Analysis of tumor tissue identified a driver mutation in 83% (24/29) of cases (*KRAS*=11, *EGFR*=10, *MET*=3, ALK=1). A genomic cancer-associated mutation was identified in 16%, 25% and 67% in stage I, II, and III, respectively. The LUNAR assay demonstrated 100% specificity for *EGFR* and *KRAS* mutations. The incorporation of the epigenomic classifier enhanced pre-operative ctDNA detection to 26% of Stage I, 50% of stage II, and 67% of stage III patients. **Conclusion:** The majority of patients with early stage LUAD had an identifiable oncogene alteration, consistent with data from advanced disease. Utilizing a plasma only, integrated genomic and epigenomic ctDNA assay demonstrated improved performance over tumor informed approaches. The ctDNA detection rate increased with disease stage, consistent with increased tumor burden. With 100% tissue concordance of *EGFR* and *KRAS* alterations identified in ctDNA, ctDNA may prove an option for not only identification of early stage LUAD, but also identifying biomarker positive LUAD eligible for clinical trials utilizing targeted therapy in the neoadjuvant setting.

Keywords: LUNAR, ctDNA, Early stage NSCLC

P2.03-07 FREQUENCY OF DRIVER GENES (EGFR, KRAS, BRAF, ALK, RET AND ROS1) ALTERATIONS IN BRAZILIAN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: Lung cancer is the deadliest cancer in the world. Several oncogenic drivers are observed in non-small cell lung cancer (NSCLC) and they have been used as therapeutic targets. The frequency of the major driver genes in lung adenocarcinoma varies based on ethnicity and the impact in the Brazilian admixture population has not been explored. Thus, we aimed to investigate the presence gene mutations of *EGFR, KRAS, and BRAF,* and *ALK, RET* and *ROS1* rearrangements in Brazilian lung adenocarcinoma and to associate the presence of these alterations with clinicopathological characteristics and genetic ancestry. **Method:** We evaluated 444 patients diagnosed with lung adenocarcinoma at Barretos Cancer Hospital. The presence of *EGFR, KRAS* and *BRAF* mutations in hotspot regions were evaluated by direct sequencing. For *EGFR/ KRAS/BRAF* wild-type samples, we investigated the presence of *ALK, RET* and *ROS1* rearrangements by the NanoString platform. Genetic ancestry was assessed by a multiplexed 46-ancestry informative markers panel. Stats: X^2 test and Cox regression model. **Result:** Overall, 232 were male (52%) and 212 female (48%) and the average mean at diagnosis was 61 years. The majority of the patients were self-reported as white (77%), smokers (68%) and most patients were diagnosed at stage IV (74%). The median overall survival in patients at stage IV was 8.8 months. The frequency of *EGFR* mutations was 22.7% (n=101) and they were independently associated with never-smokers and Asian ancestry. *KRAS* mutations were found in 20.4% (n=91) of cases and were independently associated with smoking. The frequency *BRAF* mutations was of 1% (n=4), being all of them non-V600 *BRAF*. The frequency of *ALK* rearrangements was 2.25% (n=10) and was associated with younger age, the presence of metastases and advanced disease stage at diagnosis. *RET* and *ROS1* rearrangements were only observed in 0.2% each (n=1/each) of cases. All the alterations identified in the oncogenic drivers were mutually exclusive. **Conclusion:** The evaluation of the major driver genes for NSCLC, *EGFR, KRAS*, *BRAF, ALK, RET* and *ROS1* can guide better clinical strategies for Brazilian lung adenocarcinoma, and the frequencies observed of these genes are in line with reported in other populations.

Keywords: lung adenocarcinoma, driver genes, Brazilian patients

P2.03-08 ANALYSIS OF IMMUNOSUPPRESSIVE FACTORS PRODUCED BY CSCS REVEALED GALECTIN-3 AS IMMUNE MODULATOR WITH PROGNOSTIC VALUE IN NSCLC ADENOCARCINOMA

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Background: The study of the tumor microenvironment is leading to a better understanding of the tumor escape from immunosurveillance and immunotherapy response. Cancer stem cells (CSCs) are targets poorly recognized by the immune surveillance system given that they favor an immunosuppressive microenvironment. The aim of this work is to study the interactions between CSCs and the immune microenvironment in NSCLC. **Method:** Tumor cells from 8 resected NSCLC patients and 12 cell lines were cultured using a sphere forming assay for CSCs enrichment. Adherent cultures were established as differentiated controls. The gene expression of *IL-4*, *IL-10, IL6*, *IL8 LGALS-3* was analyzed by RTqPCR. Gene expression results were validated at a protein level by a sensitivity bead-based multiplex immunoassay using the Millipore kit for Luminex 100/200. The prognostic value of these factors *in silico* was determined in a cohort of 661 patients from The Cancer Genome Atlas (TCGA) cohort. Prognostic value was assessed by Cox regression and Kaplan-Meier curves (long rank-test), considering significant when $p<0.05$. **Result:** Patients' median age was 67 years [57-74], 62% were male, and 62.5% were adenocarcinomas (ADC). Gene expression analysis revealed that lungspheres had significantly higher expression of *LGALS3* compared to differentiated adherent cells. On the contrary, adherent cells had significantly higher expression of *IL6*. In concordance with gene expression levels, we observed significant differences in the secretion of these two soluble factors (IL-6 and Galectin-3) between adherent cells and tumorspheres. Neither expression nor secretion levels of IL-10 and IL-4 were detectable. We had not observed significant results for IL-8. Survival analysis showed that ADC patients with higher *LGALS3* expression had significantly decreased overall survival (OS, 40.49 vs. 87.90 months, p= 0.005) and relapse-free survival (25.28 vs. 41.25 months, p=0.003) than the group with LGALS3 expression below the median. The multivariate analysis showed that *LGALS3* expression can be established as an independent prognostic biomarker for OS [HR=1.75; 95% CI, 1.19-2.59; p=0.004] and for PFS in lung adenocarcinoma [HR=1.68; 95% CI, 1.22-2.32; p= 0.001]. **Conclusion:** Our results suggest that Galectin-3 highly secreted by lung CSCs can be involved in the modulation of the immune microenvironment. Moreover, Galectin-3 is an independent prognostic biomarker for overall survival and relapse-free survival in lung adenocarcinomas. Supported by grants CB16/12/00350, PI18/00266 and PI15-00753 from ISCIII and ACIF/2018/275 from GVA and FSE

Keywords: cancer stem cells, lung adenocarcinoma, immunoregulatory factors

P2.03-09 ARF6-RELATED INVASIVE PATHWAY DETERIORATED PATIENTS' PROGNOSIS IN MUTANT EGFR LUNG ADENOCARCINOMA

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Background: Arf6-related pathway has been reported to be activated in the downstream of EGF stimulation and to play pivotal roles in invadopodia formation and integrin recyclying leading to cancer invasion and metastasis. EGFR is well known to be constitutively activated without EGF stimulation in lung cancer harboring the mutations in its kinase domain. Here, we have examined the clinicopathological significance of Arf6-related

pathway especially in mutant EGFR (mEGFR) lung adenocarcinomas. **Method:** Clinical samples were obtained from the 239 cases of resected lung adenocarcinoma which were consecutively operated from January 2001 to December 2007 in Kyoto University Hospital. Then, tissue microarrays (TMAs) were made from all the cases. Using DNA samples extracted from fresh frozen tumors, EGFR mutations were detected by SSCP or direct sequencing methods as previouly published. Immunohistochemical stainings were performed on TMAs against the molecules of Arf6-related pathway: Grb2, GEP100, Arf6, AMAP1, EPB41L5. The positivity of all molecules was judged according to their H-scores: intensities multiplied by percentages. Clinicopathological data were integrated and reviewed. Statistical analyses for overall (OS) or disease-free survival (DFS) were performed by Kaplan-Meirer methods and log-rank tests. Categorical data were analysed by Pearson's test. Cox hazard models were applied for multivariate analyses. P-values less than 0.05 were considered significant. **Result:** Among all cases, mEGFR was found in 113 cases, whereas 118 cases had wild type EGFR (wtEGFR) mutations. Common mutations in EGFR were detected in 104 cases (92.0%). Positivity of each molecule in mEGFR cases was the following: Grb2/ GEP100/ Arf6/ AMAP1/ EPB41L5; 11.9/ 27.7/ 48.2/ 52.7/ 56.3%. Positivity in all molecules showed no significant difference between exon 19 and exon21 mutation cases. Visceral pleural involvments were significantly increased in AMAP1- or EPB41L5-positive groups and lymph node metastases were significantly increased in Grb2- or EPB41L5-positive groups. Univariate analyses showed that 5-year OS rates were significantly low in Grb2 or AMAP1 positive groups specific to mEGFR cases (Grb2-/+: 89.0 vs 69.2%; p=0.0051, AMAP1-/+: 94.1 vs 80.3%; p=0.0057), whereas it was significantly low in EPB41L5 group specific to wtEGFR cases (-/+: 85.1 vs 62.7%; p=0.017). For DFS, all molecules were the significant recurrent factors specific to mEGFR cases (Grb2/ GEP100/ Arf6/ AMAP1/ EPB41L5; p=0.0023/ 0.0033/ 0.0411/ 0.0023/ 0.0263), whereas no molecule was significant specifc to wtEGFR cases. Multivariate analyses specific to mEGFR cases showed that Grb2 and AMAP1 were the independent prognostic factors for OS and Grb2 was the only independent recurrent factor. **Conclusion:** Arf6-related invasive pathway was significantly associated with poor prognosis specific to mEGFR adenocarcinoma. Grb2 and AMAP1 were the strong worsening effectors on the prognosis. Inhibition of this pathway should be a novel targeted therapy in mEGFR lung adenocarcinoma.

Keywords: EGFR mutation, invasion and metastasis, lung adenocarcinoma

P2.03-10 COMPREHENSIVE MOLECULAR PROFILING AND COMPARISON OF COMMON AND RARER SUBTYPES OF LUNG CANCER

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Background: Genomic profiling of tumours has become a crucial component of precision cancer medicine. In order to comprehensively characterize molecular alterations in different lung cancer subtypes, we analysed a total number of 327 samples by using Whole-Exome Sequencing (WES) and SNP genotyping arrays. Additionally, we used Targeted Capture Sequencing (TCS) for scanning a selected panel of genes (*n*=52) at high sequencing depth. **Method:** We WES (McGill University Innovation Centre in Montreal) 153 paired tumour-normal samples, with a further 174 paired tumour-normal samples undergoing TCS. Sequencing data were processed and mutations identified using BWA (v.0.7.15), Picard (v.2.17.11), GATK (v.3.7), VarScan (v.2.4.2) and VEP (v. 92) softwares. Illumina OmniExpressExome (v1.6) arrays were used for genotyping all samples and copy number alterations (CNAs) were identified using ASCAT (v.2.5.2), DNACopy (v.1.56.0) and GISTIC (v.2.0) softwares. **Result:** The analysed samples had a tumour content varying from 20 to 90%. The age range of patients was between 28 to 89 years. Out of 159 lung cancer patients, 89 patients had lung adenocarcinoma (LUAD), 36 squamous cell carcinoma (LUSC) and 34 lung neuroendocrine (NET), of which 22 were subclassified as lung carcinoid (LC), 6 small cell carcinoma (LSCLC), 5 large cell carcinoma (LCNEC) and 1 combined NET subtype. *TP53* appeared as the most mutated gene in LUSCs (82%), non-carcinoid NETs (58%) and LUADs (47%), but not in the LC subtype, while the chromatin remodelling gene *ARID1A* was altered across all subtypes (9%). Other mutated genes in LUAD were *KRAS* (31%), *STK11* (22%), *RBM10* (15%), *EGFR* (14%) *and KEAP1* (14%); in LUSC were *PTEN* (26%), *CDKN2A* (21%), *KEAP1* (21%) and *NF1* (15%); in NET, non-carcinoid top mutated genes included *RB1* (42%), *ENPP2* (33%), *ERBB4* and *STK11* (17% for each), while *ARID1A* and *ACKR3* were each present in 9.5 % of LC. In LUADs, mutations in *EGFR* and *KRAS* appeared as mutually-exclusive (*P*=0.007*)*, while gene pairs *NFE2L2 - AKT1* (*P*=0.012) and *STK11-ALK* (*P*=0.029) were co-mutated in LUAD and LUSC, respectively. Deletions in exons 19 and 20 of *EGFR* correlated with longer survival time compared to patients with wild-type *EGFR* (*P*=0.058). In NET, patients with mutated *RB1* showed lower survival time compared to patients with wild-type *RB1* (*P*=0.022). Examination of CNAs showed *TERT* amplifications (5p15.33 cytoband) were commonly found at high frequencies across all subtypes, especially in non-carcinoid NET (71.4%). Other recurrent CNAs included amplifications in *MYC* in 37% of LUAD and 40% of LUSC, and in *EGFR* in 33% of LUAD and 14% of LUSC. Deletions in the *CDKN2A* locus were seen at frequencies of 31% and 28% in LUAD and LUSC, respectively. LC patients showed longer survival time compared to other tumours (*P*=0.015). COSMIC mutational signatures 18 (of unknown aetiology) and 24 (associated with exposure to aflatoxin) were exclusively found in LC. **Conclusion:** The results confirm that lung cancer is a group of heterogenous diseases. In addition to the known effects of *EFGR* mutations, possible therapeutic avenues could be suggested for *TERT* amplifications, for which nucleoside analogues have shown to promote cancer cell death or EZH2 inhibitors for *ARID1A*-mutated cancers.

P2.03-11 IMPACT OF ETHNICITY ON OUTCOME IN NEVER SMOKERS WITH EGFR AND ALK WILDTYPE (EGFR/ALK-WILDTYPE) LUNG ADENOCARCINOMAS

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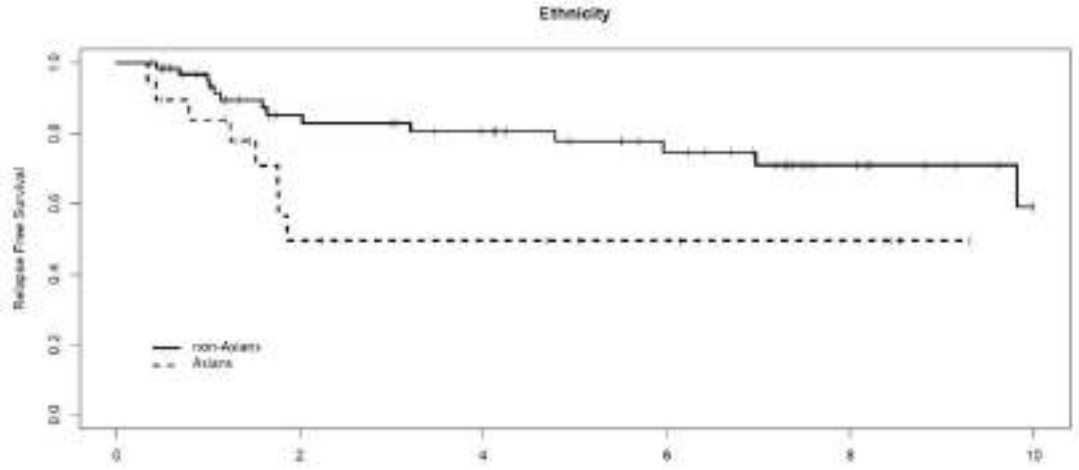
Background: *EGFR*-mutations and *ALK*-rearrangements are frequent in lung adenocarcinoma (LUAD) samples from never smoker patients. Nevertheless, up to a quarter of all LUAD cases in never smokers are *EGFR/ALK*-wildtype: these patients have limited therapeutic options and few well-established clinical and molecular predictors of outcome. Our main objectives here were to investigate the prognostic impact of ethnicity in never smoker patients with *EGFR/ALK*-wildtype LUAD and seek for specific somatic events correlated to ethnical background in these patients. **Method:** We included 85 samples from lifetime never-smoker patients with *EGFR/ALK*-wildtype LUAD collected from surgical resection with curative intent. Stages 1/2/3 were identified in 56 (66%)/15 (18%)/14 (16%) samples. A subset of those samples (n=46), with similar stage distribution, had snap-frozen tumor and paired-adjacent tissue available and were submitted to paired-end whole-exome sequencing. Fisher's exact and Chi-squared tests were used to compare specific mutations between Asians vs non-Asians. Recurrence-free-survival (RFS) was calculated based on the Kaplan-Meier method; Cox modeling was used to generate hazard ratios (HR), adjusted for key clinical features. **Result:** Most patients in the cohort were female (63/85, 74%); the median age was 68 years; median follow-up was 51 months. According to self-reports, 19/85 (22%) and 66/85 (78%) patients identified as Asians and non-Asians, respectively; no major clinical and pathologic differences were identified between these populations. Five-year recurrence free survival was significantly lower for Asians compared to non-Asians (50% vs. 78%, adjusted HR = 2.9; CI = 1.1-7.8, p=0.02), Figure 1. Among somatic events, in-frame deletions in *CNPY3* (Toll-like receptor-specific co-chaperone for HSP90B1) were more frequent in Asians (30%) compared to non-Asians (18%). In contrast, *DDX11* missense mutations (21% vs 0%; nucleic acid binding protein involved in genome stability), *NOTCH2* multi-hits and frame-shift deletions (7% vs 1%), and *KRAS* missense mutations (7% vs 0%) were more frequently altered in non-Asians than in Asians. **Conclusion:** In our cohort of never-smoker patients with *EGFR/ALK*-wildtype LUAD, Asian patients showed higher relapse rates than non-Asians. We identified differentially mutated genes by ethnicity that may partly account for these differences in outcome. (SNMF and AFF contributed equally)



Keywords: lung adenocarcinoma, Never-smokers, EGFR/ALK wildtype

P2.03-12 EPIGENOME-WIDE METHYLATION STUDY FROM BLOOD SAMPLES OF LUNG CANCER PATIENTS AND CONTROLS

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Background: Despite a concerted effort to find markers for early detection or prognosis prediction, there is no biomarker with clinical application in screening or treatment decision of lung cancer. Early diagnosis using noninvasive biomarkers could play a hopeful role in increasing the survival rate of lung cancer patients. Recently, some evidences were provided that methylation changes in peripheral blood may be predictor of lung cancer mortality and may improve prediction of lung cancer risk. We present the results of an epigenome-wide methylation study from blood of 150 pairs of lung cancer cases and controls from a Korean subjects. **Method:** For this study, we used blood samples obtained from the BioResource Center of Asan Medical Center (Seoul, South Korea) that had been donated by 150 patients who diagnosed to non small cell lung cancer (NSCLC) and 150 normal controls who has undergone a health screening in 2012 to 2014. The normal controls of 150 were selected by frequency matching with the 150 patients with NSCLC on age, sex, smoking status. Genome-wide methylation profiles were obtained by using a MethylationEPIC BeadChip kit, which covers the 850,000bp cytosine-phosphate-guanine (CpG) site. To identify differentially methylated probes (DMPs) in association with NSCLC, a logistic regression model was used with the response variable of NSCLC status and the predictor variable of methylation values. **Result:** The average age was 56 years in patients with NSCLC and control subjects. 72 never, 48 former, and 30 current smokers were included in the both groups. From association analysis, we found 11 suggestive DMPs (p<1.0E-5) associated with NSCLC after adjusting for age, gender, PCA, smoking, and the estimated cell-type proportions. From DMP analyses according to smoking status, we found 58 suggestive DMPs and two significant DMPs (cg12169243 (DPH6), p=4.3E-08 and cg25429010 (IMP3), p=5.2E-08) associated with NSCLC in group of current smokers. To affirm that smoking is associated with NSCLC in our study, as well known, we evaluated significant CpGs associated with current smoking in each groups of NSCLC patients and controls. Cg03636183 (F2RL3) and cg05934812 (AHRR), well known gene site for smoking and NSCLC, were found to be significantly associated with smoking in NSCLC patients group. **Conclusion:** This genome-wide DNA methylation study showed that DNA methylations changes were associated with NSCLC after adjusting for age, gender, PCA, smoking, and the estimated cell-type proportions, independent of smoking status. The DNA methylation changes may be candidate target regions for early detection and prevention in lung cancer.

Keywords: Lung cancer, DNA methylation, Epigenome-wide methylation study

P2.03-13 ACQUIRED RESISTANCE TO AFATINIB IN NON-SMALL CELL LUNG CANCER WITH EGFR G719X MUTATION

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Background: The frequency of EGFR mutations is said to be relatively high within East Asian population. The most common EGFR mutations such as exon 19 deletions and exon 21 L858R mutation are strong predictors of good response to EGFR-TKIs in non-small-cell lung cancer. Exon 20 T790M mutation which accounts for a large part of 1st and 2nd generation EGFR-TKI resistance, is well known to be detected after failure of prior EGFR-TKI therapy. Furthermore, T790M mutation is a predictor of good response to osimertinib, 3rd generation EGFR-TKI. Meanwhile, other uncommon EGFR mutations are identified, such as exon 18 G719X mutation, exon 20 S768I mutation, and exon 21 L861Q mutation. LUX-Lung study reported afatinib may be effective for these uncommon EGFR mutations, however, their treatments are still controversial and their resistance-gaining mechanisms to EGFR-TKI are also unknown. **Method:** We evaluated the characteristics of patients with G719X single mutation and their effectiveness of afatinib treatment. Furthermore, we analyzed the mechanism of acquired resistance to afatinib from their re-biopsied samples. **Result:** Eighteen patients had G719X single mutation, which include fifteen patients with smoking history. Of all patients with G719X mutation, ten patients were treated with afatinib, which response rate was 40% (4/10). Eight patients of those treated with afatinib underwent re-biopsy after failure of the therapy, and their results revealed that G719X mutation was disappeared in six samples, and T790M mutation was not detected after afatinib treatment. **Conclusion:** As previously reported, the presence of G719X mutation might be used as a predictor of sensitivity to afanitib therapy. Our data suggest that the loss of cancer cells with G719X mutation could be the main mechanism of acquired resistance to afanitib. Furthermore, patients with smoking history were seen frequently in those with G719X mutation. Considering that G719X mutation negative cancer cells may coexist with G719X mutation positive cells in NSCLC patients, smoking might be associated with development of its heterogeneity.

Keywords: Afatinib, G719X, Acquired resistance

P2.03-14 DEVELOPING AN IMMUNOGENIC MODEL OF NON SMALL CELL LUNG CANCER

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Background: Lung cancer is the most common form of cancer in the world both in terms of new cases diagnosed and number of deaths, which totals ~1.5 million per annum. Patient prognosis has not improved significantly over the last 40 years, and the 10-year survival rate remains ~5%. Approximately 85% of lung cancers can be classified as non-small cell lung cancer (NSCLC), of which Lung Adenocarcinoma (LuAd) is the most common histological subtype. Specific DNA mutations allow for further molecular characterisation of LuAd, for example, activating mutations in KRAS have been described in one third of cases. The oncogene MYC is a downstream target of KRAS signalling and the two oncogenes have long been known to cooperate to induce tumorigenesis. The gene editing enzyme APOBEC3B has recently been recognised as an important mechanism for fuelling genetic diversity in cancer and has been shown to be upregulated in LuAd. **Method:** The KRas-Myc (KM) mouse model of LuAd combines expression of mutant $Kras^{G12D}$ and modestly overexpressed c-MYC to drive the formation of autochthonous adenocarcinomas. Selective expression of $Kras^{G12D}$ and MYC are induced in the lung epithelium by intranasal inhalation. We have generated the KMA3B model of lung cancer in which APOBEC3B is selectively expressed in the KM model to generate tumours which have a modest overexpression of APOBEC3B. Using immunohistochemistry and FACs analysis we aim to identify the differences occurring in the KM and KMA3B models and investigate the implications of these differences. **Result:** Preliminary results show an increase in $CD8^+$ T cell infiltration has been noted in the KMA3B lungs when compared with their KM counterparts at an 8 week time point. We hypothesize that the presence of APOBEC3B results in an increased number of mutated peptides leading to increased neo-antigen presentation, and a more effective immune response to the tumours. Indeed, survival data indicates that introducing APOBEC3B to the KM genetic background extends survival by 50%. FACs analysis using a panel designed to identify T cells and their activation status indicates differences in the populations of T cells present in KMA3B vs KM tumours. **Conclusion:** We show that the modest overexpression of APOBEC3B in a KM background increases the lifespan of the mice. This increase in survival appears to correlate with an increase in cytotoxic T cell surveillance. The implications and utility of this model will be discussed.

Keywords: NSCLC, GEMM, APOBEC3B

P2.03-15 VALIDATION OF TUMOR ORGANOIDS FROM LUNG ADENOCARCINOMA AS A MODEL OF PRIMARY TUMOR GENOTYPE

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Background: Tumor organoids have shown promise as a model to predict clinical treatment response in patients with certain malignancies. However, there is a paucity of data supporting the utility of tumor organoids derived from patients with non-small cell lung cancer (NSCLC). Here, we demonstrate the feasibility of establishing tumor organoids from patients with NSCLC and examine molecular fidelity of tumor organoids derived from early-stage lung adenocarcinomas relative to their primary tumors. **Method:** 140 patients who underwent lung resection for NSCLC were consented for organoid culture. Primary tumor specimens were processed to single cell suspensions and tumor cells were grown in extracellular matrix and chemically defined media. Tumor organoids and their corresponding primary tumors were evaluated by next generation sequencing for copy number and somatic alterations. Overall concordance between primary tumor and organoid was determined by dividing the percentage of overlapping somatic single-nucleotide variant (SNV) alterations by the total somatic SNV alterations present in both tumor and organoid model. **Result:** A subset (n=11) of tumor organoids developed from patients with early-stage lung adenocarcinoma were assessed for molecular concordance as compared to the primary tumor within 12 weeks of establishment (approximately 2-4 passages). The tumor organoids enriched for protein coding SNV somatic mutations with an average of 6.8% overlap of all somatic SNV variants (n=2382) vs 34.8% overlap in coding SNV mutations (n=72); $p<0.001$. Additionally, the overlapping coding SNV mutations are further enriched in the tumor organoid as measured by allelic fraction where on average they are present at 35.3% allelic fraction as compared to 20.9% in the original tumor specimen samples tested. **Conclusion:** Early-stage primary lung adenocarcinoma tumor organoids can be reliably generated and robustly profiled in a clinically compatible time frame. Further investigation into individual driver mutations and tumor mutational burden are underway to support this novel tumor model's stability with sequential passaging and ability to prospectively predict therapeutic response, including strategies targeting immune checkpoint inhibition.

Keywords: tumor model systems, NSCLC, patient-derived tumor organoid

P2.03-16 AGREEMENT BETWEEN DIFFERENT METHODOLOGIES FOR NON-INVASIVE P.T790M AND EGFR SENSITIZING MUTATION TESTING

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Background: Tyrosine kinase inhibitors (TKIs) are the current standard of care for patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC). However, most patients progressed within 1 to 2 years. The EGFR p.T790M mutation is the most common resistance mechanism to first and second generation EGFR TKIs. The identification of p.T790M mutation is of considerable clinical relevance as osimertinib has demonstrated clinical efficacy in this setting. Guidelines recommend testing for the p.T790M mutation in blood at relapse to TKIs, and re-biopsy only in case of a negative result. Several blood based methodologies for detection of EGFR mutations have been developed in the recent years. However, the number of comparison studies between platforms is very limited. **Method:** This is a multicenter, cross-sectional study (ClinicalTrials.gov Identifier: NCT03363139) performed by the Spanish Lung Cancer Group. Samples from 75 consecutive EGFR mutant NSCLC patients were collected at disease progression to first line TKI treatment. The presence of EGFR mutations in the cfDNA was evaluated in 39 samples by 7 methodologies, namely: Cobas® EGFR Mutation Test v2 (Roche Diagnostics), Therascreen EGFR Plasma RGQ PCR Kit (Qiagen), QuantStudio® 3D Digital PCR System (Thermofisher), a 5'-nuclease real-time PCR (TaqMan®) assay in presence of PNA, OncoBEAM EGFR (Sysmex Inostics), NGS with two different gene panels: Oncomine® (Thermofisher) and Lung Cancer Panel (Qiagen). The agreement between methodologies was assessed using the kappa coefficient (K) and its corresponding 95% confidence

intervals (95% CI). For quantitative variables the concordance correlation coefficient (ccc) was used. **Result:** Complete results are available for 39 patients. Overall, the agreement between all methodologies for the detection of p.T790M mutation as well as the original EGFR sensitizing mutation was good (K=0.669; 95CI: 0.504-0.835 and K=0.750 95CI: 0.599-0.899 respectively). Remarkably, the agreement between FDA-approved methodologies for p.T790M detection was almost perfect (K=0.926; 95CI: 0.712-1) and good for the EGFR sensitizing mutations (K=0.657; 95CI: 0.417-0.902). Similarly, the agreement between NGS-based methodologies for the detection of p.T790M and the EGFR activating mutations was very high (K=0.843; 95CI: 0.567-1 and K=0.872 95CI: 0.595-1 respectively). Moreover, concordance between both technologies for p.T790M and EGFR sensitizing mutation mutant allele frequency was excellent (ccc=0.956; 95CI: 0.906-1 and ccc=0.980 95CI: 0.950-1 respectively). The proportion of samples that were positive for p.T790M detection varied from 28% (PCR based technologies) to 37% depending on the methodology. **Conclusion:** NGS and PCR-based methodologies show a good to excellent agreement for the detection of EGFR mutations, including the p.T790M. Our results support the use of liquid biopsies for non-invasive testing of clinically relevant mutations (Data from the whole cohort will be presented at the meeting).

Keywords: T790M, EGFR, liquid biopsy

P2.03-17 OPTIMIZATION OF AN EX-VIVO PRECLINICAL MODEL FOR DRUG TESTING

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Background: Predicting drug response in advanced lung cancer patients remains a major challenge. A promising approach to tackle this challenge is based on testing drugs in an *ex-vivo* preclinical model using cultured precision-cut fresh tumour slices, which maintain not only the tumour itself but also its microenvironment. However, even though different protocols have been reported for *ex-vivo* models with different time-windows in a growing list of cancer types, no standard protocols are currently defined in lung cancer. To address this limitation, we have begun to optimize a protocol for an *ex-vivo* preclinical model for drug testing in lung cancer, using samples from the standard *in vivo* model of bleomycin-induced lung fibrosis, which resembles the fibrotic stroma of non-small cell lung cancers. **Method:** Bleomycin-induced fibrotic and control rat lungs were precision-cut with a tissue-chopper and cultured on cell culture inserts up to 12 days in a sterile setting. Two main variables were tested: the coating of the cell culture insert (bare or collagen-I coated), and the interaction with the culture medium (submerged or floating). Small lung pieces were collected at days 0, 2, 6, 9 and 12 and examined by hematoxylin-eosin staining to assess their integrity and viability. **Result:** Tissue architecture was maintained equally well in all culture conditions up to 12 days. In contrast, cellular content appeared to decline after day 6; since only subsets of cells in the periphery of the explants remained viable at day 9-12. No contamination was detected at any culture time. **Conclusion:** Our preliminary results suggest that our protocols for an ex-vivo preclinical model maintain the integrity and viability of lung cells and their microenvironment up to one week, which is comparable to time-windows previously reported in other cancer types. This time-window is expected to be sufficient to test drug responses, thereby underlying the potential of this preclinical model for drug testing as well as for the study of drug resistance mechanisms.

Keywords: Non-Small Cell Lung Cancer, Drug testing, ex-vivo model

P2.03-18 PATHOGENIC GERMLINE RARE VARIANTS AND RISK OF LUNG CANCER

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Background: Recent studies suggest that rare variants, with minor allele frequencies (MAFs) of less than 0.01, exhibit stronger effect sizes than common variants, might play a crucial role in the etiology of complex traits and could account for missing heritability unexplained by common variants. **Method:** Germline DNA from 1059 lung cancer cases and 899 controls from the Transdisciplinary Research in Cancer of the Lung and International Lung Cancer Consortium study were sequenced, utilizing the Agilent SureSelect XT Custom ELID and Whole Exome v5 capture. To unveil the inherited rare causal variants, allelic association analysis of single variant and gene-based collapsing tests of multiple variants were performed, including variants per gene association test, the Kernel-based adaptive cluster test, and SNP-set Kernel association test. Odds ratio (OR), 95% confidence intervals (CIs), and false discovery rate (FDR) adjusted P values were calculated. **Result:**

Table 1. Top rare and deleterious candidates

Gene *	Variant (GRCh37)	Ref/ Alt	RS ID	Function annotation	Case/ control carriers	Allelic association P value	MAF		
							LC case	Control	Reference Database
OSBPL9	1:52082713	G/C	rs760248073	regulatory TFBS	9 / 1	0.0223	0.0043	0.0006	0.0003
SRGAP2B	1:145021232	C/T	rs1553402946	regulatory	8 / 0	0.0238	0.0028	0	0.00005
NOTCH2NL	1:145209536	G/A	rs1331542385	regulatory TFBS	8 / 1	0.0357	0.0035	0.0006	0.0004
NOTCH2NL	1:145210041	C/A	rs1553820176	regulatory TFBS	11 / 2	0.0266	0.0052	0.0011	0.0012
LAMC1	1:183101530	T/G	-	splice Region	19 / 5	0.0131	0.0090	0.0028	-
NEB	2:152359324	G/T	rs762540149	**Stop gain p.Q7971***	9 / 0	**0.0056**	0.0043	0	0.000009
OGG1	3:9816129	G/T	-	upstream	11 / 1	**0.0087**	0.0052	0.0006	-
DNAH12	3:57327780	C/T	rs1418239606	TSE 3'UTR	8 / 1	0.0356	0.0038	0.0006	0.00002
UBA3	3:69112655	C/T	rs778903475	Splice acceptor	5 / 0	0.0390	0.0024	0	0.00006
PIK3R1	5:67576349	C/T	-	Splice region	14 / 3	0.0189	0.0067	0.0017	0.00006
FER	5:108168480	C/T	-	p.L73F	6 / 0	0.0238	0.0028	0	-
TNFAIP8	5:118704106	A/T	rs1225628122	regulatory TFBS	13 / 2	0.0110	0.0061	0.0011	0.000028
DTWD2	5:118991851	C/A	-	upstream	7 / 0	0.0146	0.0033	0	-
HLA-DQB1*	6:32687464	G/A	-	downstream	6 / 0	0.0238	0.0028	0	-
RPL23P6	7:20626286	T/C	-	regulatory TFBS	6 / 0	0.0238	0.0028	0	-
FZD1	7:90895118	T/G	rs1487632879	p.L308R	5 / 0	0.0391	0.0024	0	0.000009
POT1	7:124704997	G/A	-	noncoding	8 / 1	0.0357	0.0038	0.0006	-
HOOK3	8:42888488	C/A	-	p.T654K	13 / 3	0.0280	0.0062	0.0017	-
CDKN2B*	9:22007884	A/C	-	**TSE, noncoding**	10 / 3	**0.0081**	0.0076	0.0017	-
PTEN	10:89720683	C/T	rs867171992	p.F278L	5 / 0	0.0391	0.0024	0	-
RBM4	11:66438297	G/A	-	downstream	7 / 0	0.0147	0.0033	0	-
ERC1*	12:1115120	C/T	-	upstream	6 / 0	0.0237	0.0028	0	-
CMAS	12:22215212	A/T	-	Splice acceptor	7 / 0	0.0146	0.0033	0	-
VPS29	12:110937426	G/A	-	upstream	18 / 5	0.0194	0.0085	0.0028	-
ATP6V0A2	12:124242486	G/A	-	regulatory	8 / 0	**0.0089**	0.0038	0	-
RPL21P116	15:79159142	C/A	-	upstream	7 / 0	0.0146	0.0033	0	-
TP53*	17:7572202	C/A	-	3'UTR	27 / 11	0.0341	0.0128	0.0061	-
HDAC5	17:42170176	T/G	rs751119664	Splice acceptor	12 / 2	0.0112	0.0056	0.0011	0.0002
ABCA10	17:67150543	C/A	rs1267587513	TFBS	9 / 1	0.0223	0.0043	0.0006	0.000008
KCNN4	19:44280886	A/C	-	TFBS	15 / 2	**0.0044**	0.0071	0.0011	-
PLS3	X:114871146	A/T	rs1556640309	Splice acceptor	6 / 0	0.0237	0.0028	0	0.0001

We identified 32 highly deleterious rare heterozygotes, including 14 rare and 18 novel variants -- absent from prior databases of genetic variation (Table 1). The top candidate substitutions including *NEB*stop gain p.Q7971* (nine cases *versus* zero control carriers, *P* = 0.0056), *OGG1* upstream Chr 3:9816129(11 cases *versus* one control carriers, *P* = 0.0087),*CDKN2B* transcription end site (16 cases *versus* three controls carriers, P = 0.0081), *ATP6V0A2* regulatory Chr 12:124242486 (eight cases *versus* zero control carriers, *P* = 0.0089), *KCNN4* transcription factor binding site (15 cases *versus* two controls carriers, *P* = 0.0044), and *TEX28P1* regulatory rs1445670979 (11 cases *versus* one control carriers, *P* = 0.0087). We also identified candidates in known genes which have been previously implicated in lung cancer risk, i.e., *HLA*, *TP53*, *POT1*, *PTEN, ERC, GPC, RGS17*, and *LAMC1*. Among the candidate genes with multiple rare deleterious SNVs, the top five genes with strong association (FDR adjusted P < 0.01 in burden tests) are *NBPF20* (OR5.69, 95% CI 2.4-13.5), *ERC1* (OR 4.49, 95% CI 2.19-9.23), *LOC440434* (OR 1.85, 95% CI 1.32-2.59), *GPC5* (OR 1.55, 95% CI 1.21-1.99), and *NOTCH2NL*(OR 5.46, 95% CI 1.61-18.5). The KEGG pathway analysis shown the 1st and 4th significant pathways are from small cell and non-small cell lung cancer, respectively. **Conclusion:** Our analyses led to identification of 32 pathogenic germline rare variants associated with lung cancer susceptibility. However, replication in additional populations is necessary to confirm potential genetic differences in lung cancer risk.

Keywords: Germline, Rare variants, Exome Sequencing

P2.03-19 CO-TARGETING PIM KINASE TO OVERCOME MET AMPLIFIED RESISTANCE TO EGFR TKIS IN NSCLC

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Background: Currently there are five EGFR tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib) available for treatment of EGFR-mutated non-small cell lung cancer (NSCLC). However for virtually all patients, resistance is inevitable, and disease progression occurs within 1 to 2 years of starting a TKI. Efforts to overcome resistance define the landscape of TKI research resulting in the development of second-generation and now third-generation agents and combination regimens. Third-generation agents, such as osimertinib, show improved response rates and extended median overall survival (OS), with potential to overcome previously untreatable resistance mechanisms. However acquired resistance mutations and activation of bypass RTK signalling mechanisms such as MET can mediate primary and secondary resistance to all EGFR TKIs. MET amplification has been observed after prolonged exposure of HCC827 cell lines to third-generation EGFR-TKIs (osimertinib or CNX-2006). We have pinpointed a novel strategic downstream target that plays a key role in MET regulation, cancer progression, drug resistance and immune evasion namely PIM kinase (PIM). The PIM family of serine/ threonine kinases constitute three major isoforms namely PIM-1, 2 and 3 and have been shown to synergise with c-Myc. We have shown that all three PIM isoforms are highly expressed in NSCLC cell lines and patient tumors and hypothesise that co-targeting PIM kinase and EGFR may provide a more durable response to treatment and overcome MET amplified EGFR TKI resistance. **Method:** Quantification & localisation of MET, c-MYC, PIM kinases and downstream substrates were examined by Western blot analysis and high content analysis

(HCA) in EGFR TKI sensitive (HCC827P) and resistant (HCC827ER) cell lines and selected resistant clones (HCC827ER clone 3, HCC827ER clone 10). Efficacy of pan-PIM inhibitor (AZD1208) & novel PI3K/mTOR/PIM inhibitor (IBL-302) alone and in combination with erlotinib were quantified using the CellTiter-Blue, cell viability assay, in all cell lines. Effect of PIM inhibitors on intracellular signalling was quantified by PathScan® Intracellular Signaling Arrays. **Result:** Activation of PIM-1, PIM-3 and c-MYC expression was demonstrated in MET amplified EGFR TKI resistant cells (HCC827ER) and (HCC827ER clone 3) compared to EGFR TKI sensitive cells (HCC827P). Erlotinib resistant clone that had undergone EMT (HCC827ER clone 10) had reduced expression of PIM-1, PIM-3 and c-MYC compared to MET amplified cells (HCC827ER clone 3). HCC827P and HCC827ER cells were both sensitive to AZD1208 (IC50 47.1μM versus 48.2μM). HCC827ER cells and HCC827ER clone3 cells were more sensitive than HCC827P cells to IBL-302 in a dose-response cell viability assay (IC50 0.277μM vs 0.253μM vs 0.351μM). IBL-302 inhibited downstream intracellular signalling at significantly lower concentrations than AZD1208 (250nM versus 2μM respectively). **Conclusion:** We show here for the first time that PIM kinase is activated in MET amplified EGFR TKI resistant cells. Erlotinib resistant HCC827ER cells are sensitive to pan-PIM inhibitor AZD1208 and the novel triple targeted therapy IBL-302. These data demonstrate that PIM kinase is a pivotal mechanism involved in EGFR TKI resistance and is an ideal target for dual inhibition strategies.

Keywords: Drug resistance, EGFR TKIs, PIM kinase

P2.03-20 POTENT IN VITRO ACTIVITY OF TARLOXOTINIB FOR HER2 EXON 20 MUTATIONS IN LUNG CANCER AND MECHANISM OF ACQUIRED RESISTANCE

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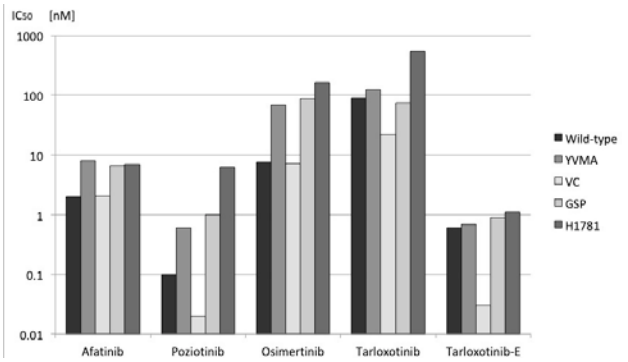
Background: Oncogenic HER2 (*ERBB2*) mutations are present in 2-3% of lung adenocarcinoma. No targeted therapy is currently approved for HER2-mutated lung cancers, and clinical trials using novel irreversible pan-HER inhibitors are underway. However, all of these irreversible pan-HER inhibitors are also active against wild-type (WT) EGFR, resulting in dose limiting toxicities. Tarloxotinib is a novel clinical-stage prodrug that releases a potent, irreversible pan-HER inhibitor (tarloxotinib-E) selectively in pathologically hypoxic regions of tumors. In this study, we evaluated tarloxotinib-E activity against various HER2 exon20 insertion mutations and explored the resistance mechanisms to tarloxotinib-E. **Method:** We introduced WT HER2 or HER2 activating mutations, including A775_G776insYVMA, G776delinsVC, and P780_Y781insGSP into Ba/F3 cells by retroviral transfection. Growth inhibitory assays were performed in these Ba/F3 cells and in H1781 cells (G776delinsVC). Tarloxotinib-E resistant clones were established by exposing these Ba/F3 cells to 200nM of tarloxotinib-E after treatment with N-ethyl-N-nitrosourea. Acquired resistant cells to tarloxotinib-E were also developed from H1781 cells via chronic exposure to increasing concentrations of tarloxotinib-E. HER2 secondary mutations were detected by direct sequencing. **Result:** Tarloxotinib-E displayed potent activity against WT and mutant HER2 Ba/F3 cells and H1781 cells. Furthermore, the IC_{50} of tarloxotinib (prodrug) for wild-type HER2 was > 100 times higher than that of tarloxotinib-E (active drug). So far, we established 12 tarloxotinib-E resistant clones from Ba/F3 models (6 with A775_G776insYVMA and 6 with G776delinsVC), all of which harbored C805S secondary mutation (corresponding to C797S of the EGFR).



Conclusion: Tarloxotinib-E exhibited potent activity for all HER2 exon 20 mutations. We identified secondary HER2 C805S mutation as a common mechanism of acquired resistance, consistent with the covalent binding mode of tarloxotinib via this residue. Additional resistant clones are currently being evaluated.

Keyword: HER2, Exon 20, Tarloxotinib

P2.03-21 MUC16 GERMLINE MUTATIONS MAY ASSOCIATE WITH INHERITED LUNG CANCER

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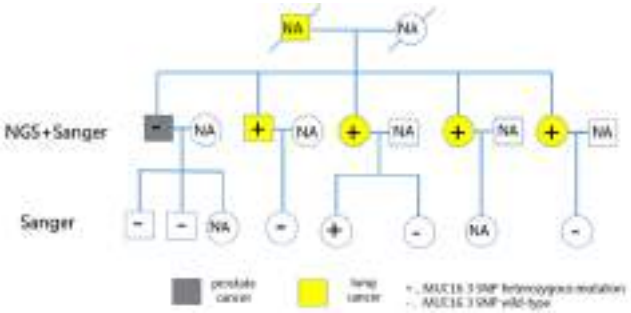
Background: Study of inherited cancer may facilitate the understanding of the molecular mechanism of tumorigenesis. Though sporadic reports have shown that mutations in *EGFR* or *ERBB2* may associate with familial lung cancer, the knowledge of the genetic causes for inherited lung cancer is still limited. **Method:** Genomic DNA (gDNA) from cancer patients or healthy people were extracted from whole blood samples and analyzed using a 500-gene next generation sequencing (NGS) panel. Variants identified by NGS panel were confirmed by Sanger sequencing. **Result:** In November 2017, four siblings in a Chinese family were diagnosed with lung adenocarcinomas. Additionally, the 5th sibling in the family had prostate cancer. A questionnaire for the family did not reveal significant environmental or habitual reasons leading to cancer in the family, suggestive of possible genetic causes. NGS analysis for gDNA samples indicated all 4 siblings with lung cancer had 3 heterozygous alleles of SNPs in *MUC16*, namely rs754254000, rs754856910, and rs746152510. In contrast, the sibling with prostate cancer was wild-type for all of the three alleles (Figure below). The NGS results were then confirmed by Sanger sequencing. The three germline mutations in *MUC16* all had very low population minor allele frequency (below 0.1%). We further analyzed the gDNA of the children in the family, and detected the 3 heterozygous SNPs in a child whose parent had lung cancer, whereas both children of the prostate cancer patient were wild-type for the 3 *MUC16* alleles. Taken together, these results are consistent with a hypothesis that germline mutation of rs754254000, rs754856910, and rs746152510 may predispose the family members to lung cancer. MUC16, also known as CA125, is a biomarker for ovarian cancer, and also shown to be involved in tumorigenesis and metastasis of lung cancer cells. The child with heterozygous SNPs of *MUC16* need be cautious in the future routine check-ups.



Conclusion: In this study, we have demonstrated that germline mutations of *MUC16* may associate with inherited lung adenocarcinomas, which warrants further mechanistic study of *MUC16* gene in lung cancer.

Keywords: inherited lung cancer, MUC16, Germline mutation

POSTERS

P2.03-22 CHROMATE EXPOSURE INDUCES DNA HYPERMETHYLATION OF THE MISMATCH REPAIR GENE MLH1 IN LUNG CANCER

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Background: Hexavalent chromium is recognized as a human carcinogen. To elucidate the role of chromate on carcinogenesis, we have investigated molecular features of LC from chromate workers (chromate LC). Chromate LC frequently had the microsatellite instability (MSI), and that the MSI was associated with repression of MLH1, which is one of the essential DNA mismatch repair (MMR) proteins. In the present study, we investigated methylation status of the promoter region of *MLH1* determined quantitatively by bisulfite-pyrosequencing in the paired tumorous/ non-tumorous sample sets of chromate and non-chromate LCs. Moreover, we analyzed three DNA double-strand break (DSB) repair genes (*MRE11*, *RAD50*, and *DNA-PKcs*) as possible targets of MSI by fragment length polymorphism analysis. **Method:** Thirty-two lung tumor samples were obtained from chromate workers with LC during surgery or at autopsy at 5 hospitals between August 1975 and October 1997. Thirty-one tumors were obtained from LC patients without chromate exposure during surgery at Tokushima University Hospital as a control group (non-chromate LC). DNA was extracted and bisulfite conversion of DNA was conducted using the EpiTect Bisulfite Kit (QIAGEN). PCR primers and sequencing primer for quantification of methylation level in region -209 nucleotides (nt) to -181 nt from the transcription start site in the *MLH1*. Pyrosequencing of 5 CpG sites in *MLH1* was performed with sequencing primers using a PyroMark 24 Pyrosequencing System, version 2.0.6 (QIAGEN). Regions encompassing mononucleotide repeated sequences of genes were amplified using nested-PCR procedure. Fragments were separated by automated capillary electrophoresis in an ABI Prism 3130/3130xl Genetic Analyzer (Applied Biosystems) and electropherograms were analyzed using the GeneMapper software (Applied Biosystems). **Result:** The mean methylation level of tumorous tissue was 21.1±15.7% and was significantly higher than that of non-tumorous tissue, 10.9±9.4% (P = 0.004) in chromate LC. In non-chromate LC, there was no significant difference between tumorous and non-tumorous tissues: 3.9±5.1% in tumorous tissue versus 4.9±4.1% in non-tumorous tissue. The mean methylation level of tumorous tissues was significantly higher in chromate LC than in non-chromate LC (P < 0.001). The mean methylation level of non-tumorous tissues tended to be higher in the chromate LC than in non-chromate LC (P = 0.062). There was a significant positive correlation between the methylation level and chromate exposure period in tumorous tissue of chromate LC (r = 0.481, P = 0.017). The methylation level was significantly higher in LCs with reduced expression of MLH1 than in LCs with normal expression of MLH1(P = 0.019). The incidence of mutations at mononucleotide repeats was observed in 50.0% of chromate LC and 28.6% of non-chromate LC in *MRE11*, and 17.4% of chromate LC and 0.0% of non-chromate LC in *RAD50*, and in 53.8% of chromate LC and 46.2% of non-chromate LC in *DNA-PKcs*. The incidence of mutation of mononucleotide tended to be higher in chromate LC than in non-chromate LC in *MRE11*. In *RAD50*, the mutation was significantly higher frequency in chromate LC than in non-chromate LC. **Conclusion:** These results suggest that chromate exposure might induce *MLH1* hypermethylation in LC, which is possible cause of carcinogenesis.

Keywords: chromium, hMLH gene, DNA methylation

P2.03-23 UHRF1 AS A POTENTIAL THERAPEUTIC TARGET FOR KRAS MUTATED NON-SMALL CELL LUNG CANCER

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Background: KRAS mutation occurring in approximately 20% of non-small cell lung cancer (NSCLC) functions as a driver oncogene and it serves as a potential therapeutic target. However, development of *KRAS*-targeted drugs has not been successful primarily because of difficulty in pharmacologically inhibiting a constitutively activated *KRAS* signaling. Activation of several driver oncogenes including mutant *KRAS* in normal cells causes cellular senescence, leading to permanent cell cycle arrest, which is termed oncogene-induced senescence (OIS). Thus, *KRAS* mutated cancers are thought to acquire additional alterations that allow bypassing OIS and such alterations could be good targets for them. With this background, we designed the present study to identify therapeutic targets whose inhibition cause growth suppression in *KRAS* mutated NSCLC through inducing OIS. **Method:** We established *cdk4/hTERT*-immortalized normal human bronchial epithelial cell (HBEC) that expresses mutant *KRAS* upon tetracycline treatment (designated HBEC-RIN). A semi-genome wide shRNA library (DECIPHER) targeting 5,000 genes was transduced in HBEC- RIN. Each shRNA vector is barcoded with unique sequence for quantification. Two weeks after culturing the cells, we extracted genomic DNA from cells at two points: before (point#1) and after (point #2) tetracycline treatment. The barcodes of DNA were sequenced with NGS at a depth of 20 million reads. The effects of senescence-bypass were determined by dividing the normalized barcode abundance at point #2 by that of point#1. The significance of change of each gene was determined by performing *t*-test to compare replicates of shRNA with a given gene with those of luciferase. Senescence was evaluated by senescence associated b-gal staining. Three *KRAS* mutated lung cancer cell lines (A549, H2009, and H460) were used to examine effects of silencing candidates of OIS-bypassing genes. Association between prognosis and expression of candidate genes in NSCLC patients was analyzed with several online datasets. **Result:** We drew a volcano plot from results of a shRNA screen. We selected genes based on significant average suppressive effects. In the present study, we focused on Ubiquitin-like, containing PHD and RING finger domains, 1 (*UHRF1*) because we were able to confirm OIS-bypassing ability of this gene in HBEC-RIN by its transient silencing with synthetic siRNA. Colorimetric growth and colony formation assays showed that *UHRF1* knockdown suppresses cell growth and colony formation in H2009 but not in A549 or H460. Importantly, we found that expression of *UHRF1* mRNA correlated with worse prognosis in patients with NSCLC in multiple independent datasets, suggesting its potential as a prognostic marker. **Conclusion:** These results suggest that *UHRF1* is a potential therapeutic target for *KRAS* mutated NSCLC and that it is a prognostic marker for NSCLC.

Keywords: NSCLC, UHRF1, KRAS

P2.03-24 CONCURRENT ABERRATIONS IN G2/M-PHASE TRANSCRIPTIONAL PROGRAMS AND GENOMIC GATEKEEPERS HIGHLIGHT LUNG CANCER PREDISPOSITION IN COPD PATIENTS

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Background: Chronic obstructive pulmonary disease (COPD) is associated with a 7-fold increased risk of lung cancer occurrence. COPD is defined by clinical symptoms and lung function measurement. It is characterized by chronic inflammation, small airway remodelling and loss as well as destruction of alveoli (emphysema). While an important lung cancer risk factor, the molecular overlap between COPD and lung cancer tumorigenesis is relatively understudied. **Method:** In order to examine the commonalities between these two diseases, we first analyzed small airway epithelial gene expression profiles from 127 COPD and 140 non-COPD ever-smoker patients obtained by bronchial brushing. We performed weighted gene correlation network analysis (WGCNA) on these gene expression profiles to discover deregulated gene modules ('metagenes') associated with reduced lung function (Forced Expiratory Volume at 1 second, FEV_1)—a clinical measure of COPD severity most robustly negatively correlated with lung cancer risk. We then assessed the preservation of these modules in two non-small cell lung cancer (NSCLC) tumour/normal data sets (lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC), n= 887 tumors total). Airway and tumor patient cohorts were matched for age, gender, tumour stage, and smoking status. **Result:** We discovered 10 distinct small airway expression modules, two of which were significantly negatively correlated ($p < 0.05$) with patient FEV_1. One of these FEV_1 modules was the top overall module preserved in both NSCLC subtypes. This lung cancer-FEV_1 module contained 31 genes solely enriched for two related mitotic functions— G2/M phase transition

(BH-p = 0.02) and mitotic roles of polo-like kinase (BH-p = 0.001, n=31). Of these, 28 genes were significantly overexpressed in both LUAD and LUSC, and mapped to a highly-clustered sub-network of 23 proteins with 465 known and *in silico* predicted protein-protein interactions. When tumours enriched for this lung-cancer-FEV_1 gene signature were further examined, we observed a significant co-occurrence of DNA-level alterations in DNA damage associated checkpoints, specifically mutated *TP53*. **Conclusion:** Coordinated gene expression changes associated with COPD severity measures in small airways and preserved in NSCLC tumors are enriched for G2/M phase transition genes. These genes are further disrupted in tumors, where co-occurring mutations to gate-keeper genes occur. Progression of mitosis during abnormal aneuploidy in lung tissues of COPD patients may confer increased risk of oncogenic transformation in this population, and may underlie the molecular link between COPD and lung cancer.

P2.03-25 ASSESSING THE IMPACT OF CLONAL HEMATOPOIESIS IN DISEASE MONITORING USING TARGETED CELL-FREE DNA (CFDNA) SEQUENCING TECHNOLOGY

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Background: Somatic variants found in plasma cell-free DNA (cfDNA) may derive from either solid tumors or clonal hematopoiesis (CH). Little is known about how this may impact plasma-based longitudinal disease monitoring using targeted sequencing of circulating tumor DNA (ctDNA). **Method:** To assess the potential impact of CH in disease monitoring, we evaluated monitoring algorithms by targeted sequencing with and without matched peripheral blood mononuclear cells (PBMC). Samples were collected from a prospective observational study, where 62 late stage lung adenocarcinoma subjects were treated with first-line chemo or chemoradiation therapy. Pre-treatment plasma cfDNA and matched PBMC were analyzed with the AVENIO ctDNA Surveillance Kit (For Research Use Only, not for use in diagnostic procedures), a sequencing panel of 198 kilobases targeting cancer genes. Median input amounts of 25 ng cfDNA and 50 ng PBMC DNA were sequenced to median deduplicated depths of 4582 and 6134, respectively. **Result:** A median of 120 single nucleotide variants were detected per cfDNA sample, with 93.1% of these identified in matched PBMC. Most PBMC-matched cfDNA variants were germline SNPs, with allele frequency (AF) at approximately 50% or 100%. A median of 1 (range 0-5) PBMC-matched cfDNA variants per sample were detected with an AF <10%, consistent with CH. The number of these variants was positively associated with age (p-value = 0.0039) and the most frequently mutated gene was TP53. The remaining somatic variants (i.e., in cfDNA and not PBMC) had an AF range 0.03-40.9%. These PBMC-informed variants (median of 7 per sample) were used in longitudinal monitoring in the first post-treatment plasma sample to assess early response to therapy. Association between ctDNA level and progression-free survival using the same monitoring algorithm yielded nearly identical results on somatic variants derived from filtering approaches independent of matched PBMC (HR 0.32; 95% CI 0.16 - 0.65; log-rank P = 0.0009) and the PBMC-informed method (HR 0.31; 95% CI 0.14 - 0.66; log-rank P = 0.0013). **Conclusion:** A targeted panel focused on solid tumors by design has limited impact from CH. For disease monitoring applications in a non-MRD setting, measuring multiple variants instead of a single variant further enables robust classifiers that can moderate the impact of variants, if any, from CH.

Keywords: ctDNA, clonal hematopoiesis, disease monitoring

P2.03-26 ELUCIDATING MECHANISMS OF RESISTANCE TO TARGETED THERAPIES IN MUTANT EGFR OR KRAS DRIVEN LUNG ADENOCARCINOMA HARBORING DUAL LOSS OF P53 AND RB1

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Background: Inactivation of the two canonical tumor suppressors, p53 and RB1, is a genetic hallmark of small-cell lung cancer (SCLC). In contrast, lung adenocarcinomas (LUADs) preferentially harbor alterations in the p16 pathway over RB1. Nonetheless, despite being rare, concurrent loss of p53 and RB1 occurs in a subset of LUADs and this is hypothesized to be necessary for the histological transformation of LUAD to SCLC, observed during treatment with tyrosine kinase inhibitors (TKIs). However, whether the dual loss of p53 and RB1 is sufficient for this histological transformation remains unknown. Furthermore, loss of RB1 in LUADs with *EGFR* mutations is associated with poor response to TKIs in the absence of SCLC transformation. Here, we aimed to explore how loss of p53/RB1 affects the biology of p16 pathway-altered LUAD, particularly in the context of acquired resistance mechanisms to targeted therapies. **Method:** Four *TP53*-mutated LUAD cell lines were used: two *EGFR* mutation-positive (PC9 and H1975) and two *KRAS* mutation-positive (H1792 and H358). All these cell lines possess p16 pathway alterations: *p16* (*CDKN2A*) mutations in PC9 and H1975, *CDK4* amplification in H1792, and silenced *p16* in H358. Inactivation of *RB1* was carried out using CRISPR-Cas9 and *RB1* knockout monoclonal cells were established. Cell proliferative and clonogenic abilities were assessed. In addition, osimertinib-resistant (PC9 and H1975) and trametinib-resistant (H1792 and H358) cells were generated (initial high dose and/or stepwise dose escalation methods). Acquired resistance mechanisms were evaluated by MSK-IMPACT profiling. **Result:** Two *RB1* knockout clones were established for each cell line. No advantageous effects were observed for proliferative and clonogenic abilities after *RB1* knockout. Although loss of p53 and RB1 has been reported to result in lineage shift in prostate cancer through the upregulation of SOX2, deregulation of SOX2 expression was not observed upon *RB1* knockout in the *TP53*-mutant LUAD cells. In addition, although loss of RB1 caused a modest reduction in osimertinib and trametinib sensitivities of H1975 and H358 cells, respectively, no effect was observed in PC9 and H1792 cells. After becoming resistant to osimertinib or trametinib, transformation to SCLC was not observed. Individual resistance mechanisms are currently being assessed by MSK-IMPACT. **Conclusion:** Dual loss of p53 and RB1 caused no advantageous effects in *TP53*-mutated and p16 pathway-altered LUAD cells and did not initiate transformation to SCLC as a resistance mechanism to targeted therapies. *TP53*/*RB1* deficiency-related acquired resistance mechanisms to osimertinib or trametinib will be further explored and presented.

Keywords: p53, RB1, Resistance mechanisms

P2.03-27 DISCOVERY OF WNK1-ROS1 FUSION IN A LUNG ADENOCARCINOMA PATIENT AND THE PRECISE GUIDANCE FOR TARGETED THERAPIES

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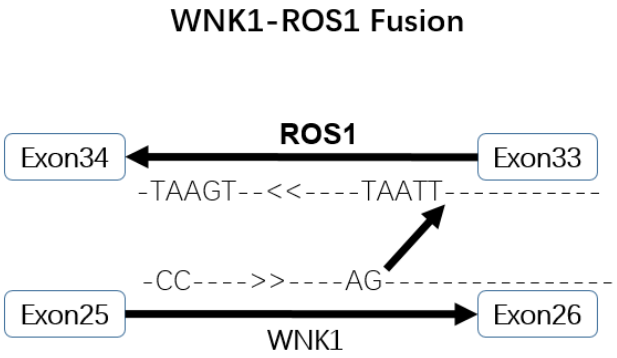
Background: Lung cancer can be driven by activation of tyrosine kinases including *EGFR* mutations, *ALK, ROS1, RET*, or *NTRK* fusions. New partners of gene fusions remain to be identified and their response to targeted therapy need be carefully evaluated in the clinical practice. **Method:** A targeted next-generation sequencing (NGS) panel was used to analyze DNA extracted from tumor tissue and plasma samples from a lung adenocarcinoma patient. The fusion detected by NGS panel was confirmed by Sanger sequencing. **Result:** Using a targeted NGS lung cancer panel, we identified a novel *ROS1* fusion from a 39-year old Chinese female with lung adenocarcinoma. No *EGFR, MET, KRAS, ALK, ROS1* or other driver mutations of lung cancer were detected in the patient. Intron 25 of *WNK1* was translocated to intron 33 of *ROS1* (Figure blow), which resulted in an in-frame fusion transcript of WNK1-ROS1 at the breakpoints of

exon 25 and exon 34, respectively. Sanger sequencing confirmed the fusion and the breakpoints. This novel *WNK1-ROS1* fusion encoded a chimera protein of which the transmembrane and kinase domains of *ROS1* remained intact. The patient received treatment with crizotinib targeting to *ROS1,* and partial response was achieved 3 months later. Resistance to crizotinib occurred at 5 months after the treatment. Analysis of the ctDNA from the patient's plasma sample identified *ROS1* G2032R mutation, a well-known mechanism of *ROS1* resistance to crizotinib. The patient was subsequently treated with TPX-0005, which is effective to *ROS1* G2032R mutant. Decreased CEA level was observed 2 months after TPX-0005 treatment, suggesting the patient was responsive to the targeted therapy.



Conclusion: We identified a lung adenocarcinoma patient with a novel *WNK1-ROS1* fusion who was sensitive to crizotinib and developed crizotinib resistant *ROS1* G2032R mutation at progression but appeared to be responsive to the new generation of TPX-0005 therapy. These results suggest that *WNK1-ROS1* fusion is a new molecular mechanism leading to lung adenocarcinoma and targetable to ROS1 tyrosine kinase inhibitors.

Keywords: ROS1, fusion, crizotinib

P2.03-28 A 500-GENE PANEL TO DETECT TUMOR MUTATION BURDEN OF TISSUE AND PLASMA SAMPLES FROM LUNG CANCER PATIENTS

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Background: Tumor mutation burden (TMB) from cancer tissue is an FDA approved biomarker for selecting appropriate patients for immunotherapy. However, tissue samples are not readily accessible. Though reports have shown correlation between tissue TMB and plasma based TMB (bTMB), no FDA approved bTMB product is available yet. More assay needs to be evaluated for correlation analysis of TMB and bTMB. **Method:** Matched gDNA, ctDNA, and tumor tissue DNA samples from the same patient with non-small-cell lung cancer (NSCLC) were extracted from blood, plasma, and formalin-fixed paraffin-embedded (FFPE) tissue using Qiagen DNA extraction kits. DNA libraries were prepared using Agilent SureSelectXT HS Reagent Ki and were sequenced by a comprehensive 500-gene NGS cancer panel. After variant calling, non-synonymous variants were included to calculate TMB and bTMB using allele frequency cutoffs at 5% and 0.8%, respectively. An in-house bioinformatics method to get rid of germline mutations were also validated in our dataset. **Result:** To validate the 500-gene panel for TMB and bTMB analysis, we first retrieved TCGA whole exome sequencing (WES) data including 1144 lung cancer patients and about 15500 pan-cancer patients. We then calculated the correlations between the 500-gene panel and WES data on the two datasets and acquired R-square values of 0.93 and 0.94, respectively. Such data demonstrated that our 500-gene is a suitable panel to substitute WES for TMB analysis. We then used the 500-gene panel to analyze 17 NSCLC patients with matched FFPE, ctDNA, and gDNA samples. Using 5% and 0.8% as the allele frequency cutoffs for the variants called from the tissue DNA and ctDNA samples, we found a 0.84 R-square correlation between TMB and bTMB analysis. These results suggest that the bTMB from plasma samples of cancer patients highly correlates to the TMB of the paired tissues using our 500-gene panel. **Conclusion:** We have demonstrated in this study that a 500-gene panel is suitable for TMB analysis of cancer tissues. We further show that bTMB analysis using the 500-gene panel is close and highly correlate to the TMB from paired cancer tissues. Upon further clinical studies, the TMB and bTMB analysis using the 500-gene panel may represent a good biomarker for patient selection using either cancer tissue or plasma samples.

Keywords: bTMB, NGS, TMB

P2.03-29 CIRCULATING LEVELS OF LIGANDS FOR RECEPTOR TYROSINE KINASES MAY CONTRIBUTE TO AN IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT

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Background: Metabolic reprogramming of tumor cells is one of the key mechanisms leading to an immunosuppressive tumor microenvironment (TME) that dampens the therapeutic benefit of immune checkpoint inhibition in subsets of patients. An improved understanding for the role of circulating factors that regulate the tumor's metabolic phenotype may provide insights that will help identify adjunct therapeutic strategies for PD-1/-L1 directed immunotherapy. Metabolic reprogramming in lung adenocarcinoma is predominately regulated at the level of receptor tyrosine kinase (RTK) activation and post-translational modifications (PTM) of intracellular proteins that ultimately regulates the metabolic phenotype of the tumor. In this study we evaluated the impact of circulating ligands for 17 common RTKs for their ability to induce RTK activation and intracellular signaling cascades capable to modulating central metabolism. **Method:** Pretreatment peripheral blood were prepared from either from non-cancer control patients (n=30) from lung cancer screening studies or those with pathologically-confirmed lung adenocarcinoma, consisting of patients with stage I (T1a/bN0M0, n=25); locoregionally progressed (T1-4N1-3M0, n=31) or stage IV disease (n=48). All sera were individually used to screen cultures of A549 lung adenocarcinoma cells for the ability to induce RTK autophosphorylation in a high-throughput manner using Luminex immunobead assays. RTKs evaluated as part of this study included: c-Kit, c-Met/HGFR, EGFR, ErbB2, ErbB3, ErbB4, FLT3, IGF-1R, IR, M-CSFR, PDGFR-α, PDGFRß, Tie1, Tie2, VEGFR1, VEGFR2, VEGFR3, and FGFR1. In parallel, we characterized each patient serum specimen for relevant RTK ligands and decoy receptors also via Luminex. ANOVA with LSD post-hoc was used to assess differences in each group to induce intracellular signaling cascades. **Result:** Patient sera were contrasted based on groupings consisting of the following: a control group from lung cancer screening studies, stage I disease, cases with locoregional progression, and cases with disseminated disease. IGF-1R autophosphorylation was significantly lower (p=0.002) in stage I adenocarcinoma cases relative to control cases lacking a malignancy, which corresponded well with reduced free IGF-1 levels (p=0.011) observed in the stage I group. Any additional stage-based changes in free IGF-1 levels were likely due to ligand sequestration by increased IGFBP-1, IGFBP-3, and IGFBP-5 levels (all p<0.05), but had no impact on IGF-1R activation. Circulating HGF (c-Met ligand) levels were significantly increased in both locoregional metastatic progression and systemic dissemination (both p<0.01), which was accompanied by level-dependent increase in c-Met autophosphorylation (p=0.004). Circulating levels of soluble c-Met are pending analysis. Similarly, metastasis-associated increases in the ligands for VEGFR3 were observed, particularly upon systemic dissemination (p<0.01 for both VEGF-C and VEGF-D), but were accompanied by an unanticipated decrease in RTK autophosphorylation (p=0.002). Other RTKs differentially modulated by sera from the patient groups include c-Kit (locoregionally advanced vs stage IV; p=0.01); Insulin Receptor and PDGFRα (locoregionally advanced vs stage IV; p=0.05) and EGFR (control vs stage IV, p<0.01). **Conclusion:** Stage-dependent differences in circulating ligands for RTKs associated with the modulation of tumoral metabolic phenotype were observed and associated with stage-dependent RTK activation. This study is currently being expanded to provide direct metabolic flux information in conjunction to the RTK data using Seahorse metabolic phenotype assays.

Keywords: NSCLC, RTK, immunosuppressive tumor microenvironment

P2.03-30 GENETIC CHARACTERISTICS OF LUNG CANCER IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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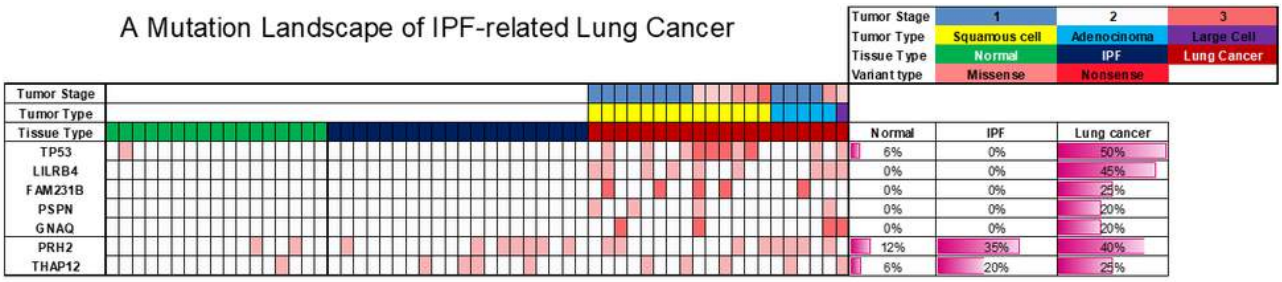
Background: Idiopathic pulmonary fibrosis (IPF) is well known to be associated with lung cancer. However, the genetic alteration contributing to lung cancer development from IPF has not been elucidated. The objective of this study is to investigate the genetic characteristics of IPF-related lung cancer by using next-generation sequencing. **Method:** Patients with IPF who diagnosed lung cancer and underwent pulmonary resection surgery at Seoul National University Bundang Hospital were included. We extracted DNA from three parts of pathologic specimen of the same patient; normal, IPF, and lung cancer tissue. Using the DNA extracted from each tissue, whole exome sequencing was performed. **Result:** Twenty consecutive IPF patients with lung cancer were included. Median age at diagnosis was 72 years, all patients were male and 19 patients (95%) were former or current smokers. Fourteen patients (70%) had squamous cell carcinoma, five patients (25%) had adenocarcinoma, and one (5%) had large cell carcinoma. TP53 (10/20, 50%) was the most frequently identified genetic mutation in lung cancer tissue, followed by LILRB4 (9/20, 45%). These genetic mutations were not observed in IPF tissue of the same patient. The genetic mutations of FAM231B (5/20, 25%), PSPN (4/20, 20%), GNAQ (4/20, 20%) were also observed in lung cancer tissue, but not in IPF tissue. Genetic mutations of PRH2 and THAP12 were identified both IPF and lung cancer tissue. The frequency of mutations was observed to increase in the order of normal, IPF, and lung cancer tissue (PRH2, 12% vs 35% vs 40%; THAP12, 6% vs 20% vs 25%).



Conclusion: Various genetic mutations are associated with the development of lung cancer from IPF. Certain sequential patterns of genetic mutations may be present in IPF-associated lung cancer. Our findings provide insight into the genomic landscape about IPF-related lung cancer.

Keywords: idiopathic pulmonary fibrosis, Next generation sequencing, Lung cancer

P2.03-31 CHEMOKINE RECEPTOR CXCR7 REACTIVATES ERK SIGNALING TO PROMOTE RESISTANCE TO EGFR KINASE INHIBITORS IN NSCLC

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Background: Activating EGFR mutations in NSCLC confer sensitivity to reversible EGFR TKIs, including gefitinib and erlotinib. Despite promising initial response, acquired resistance develops mediated by the emergence of the secondary T790M mutation or by focal amplification of MET. An epithelialtomesenchymal transition (EMT) is clinically linked to NSCLCs with acquired EGFR TKI resistance. The exact mechanisms of EGFR TKI resistance with EMT phenotype remain elusive. **Method:** We have engineered EGFRmutated NSCLC cell lines with a mesenchymal phenotype by stably depleting ECadherin, overexpressing Snail, or chronically exposing the cells to TGFβ1. The resulting mesenchymal cells are resistant to EGFR TKIs. We employed genomic analyses to identify commonly activated oncogenic drivers that maintain signaling pathways upon EGFR inhibition. We also used EGFRmutated HCC4006 NSCLC cells grown resistant to gefitinib that developed a mesenchymal phenotype (HCC4006GeR). To extend our findings to *in vivo*, we have utilized matched pre- and post-EGFR TKI treatment samples from NSCLC patient and mouse models of acquired EGFR TKI resistance to test if our approach using these cell lines is instructive. **Result:** We discovered that an atypical GPCR, CXC chemokine receptor type 7 (CXCR7), is commonly overexpressed in the cell line models of EGFR TKI resistance with a mesenchymal phenotype. The murine tumors driven by human EGFR exon19 deletion/T790M (TD) with acquired resistance to WZ4002 present mesenchymal phenotype and overexpress CXCR7. 50% of NSCLC patients harboring an EGFR kinase domain mutation who progressed on EGFR inhibitors showed an increase in CXCR7 expression. Using the cell line model of EGFR TKI acquired resistance with a mesenchymal phenotype, we find that CXCR7 activates the MAPK-ERK pathway via b-arrestin. Depletion of CXCR7 abrogates the MAPK pathway and significantly attenuated EGFR TKI resistance in the cells with a mesenchymal phenotype. In the long term, the depletion of CXCR7 resulted in mesenchymal to epithelial transition. Ectopic overexpression of CXCR7 in HCC4006 cells was sufficient in activation of ERK1/2 for the generation of EGFR TKI resistant cells. Furthermore, CXCL12 stimulation resulted in an increase in ERK phosphorylation while EGFR was inhibited in HCC4006Ge-R cells. Similarly, we found we found CXCL12 expression is elevated in patient samples with increased CXCR7 expression. **Conclusion:** Taken together, we discovered that the CXCR7-CXCL12 signaling axis is necessary and sufficient for the maintenance of EGFR TKI resistance with mesenchymal phenotype and CXCR7 inhibition could significantly delay and prevent the emergence of acquired EGFR TKI resistance in EGFR mutant NSCLC.

Keywords: NSCLC, GPCR, Drug resistance

POSTERS

P2.03-32 METASTATIC LYMPH NODES AS HIGH IMMUNOGENICITY MEDIA FOR PERIOPERATIVE IMMUNOTHERAPY IN LOCALLY ADVANCED NSCLC

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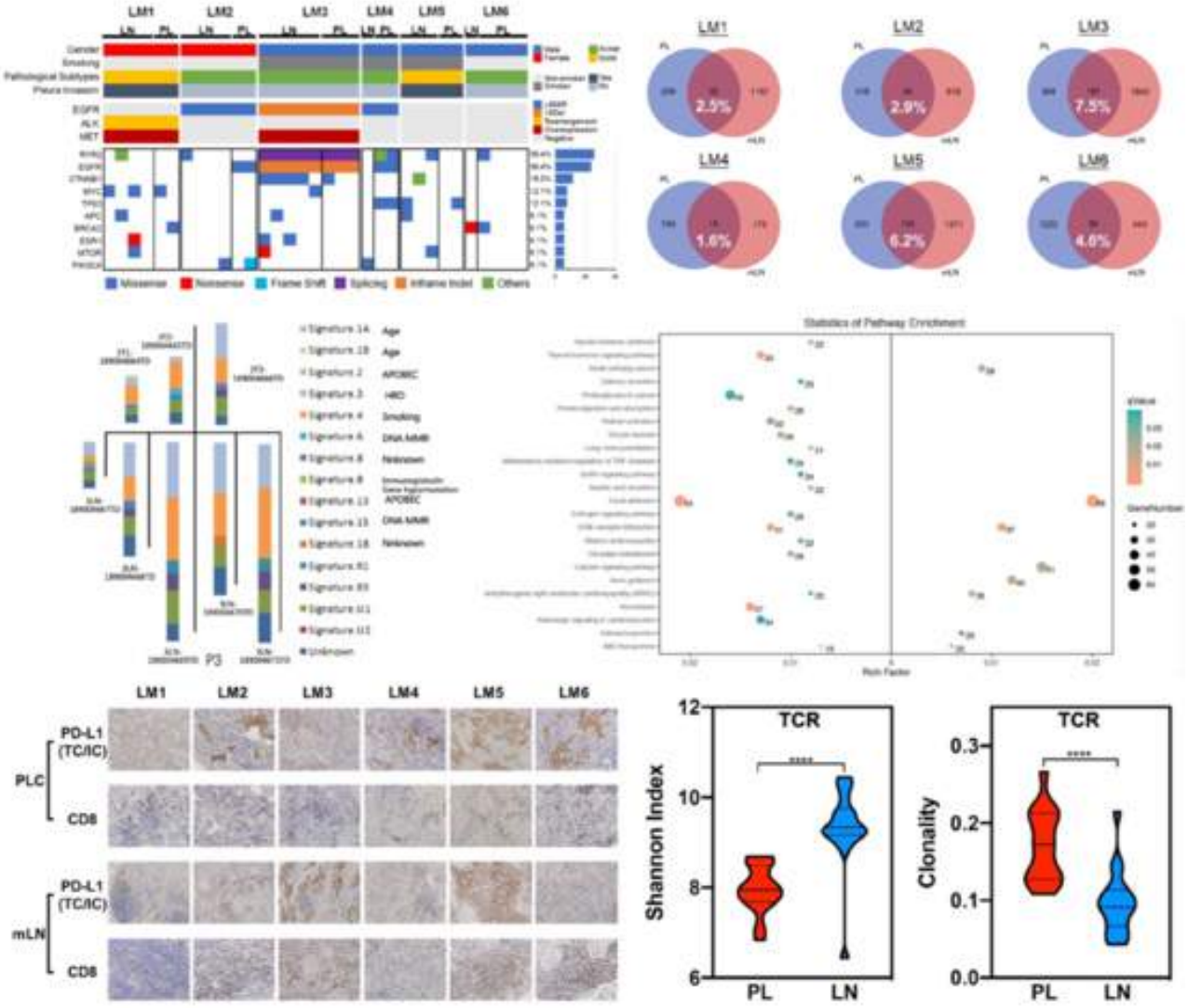
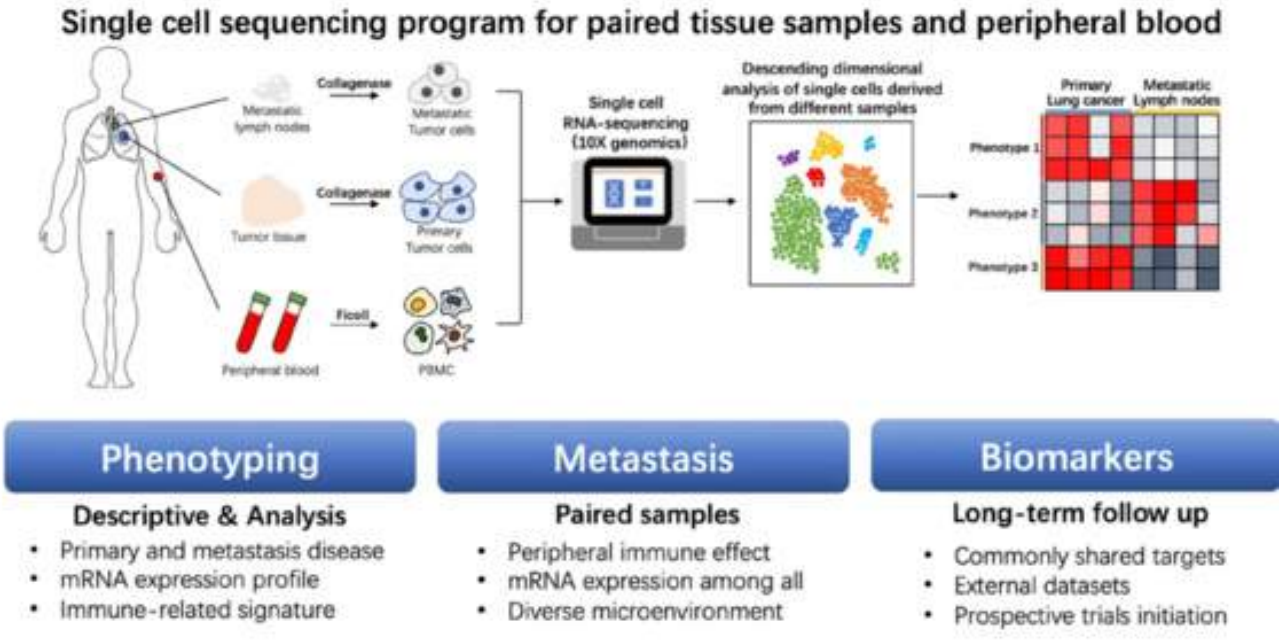
Background: Perioperative chemotherapy showed limited survival benefit and increased toxicities while neoadjuvant immunotherapy achieved great success in early phase trials. Both inter/intra-tumoral heterogeneity (ITH) between primary lesion and metastatic lymph nodes (mLNs), and rationale of superior efficacy for immunotherapy remained poorly explored in locally advanced non-small cell lung cancer (NSCLC). **Method:** We retrospectively collected 6 locally advanced lung adenocarcinoma (LUAD) patients. 15 tissue samples were performed multi-region whole exosome sequencing and TCR repertoire analysis as well as 18 matched metastatic lymph nodes (mLNs). **Result:** 290 somatic mutations in average were identified in primary LUAD (PL) and 441.6 for mLNs. Tumor mutation burden as well as tumor neoantigen burden was significant higher in mLNs than in primary LUAD (median value, 6.6mut/Mb vs. 3.4mut/Mb, P=0.0376; 229.5 neo counts vs. 165 neo counts, P=0.0287). Increased transversion ratio was found in mLNs compared to primary lesions. The genomic concordance between primary lesions and mLNs was 58.4%±12.5% and 33.3% for EGFR-mutation. 87 copy number variants were detected in 14 samples with 3q, 8q and X chromosome as frequently mutated cytobands. Small cell lung cancer functional pathway was enriched in mLNs exclusively. Both expression of PD-L1 and CD8 revealed high level (median value 20% and 40%) and consistence (5/6, 83.3%) between primary and metastatsis lesions. TCR clonality was 17.2% and 9.1% for primary and metastasis lesions, respectively with higher T cell diversity and intra-tumoral heterogeneity of TCR found in mLNs.





Conclusion: Extensive genomic and TCR ITH was found between primary LUAD and mLNs which may lead to mixed response to perioperative treatment. mLNs may serve as a better immunogenicity media for perioperative immunotherapy suggesting a potential adjuvant modality of immunotherapy performing lymph nodes sampling during surgery. Results of an initiated single cell sequencing program including paired samples were pending to further provide insights of diverse immune-microenvironment.

Keywords: locally advanced lung cancer, intra-tumoral heterogeneity, perioperative immunotherapy

P2.03-33 CTDNA LEVELS SIGNIFICANTLY PREDICTS SURVIVAL IN NSCLC PATIENTS WITH AN EGFR ACTIVATING MUTATION

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Background: Circulating tumor DNA (ctDNA) have been shown to be useful for non-invasive biomarker testing in non-small cell lung cancer (NSCLC). In addition, there is growing evidence supporting that ctDNA levels can be useful for tumor response to treatment monitoring. Nevertheless, data from large prospective clinical longitudinal studies still limited. **Method:** 300 plasma samples from 100 advanced NSCLC patients, with tumors harboring an EGFR activating mutation and treated with a first line tyrosine Kinase inhibitor were analyzed. Samples were collected before the start of treatment, at first follow up evaluation, at 7 month and at disease progression. ctDNA was analyzed by dPCR. **Result:** Median follow up was 11.3 months. There were not significant differences in progression free survival (PFS) or overall survival (OS) according to treatment (erlotinib, afatinib or gefitinib). Patients harboring a deletion in exon 19 or a mutation in exon 21 exhibited better survival than those with an insertion in exon 20 (P<0.001). dPCR detected EGFR sensitizing mutation in 77% of the pre-treatment samples. ctDNA levels before the start of the treatment did not significantly predict survival, although a tendency was observed, with patients with high levels of ctDNA showing poorer outcome. On the contrary, patients in which the EGFR sensitizing mutation was undetectable at first follow up had a markedly better PFS and OS (HR=2.7; 95IC= 1.4-5.5 and HR= 5.5 95IC: 1.8-17 respectively). In the same way, patients in which the EGFR sensitizing mutation remained negative at 7months had a significantly increased PFS (HR: 2.8; 95IC: 1.2-6.6). None of the patients with undetectable levels at 7 months has deceased. **Conclusion:** ctDNA levels is of prognostic significance in EGFR positive NSCLC patients with advance disease and can be useful to monitor treatment outcome

Keywords: ctDNA levels, EGFR positive NSCLC

P2.03-34 FRACTALKINE ATTENUATE IRRADIATION-INDUCED BRAIN INJURY THROUGH PROMOTING THE M2 POLARIZATION OF MICROGLIA

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Background: Radiation-induced brain injury (RIBI) is an unavoidable adverse side-effect induced by cranial radiation therapy. The neuro-inflammation mediated by activated microglia has been proved to be a key role in RIBI by our previous researches. Studies have demonstrated that vascular endothelial cells are damaged by irradiation and Fractalkine (FKN), a crucial mediator modulating the biological activity of microglia, is released. However, the role of FKN in RIBI was poorly understood. The aim of this study was to investigate the effect of FKN on RIBI and its underlying mechanisms. **Method:** Human Umbilical Vein Endothelial Cells (HUVEC) was subjected to 10 Gy or sham irradiation, FKN expression was detected by Western blotting (WB), qRT-PCR and ELISA, γH2AX formation and nuclear translocation of p65 was analyzed by immunocytochemistry (ICC). BV-2 cells received 10-Gy irradiation after being cultured for 3 h with or without FKN (100ng/ml), or co-cultured with HUVEC. Moreover, the CX3CR1 (the receptor of FKN on microglia) wide-type ($CX3CR1^{WT}$) and CX3CR1-knockdown ($CX3CR1^{-/-}$) mice were employed and subjected to lateral ventricular injection (ICV) of 5 μl FKN lentivirus or vector 3 days before 10-Gy whole brain irradiation. The polarization of microglia *in vitro* or in hippocampus and its inflammatory factors release were evaluated through measuring the signature genes, protein and cytokines of M1/M2 phenotype by RT-PCR, WB and ELISA at different time-points after irradiation. Hippocampus neurogenesis was evaluated through detecting the proliferation marker BrdU/nestin and differentiation marker BrdU/NeuN by immunofluorescence (IF) respectively. Neurological function was evaluated by morris water maze (MWM) at 6 weeks after RIBI, and the relationship between microglia and vascular was explored by IF. Then the *in vitro* phagocytosis assays were performed to investigate if FKN could promote BV2' phagocytic function. **Result:** The expression of FKN in HUVEC was increased by 10 Gy irradiation, simultaneously, γH2AX formation and p65 nuclear translocation were observed. FKN regardless from exogenous or secreted by HUVEC could promote the M2 polarization of microglia and inhibit inflammatory response *in vitro*, it also enhanced neurogenesis in hippocampus, and improved function recovery in $CX3CR1^{WT}$ mice, but not in $CX3CR1^{-/-}$mice after RIBI. More interestingly, activated microglia migrated to blood vessels in $CX3CR1^{WT}$ mice was observed *in vivo* by IF. What's more, BV2 cells phagocytized more fluorescent microspheres when treated with FKN. **Conclusion:** The FKN/CX3CR1 axis plays an important role in RIBI, and might be an underlying target for the treatment of radiation-induced cognitive impairment.

Keywords: irradiation-induced brain injury, fractalkine, microglia

P2.03-35 STROMAL TIMP-1 DRIVES TUMOR PROGRESSION IN LUNG ADENOCARCINOMA THROUGH CD63 INTERACTION

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Background: Tumor associated fibroblasts (TAFs) are important regulators of tumor growth and resistance to therapies. We have recently shown that TAFs *in vitro* from lung adenocarcinoma (ADC) and squamous cell carcinoma (SCC) respond positively to the antifibrotic drug nintedanib in the former only, thereby mimicking the selective therapeutic effects of nintedanib in ADC reported in the LUME-Lung1 clinical trial. We also showed that the tumor-promoting effects of TAFs are driven by different mechanisms in ADC and SCC. However, it remains to be elucidated the key signaling molecules involved in the aberrant fibroblast-carcinoma crosstalk in ADC. Tissue inhibitor of metalloproteinases 1 (TIMP-1) is a multifunctional protein that has been associated with poor prognosis in lung cancer and other cancer types, and is downregulated by nintedanib in a bleomycin model of pulmonary fibrosis. Moreover, our preliminary analysis revealed that the TIMP-1 cell surface binding protein CD63, is overexpressed in ADC compared to SCC. Therefore, our objective was to study whether the selective tumor-promoting effects of ADC-TAFs are mediated by the interaction of stromal TIMP-1 with epithelial CD63. **Method:** ADC-TAFs and SCC-TAFs were stimulated with TGF-β1 in the presence or absence of nintedanib, and the TIMP-1 content in their conditioned medium was determined by ELISA. TIMP-1 was reduced in ADC-TAFs by siRNA, and the corresponding conditioned medium was used to assess the impact of TIMP-1 on the growth, invasion and survival of the CD63-high ADC cell line H1437. Likewise, CD63 expression in H1437 cells was reduced, by siRNA. In addition we performed immunohistochemical analyses of CD63 in tissue sections from lung cancer patients. **Result:** Our results showed that TIMP-1 secretion induced by TGF-β1 is significantly larger in ADC-TAFs compared to SCC-TAFs. Likewise, nintedanib elicited a larger downregulation of TIMP-1 secretion in ADC-TAFs compared to SCC-TAFs. We also confirmed that CD63 expression is higher in ADC patients than SCC, and revealed that knocking-down CD63 in H1437 ADC cells is sufficient to reduce the growth and invasion elicited by the conditioned medium of activated ADC-TAFs. Likewise, knocking-down TIMP-1 in ADC-TAFs was sufficient to downregulate the growth, invasion and survival of H1437 elicited by the conditioned medium of these TAFs. **Conclusion:** Collectively, our results unveil a novel stroma-carcinoma interaction driven by TIMP-1 and CD63 selectively in lung ADC, and support that such crosstalk is a major regulator of the aberrant tumor-promoting effects of ADC-TAFs that are downregulated selectively by nintedanib.

P2.03-36 TTMB AND BTMB IN EAST ASIAN LUNG CANCER PATIENTS WITH NO TKI-RELATED DRIVER GENE MUTATIONS

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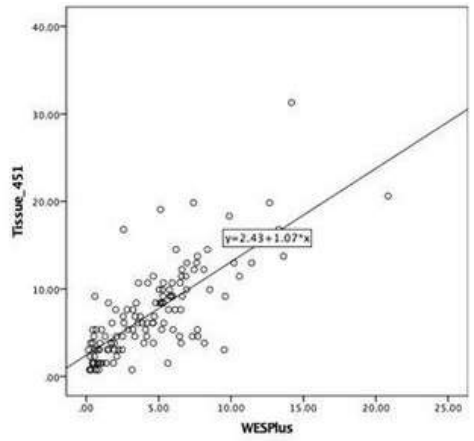
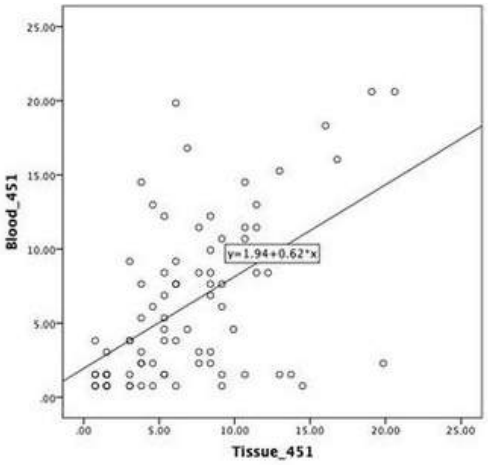
Background: High-level TMB was shown to be correlated with the better response of immunotherapy in lung cancer patients. However, the correlation between tissue tumor mutational burden (tTMB) with the blood tumor mutational burden (bTMB) in lung cancer patients has not been fully defined, and the tTMB and bTMB of East Asian lung cancer patient harboring no TKI-related driver gene mutations remains unexplored. This study aimed to define the tTMB and bTMB in East Asian by whole-exome sequencing (WES) and panel-based sequencing, and interrogate the correlation between gene mutations and TMB in lung cancer patients with no TKI -related driver gene mutations. **Method:** In this cohort study, 122 primary lung cancer patients without TKI-related driver gene (EGFR, ALK, ROS1, RET, BRAF, C-MET, HER2) mutations were included. tTMB and bTMB were determined by whole-exome sequencing (WES) and a targeted 451-gene panel sequencing. The correlation between any two among the WES-tTMB, the panel-tTMB and the panel-bTMB were determined, and the relationship between gene mutations and tTMB were analyzed. Statistics was performed with the SPSS 20 software. **Result:** The mean tTMB measured by WES (WES-tTMB), the 451-gene panel (panel-tTMB) and bTMB measured by the 451-gene panel (panel-bTMB) was 4.5, 7.2 and 6.1 mutations/Mb, respectively. Significant correlation was found between panel-tTMB and WES-tTMB (Pearson r=0.76, P<0.001) or panel-bTMB (Pearson r=0.52, P<0.001), but WES-tTMB showed no correlation with panel-bTMB (Pearson r=0.189, P=0.75). The relationship between gene mutations and WES-tTMB was further explored. Patients with p53, TTN, CSMD3, ZFHX4, RYR2, MUC16, MUC12 and USH2A gene mutations had dramatically higher tTMB (P<0.001), while no significant relationship between CDKN2A or KRAS gene mutations and TMB was identified (p>0.05). In contrast, patients harboring both KRAS and P53 mutations showed significantly higher TMB than those with either gene mutations or no mutations in both genes (P<0.001).



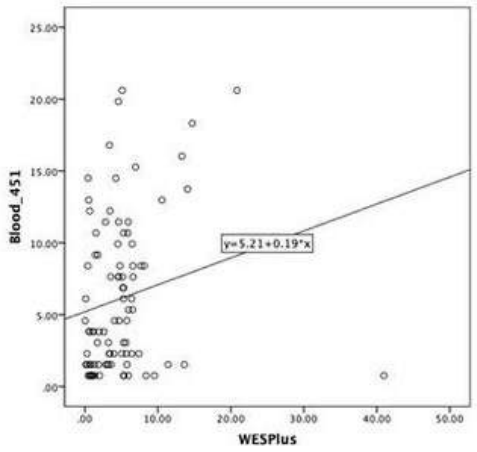
Correlations

		WESPlus	Tissue_451
WESPlus	Pearson Correlation	1	.756**
	Sig. (2-tailed)		.000
	N	125	125
Tissue_451	Pearson Correlation	.756**	1
	Sig. (2-tailed)	.000	
	N	125	125



Correlations

		Tissue_451	Blood_451
Tissue_451	Pearson Correlation	1	.524**
	Sig. (2-tailed)		.000
	N	80	80
Blood_451	Pearson Correlation	.524**	1
	Sig. (2-tailed)	.000	
	N	80	80



Correlations

		WESPlus	Blood_451
WESPlus	Pearson Correlation	1	.189
	Sig. (2-tailed)		.075
	N	90	90
Blood_451	Pearson Correlation	.189	1
	Sig. (2-tailed)	.075	
	N	90	90

Conclusion: Our study suggested that discrepancies exist in TMB measurement using different NGS-based detecting methods with tissue or blood sample types. The cut-off values should be determined based on detecting methods and samples types. Panel-tTMB was stronger correlation with WES-tTMB and panel-bTMB. Gene mutations were correlated with high TMB might be stronger predictors for TMB status in lung cancer patients without TKI-related driver gene mutations. Our observations provided new insights in TMB determination in East Asian lung cancer patients with NGS-based methods in various samples types and might improve the prediction of therapeutic effect and prognosis in future immunotherapy.

Keywords: lung caner, tTMB, bTMB

P2.03-37 GENOMIC LANDSCAPE OF EGFR/ALK WILD-TYPE LUNG ADENOCARCINOMAS IN NEVER-SMOKERS AND IMPORTANCE OF EPITHELIAL-MESENCHYMAL-TRANSITION

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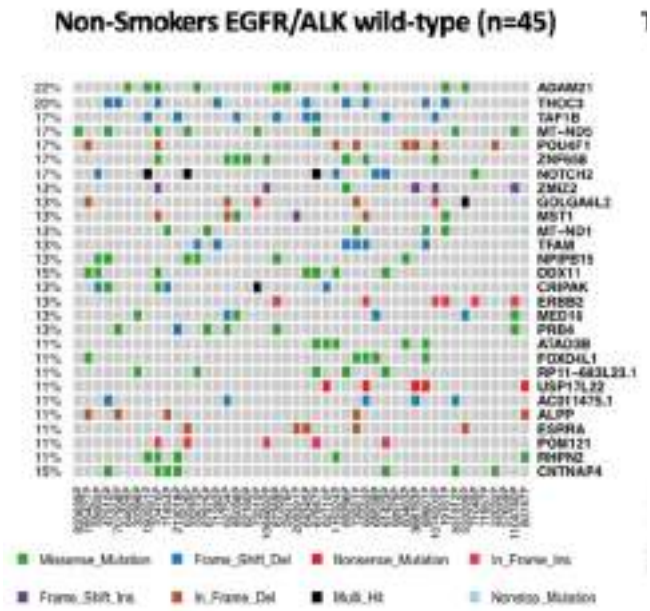
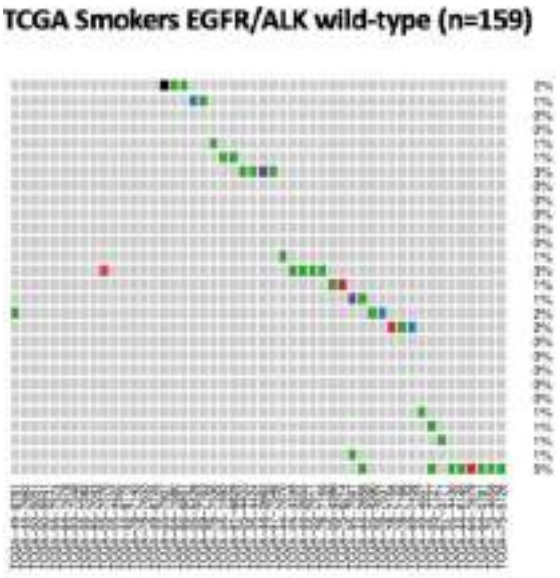
University Health Network, Toronto/Canada

Background: The molecular landscape of EGFR/ALK wild-type Lung Adenocarcinomas in never-smokers is poorly understood. Never-smokers usually have low PD-L1 expression and low Tumor Mutation Burden, challenging treatment strategies when no known driver-mutations are found. To identify putative driver mutations, we compared whole exome sequencing (WES) results in the EGFR/ALK wild-type Lung Adenocarcinoma in the never smokers Toronto cohort with a corresponding EGFR/ALK wild-type Lung Adenocarcinoma group of smokers from TCGA. **Method:** For never-smokers with resected EGFR/ALK wild-type Lung Adenocarcinomas, frozen tumor and paired-normal-lung were evaluated by WES at a mean coverage of 238x. The paired-end reads were aligned using BWA and were further processed using the standard GATK pipeline. Somatic mutations and indels were identified using MuTect and VarScan, respectively. We compared mutations from our cohort to the TCGA smokers who had EGFR/ALK wild-type Lung Adenocarcinomas from publicly available data (TCGA) to identify genes at least 10% more frequently mutated in never smokers compared to the TCGA cohort. **Result:** In our cohort with 45 never-smoker patients, 80% were females; median age was 70y; 29% were Asians; Stage I/II/III+ were 71%/15%/13%; after a median follow-up of 69 months, 24% had recurred. Median non-synonymous Tumor Mutation Burden was 1.3mut/Mb in never-smokers. We identified 39 genes that were more frequently mutated in never-smokers vs smokers, including some known tumor suppressor genes. The most prevalent genes included ADAM21 missense mutations (21% vs 1%; adj p=0.003), NOTCH2 frame-shift deletions and multi-hit mutations (40% vs 17%; adj p=0.04), MST1 missense mutations and in-frame deletions (13% vs 0%; adj p=0.008), ZMIZ2 frame-shift insertions (13% vs 0%; adj p=0.008) and FOXD4 missense mutations (10% vs 0%; adj p=0.02). Many of these differentially mutated genes have been previously associated to epithelial-mesenchymal-transition signaling pathways. Conversely and as expected, KRAS, TP53, STK11 and KEAP1 were more frequently mutated in the TCGA smokers EGFR/ALK wild-type Lung Adenocarcinomas cohort.





Conclusion: We identified multiple genes, particularly involved in the epithelial-mesenchymal-transition signaling pathways that are over-represented in never-smokers with EGFR/ALK wild-type Lung Adenocarcinomas, when compared to smokers with EGFR/ALK wild-type Lung Adenocarcinomas. This is a novel finding with potential clinical importance. Validation studies, analyzing epithelial-mesenchymal-transition signaling activation pathways on the EGFR/ALK wild-type Lung Adenocarcinomas never smokers population are needed to best identify the actual role in carcinogenesis and metastasis, guiding future treatment strategies. (AFF and SNMF contributed equally).

Keywords: Never Smokers, Whole-Exome-Sequencing, Epithelial-Mesenchymal-Transition

P2.03-38 IDENTIFICATION OF A NOVEL SYNTHETIC LETHAL VULNERABILITY IN NON-SMALL CELL LUNG CANCER BY CO-TARGETING TMPRSS4 AND DDR1

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Background: Synthetic lethality has been defined as the inability of cells to proliferate when co-targeting two genes, with a synergistically superior inhibition than that found for each individual gene. Consistent co-expression of two genes involved in a similar function is a predictor of synthetic lethality, a strategy that is being applied to find out novel cancer vulnerabilities. **Method:** Large-scale bioinformatics analyses across 5 public databases were used to identify genes consistently co-expressed with TMPRSS4, a novel therapeutic target that we have previously identified in NSCLC. Pyrosequencing was used to evaluate methylation levels in patients and cell lines. Functional *in vitro* experiments and animal models were used to assess synthetic lethality of TMPRSS4 and DDR1 in NSCLC. **Result:** Consistent co-expression between TMPRSS4 and DDR1 was found in all NSCLC databases evaluated. Similar to TMPRSS4, DDR1 promoter was hypomethylated in NSCLC in 3 independent cohorts and hypomethylation was an independent prognostic factor of disease-free survival. Treatment with 5-azacitidine increased DDR1 levels in cell lines, suggesting an epigenetic regulation. Cells lacking TMPRSS4 were highly sensitive to the cytotoxic effect of the DDR1 inhibitor dasatinib. TMPRSS4/DDR1 double knock-down cells, but not single knock-out cells suffered a G0/G1 cell cycle arrest with loss of E2F1 and cyclins A and B, increased p21 levels and apoptosis. Moreover, double knock-down cells were highly sensitized to cisplatin, which caused massive apoptosis (~40%). *In vivo* studies demonstrated tumor regression in mice injected with double knock-down-injected cells and lack of 18FDG-uptake by microPET analysis. **Conclusion:** We have identified a novel vulnerability in NSCLC resulting from a synthetic lethal interaction between DDR1 and TMPRSS4. This may help designing therapeutic strategies to impair NSCLC growth by co-targeting both genes.

Keywords: DDR1, synthetic lethality, TMPRSS4

P2.03-39 SYSTEMATIC EVALUATION OF EGFR VARIANT BIOLOGY IN CANCER

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Background: Lung cancer is the leading cause of cancer related deaths world-wide, with non-small cell lung cancer (NSCLC) accounting for a majority of all cases. Approximately 14% of adenocarcinomas, a NSCLC subtype, are characterized by activating mutations in the epidermal *g*rowth *f*actor *r*eceptor, EGFR. In NSCLC, there are several well-established hotspot mutations in EGFR, such as in-frame deletions in exon 19 and point mutations at residue L858, that have demonstrated dramatic responses to molecularly targeted therapies in subsets of patients. Beyond hotspot mutations, subsets of patients can present with rare EGFR variants at residues G719, L861, or S768, all of which are known to be oncogenic drivers. However, a subset (~5%) of observed EGFR variants remain functionally uncharacterized. Given the increase in targeted panel sequencing of cancer patients, it is feasible that additional EGFR variants will be revealed beyond those already functionally annotated. Additionally, pre-clinical and clinical investigations have revealed that EGFR variants, rare or not, can have differential sensitivity to EGFR TKIs (tyrosine kinase inhibitor), however, the mechanism for this differential sensitivity remains to be elucidated. If we could systematically assess whether

an EGFR variant is a possible driver and determine its TKI sensitivity profile, this could pave the way towards enhanced patient care by providing a catalogue of treatment strategies for specific EGFR variants. **Method:** To systematically evaluate all possible EGFR variants, we employed a high throughput forward genetic screening approach. To generate all possible EGFR variants, we used a saturation mutagenesis strategy, which entailed substituting each amino acid for all other possible amino acids including stop codons, generating a library of approximately 25,000 EGFR variants. We expressed our pooled library in two distinct lung cancer models and assessed the ability of each EGFR variant to grow compared to EGFR WT in the presence of inhibitors using changes to population doublings as a readout for variant functionality. **Result:** Our screens revealed functional information for somatic mutations observed in patients that previously were uncharacterized. Firstly, in both screens, we observed variant enrichment in the kinase domain, which was expected and gives us confidence that our screens have yielded relevant EGFR variant biology. Furthermore, in our oncogenesis screen, we unexpectedly identified variant enrichment in specific EGFR extracellular domains. Conversely, in the second screen, which measured EGFR activity and insensitivity to erlotinib, we observed a distinct variant enrichment pattern in both the EGFR extracellular domain and the transmembrane domain. **Conclusion:** Our strategy is a powerful tool to uncover novel functional information for variants of unknown significance (VUS). Together, our screening results give a comprehensive understanding of the EGFR variant landscape, which has implications for both EGFR biology and patient treatment strategies.

Keyword: EGFR variant biology

P2.03-40 PARTICLE MATTERS INDUCE CARCINOGENIC PHENOTYPE AND GENE EXPRESSION CHANGES IN MURINE PULMONARY PROGENITOR CELLS

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Background: The leading cause of cancer deaths points to lung cancer which tends to exacerbate, especially the cases of never-smokers in East Asian. While environmental exposure to air pollutants-particle matters (PMs) has been reported to increase the risk of lung cancer; the organic or inorganic chemicals absorbed in the surface of particles, including polycyclic aromatic hydrocarbons (PAHs), dioxins or other heavy metals are identified as carcinogens. However, the underlying mechanisms and the extent to which the toxicity of co-exposure to PMs and environmental carcinogens in pulmonary cells remain unclear. **Method:** Here, we used a well-developed murine lung progenitor cell model with the cells primary cultured from neonatal mice and sorted as the OCT4+/CARHi sub-population to expose with fine PMs (urban dust) or ultrafine particles (nano-carbon black, nCB) with/without carcinogens (Benzo[a] pyrene, B[a]P and 2,3,7,8-Tetrachlorodibenzo-p-dioxin, TCDD). High content analysis (HCA) was applied to quantify the progenitor cell population and differentiated alveolar epithelial cells; and the cellular heterogeneity was also examined. The transcriptomics and gene enrichment analysis were also performed to explore the molecular mechanisms via the gene set enrichment analysis with the molecular signatures database. **Result:** We found that co-stimulating the progenitor cells with TCDD and nCB can cause most significantly effects on activating cell proliferation, reducing cell differentiation and remarkably morphological diversity. The potential stemness sub-population of CAR-positive lung progenitor cells was increased following TCDD treatment and forming more significantly colony in the TCDD-nCB co-exposure group; whereas, the population of differentiated pulmonary lung epithelial cells was reduced. Transcriptomic analysis showed that the TCDD-induced genes: AHR, Cyp1A1, COX-2, and TCDD-inducible poly(ADP-ribose) polymerase are significantly up-regulated. The pathway analysis revealed important oncogenic transcriptional factors (TFs): STAT2, IRF1, AHR, BRCA1, and FOS are highly enriched and several key factors on EGFR, RAF, AKT, E2F1, MEK, and LTE2 were identified via the MSigDB oncogenic signatures. Furthermore, the co-exposure of TCDD with nCB also dysregulated the Wnt signaling pathway, cytokine networks (CCLs-CXCLs-CXCRs), antigen processing and presentation, IL-2 receptor signaling, interferon and TNF signaling that are critical on immune homeostasis in the microenvironment. **Conclusion:** In conclusion, co-exposure of ultrafine particles with carcinogens could induce cell proliferation and suppress differentiation in mice lung progenitor cells; and lead to oncogenic and immune-modulatiing gene dysregulation. This study suggests the synergistic effects of the environmental carcinogens and PMs on the initiation of hyperplasia and malignant transformation of the lung progenitor cells via regulating gene expression related to oncogenic TFs, immunity and paracrine niche.

Keywords: Lung Progenitor Cells, Particle Matters, Carcinogens

P2.03-41 IDENTIFICATION OF NOVEL BLOOD-BRAIN BARRIER PENETRATING DNA APTAMERS

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Background: A significant portion of lung cancer patients develops central nervous system (CNS) metastasis at certain time points in their disease courses. The structure of blood-brain barrier (BBB) strictly regulates brain homeostasis and protects the brain from exogenous damage. At the same time, these features impede effective drug delivery in to CNS, including antibody-based molecular probes. Therefore, detection of small CNS lesions and effective drug delivery across the BBB can be very challenging. Aptamers, also known as chemical antibodies, are small synthetic DNA or RNA oligonucleotides. With its inborn nature of low molecular weight, aptamers may possess better tissue penetrating ability comparing to antibodies. The current study aims to develop BBB-penetrating aptamers for CNS metastatic lung tumor targeting. **Method:** In vivo SELEX (Systematic Evolution of Ligands by Exponential enrichment) was used for aptamer identification in the current study. In brief, we established CNS lung cancer mouse models by intra-ventricular inoculation of lung cancer cells. The single-stranded DNA oligonucleotide library was then intraperitoneally injected to the tumor-bearing mice. The mouse was perfused with SELEX buffer and the CNS tissues were carefully isolated. Tissue/tumor-binding oligonucleotide sequences were extracted and amplified by PCR. The procedure was repeated for several rounds and the products of the final SELEX round was subjected for sequencing. **Result:** Our data showed that the CNS lung cancer mouse model was nicely established. The growth of tumors was in vivo monitored by IVIS imaging system and confirmed by immunohistochemistry staining. Through in vivo SELEX using the well-established mouse model, a group of potential BBB-penetrating aptamers was identified. By sequence analyses and secondary structure prediction, we further categorized a subset of aptamers that may possess CNS lung tumors targeting ability. Aptamer signals were in vivo captured by IVIS imaging system and was confirmed by confocal microscopy images showing the colocalization of aptamer and lung cancer cell signals. **Conclusion:** We have identified BBB-penetrating aptamers that may possess CNS lung tumor targeting ability. The aptamers may serve as guiding molecules for drug delivery and/or probes for molecular imaging. Further studies are required to determine their translational potential.

Keyword: BBB-penetrating aptamer, lung cancer targeting, molecular probe

P2.03-42 HIGHLY SENSITIVE SEL-CAPTM LUNG CANCER PANEL NGS FOR DETECTION OF TUMOR-DERIVED EGFR MUTATIONS IN PLASMA CELL-FREE DNA IN LUNG CANCER

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Background: Next-generation sequencing is a genetic analysis platform for multiple analysis and large-scale analysis. Sensitivity is limited by methods for detecting cancer mutations that are contained at low rates in blood. With two highly sensitive detection techniques for genetic alterations, we evaluated their diagnostic value for tumor-derived EGFR mutations in plasma cell-free DNA

(cfDNA) and measured concordance rate of activating EGFR mutations between cfDNA and tumor tissue. **Method:** We conducted this study using FFPE tissue and plasma samples which were donated from NSCLC patients (N=316) between 2011 and 2013 and stored in the Human-derived Biomaterials Bank in Seoul St. Mary's Hospital. Meanwhile, we prospectively collected plasma samples simultaneously when tumor tissue was taken out by surgery. We also collected peripheral blood just before administration of EGFR TKIs and each time imaging study was done during the administration of EGFR TKIs. We analyzed activating EGFR mutations in both cfDNA and tumor tissues using PNAclamping, Cancer panel and Sel-Cap™ Lung Cancer Panel. **Result:** The sensitivity and specificity of three detection techniques, PNAclamp, cancer panel and Sel-Cap™ Lung Cancer Panel NGS for EGFR mutations in tumor tissues were more than 90% in all. In particular, EGFR T790M was found not only in the patients acquiring drug resistance approximately 10-12 months following the administration of 1st or 2nd generation EGFR TKIs, but also in the patients in whom EGFR TKI was continuously maintained over 30 months. The sensitivity of Sel-Cap™ Lung Cancer Panel NGS for EGFR exon19 deletion and exon21 L858R in cfDNA was 76.2% and 61.1%, respectively. In addition, the sensitivity for double mutation of 19del and T790M was about 30% higher compared to that of cancer panel sold domestically (2/20, 10.0% vs. 9/20, 45.0%), suggesting that Sel-Cap™ Lung Cancer Panel NGS enables to detect EGFR mutation up to 0.1% in plasma cfDNA. As a result of tracking of outcomes of EGFR TKIs treatment over time for patients with low frequency of EGFR mutations, we found that 1st or 2nd generation EGFR TKIs were switched into 3rd generation EGFR TKIs on the basis of disease progression on radiologic imaging, when an average of 6.8 months (0.2-25.4 months) elapsed from the first detection time of T790M in cfDNA. The presence of T790M in peripheral blood harvested periodically from patients receiving EGFR TKIs was initially identified about 3-5 months ahead of disease progress assessed by imaging study. **Conclusion:** With regard to the detection of EGFR mutations in lung cancer patients, Sel-Cap™ Lung Cancer Panel NGS platform showed superior sensitivity to conventional NGS-based cancer panels as well as higher concordance rate between tumor tissues and plasma cfDNA. In longitudinal plasma cfDNA samples isolated from periodic liquid biopsies, quantitative changes of EGFR mutation were found to be significantly correlated to tumor response by EGFR TKIs. Our data suggest that Sel-Cap™ Lung Cancer Panel NGS is a highly sensitive diagnostic platform for detection of EGFR T790M induced by long-term administration of EGFR TKIs and for determining when 3rd generation EGFR TKI be begun.

Keywords: Sel-CapTM Lung Cancer Panel NGS, EGFR mutation, cell-free DNA

P2.03-43 WTAP ACTIVATES ONCOGENES AND ACCELERATES TUMOR AGGRESSIVENESS THROUGH ADDING M6A RNA MODIFICATION IN NON-SMALL-CELL LUNG CANCER

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Background: N6-methyladenosine (m6A) is one of the RNA modifications affecting multiple cellular processes such as RNA metabolism, stem cell self-renewal, and cell differentiation in eukaryotes. m6A is dynamically regulated by three types of enzymes called writer, eraser, and reader. WT1-associated protein (WTAP) is an important component of the m6A writer complex to which the majority of m6A is attributed. Despite having been revealed in several types of cancers, the relevance and roles of m6A and its modifiers are unclear in non-small cell lung cancer (NSCLC). We here quantified the global m6A levels in NSCLC tissues and associated them with clinical data. In addition, the roles of WTAP in the context of m6A regulation were explored *in vitro*. **Method:** Amounts of global m6A in the purified RNAs extracted from 126 paired tumor and adjacent normal tissues were evaluated using liquid chromatography mass spectrometry/mass spectrometry. The clinicopathological data were retrospectively retrieved. The expression levels of the three major m6A writers (WTAP, METTL3, and METTL14) in lung cancer cell lines (H1299, PC3, and PC9) were assessed using RT-qPCR and western blot. *WTAP* knockdown was carried out using siRNAs and its effects on tumoral activities. Also the changes of global and specific transcripts in WTAP-deprived PC9 cells were evaluated using a microarray analysis and m6A specific RNA immunoprecipitation (RIP) assay. WTAP protein expression levels in 641 resected NSCLC were assessed using immunohistochemistry and their prognostic role was determined. **Result:** The m6A/A was significantly higher in tumor tissues than adjacent normal tissues (P <0.001), and higher m6A/A was significantly associated with worse overall survival (Log-rank, P=0.041). Among the three major writer enzymes assessed, WTAP was identified as the most significant modifier of global m6A. Phenotypically, *WTAP* knockdown reduced proliferation, invasion, and migration. The microarray analysis showed that *WTAP* knockdown was significantly associated with reduction of activities in several important signaling pathways such as EGFR, KRAS, and MYC. Furthermore, the significant decrease of m6A in individual transcripts such as *EGFR, MAPKAPK2,* and *MYC* was confirmed in *WTAP*-deprived PC9 cells. Reporter assays containing wild type or mutant *EGFR*-3'UTR at m6A modification sites indicated that EGFR expression change was mediated by WTAP through its regulation of m6A abundance. Immunohistochemical analysis demonstrated that increased WTAP expression was an independent worse prognostic factor in patients with NSCLC (hazard ratio 1.892; 95% confidence interval 1.356-2.64; P<0.001). **Conclusion:** WTAP accelerates tumor aggressiveness through, in part, adding m6A in several important oncogenic transcripts such as *EGFR* and therefore increasing their expression. Both global m6A abundance and WTAP expression levels are prognostic in patients with NSCLC.

Keywords: m6A, WTAP, NSCLC

P2.03-44 BLU-667 DEMONSTRATES ROBUST ACTIVITY IN RET FUSION-DRIVEN INTRACRANIAL TUMOR MODELS

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Background: Oncogenic *RET* fusions and mutations have been identified in several cancer types including non-small cell lung cancer (NSCLC), papillary thyroid cancer and medullary thyroid cancer. Current treatment of *RET*-altered cancers is generally limited to multikinase inhibitors (MKIs) designed to target other kinases, and chemotherapy, which often have limited efficacy and carry significant off-target toxicities. BLU-667 is an investigational oral precision therapy that is a potent and highly selective inhibitor of oncogenic *RET* fusions and mutations (IC_{50} = 0.4 nM) and has demonstrated tumor growth inhibition and RET signaling abrogation in numerous subcutaneous models of *RET*-driven disease (Subbiah et al. 2018). Early phase 1 results with BLU-667 have demonstrated promising clinical activity in both *RET* fusion and *RET* mutant-driven tumors. As brain metastases occur in up to half of patients with NSCLC, we developed several preclinical intracranial models of *RET*-driven disease and demonstrate robust activity of BLU-667 in this setting. **Method:** KIF5b-RET-Ba/F3 cells engineered to express luciferase or CCDC6-RET CRC PDX tumors were implanted intracranially in Balb/c nude mice. Efficacy was determined by survival or imaging after luciferin tail vein injection. Pharmacodynamic confirmation of RET kinase inhibition was assessed by immunoblot or qRT-PCR of RET pathway transcriptional markers DUSP6 and SPRY4 in harvested tumors. **Result:** In *RET* fusion-driven intracranial mouse tumor models, oral BLU-667 treatment demonstrated significant survival benefit at well tolerated doses. This benefit occurred with BLU-667 doses (10 or 30 mg/kg BID) also shown to be efficacious in subcutaneous *RET*-driven tumor models and at drug exposures below those achieved at the recommended phase 2 dose in humans (400 mg) established in the BLU-667 phase 1 clinical trial. BLU-667 activity was consistent in both *KIF5b-RET* and *CCDC6-RET* fusions, the most common RET fusions found in NSCLC. Pharmacodynamic analysis of intracranial tumor tissue after BLU-667 treatment confirmed dose dependent inhibition of RET pathway signaling (P-RET, P-SHC) and >90% downregulation DUSP6 and SPRY4, consistent with full pathway inhibition. In intracranial Ba/F3-KIF5b-RET tumors expressing luciferase, imaging analysis established near complete inhibition of tumor growth in mice treated with BLU-667. **Conclusion:** In intracranial tumor models driven by KIF5b-RET or CCDC6-RET fusions, BLU-667 inhibits RET kinase activity and increases survival. These data suggest BLU-667 has promise as an investigational agent for RET fusion NSCLC with or without brain metastasis. As such, BLU-667 is currently being evaluated in a clinical trial for patients with *RET*-driven solid tumors including NSCLC (NCT03037385) with registrational intent.

Keywords: RET, kinase, BLU-667

P2.03-45 PKCι-PAK1 PATHWAY MODULATES SENSITIVITY TO THERAPY IN EGFR, KRAS MUTANT ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

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Background: p21-activated kinase 1 (PAK1) stimulates growth and metastasis in several types of tumors, including non-small cell lung cancer (NSCLC). Protein kinase C iota (PKCi) is an enzyme highly expressed in NSCLC that regulates PAK1 signaling. To understand intrinsic and acquired resistance to different MAPK signaling inhibitors, we explored PKCι-PAK1 signaling in EGFR/KRAS mutant adenocarcinoma or squamous cell carcinoma (SCC) cell lines by combination therapy using PAK1 inhibitor and PKCι inhibitor. **Method:** Three lung cancer cell lines were used: HCC827 and H23 lung adenocarcinoma cells that carries EGFR and KRAS mutations, respectively, and H520 (PAK1 amplified squamous cell carcinoma). Cell viability assays and western blotting were applied to evaluate the effect of IPA-3 (PAK1 inhibitor) plus auranofin (PKCι inhibitor). Since IPA-3 is only for laboratory use, we explored alternative PAK-1 inhibitor and tested combination effect with auranofin. **Result:** IPA-3 plus auranofin was highly synergistic (Combination index was less than 0.4) in EGFR mutant adenocarcinoma (HCC827), KRAS mutant adenocarcinoma (H23) and SCC with PAK1 amplification (H520) cell lines in MTT assay and colony forming assay. We revealed OTSSP167 (a MELK inhibitor in phase I/II trials) inhibits phosphorylated PAK1 and combination of OTSSP167 plus auranofin showed similar synergism in the 3 cell lines. The combination of auranofin with either IPA-3 or OTSSP167 ablated EGFR phosphorylation and downstream signaling pathways: ERK, AKT, STAT3, YAP1 and inhibited the expression of RTKs: AXL, MET, and CDCP1. **Conclusion:** The combination of IPA-3 plus auranofin is promising treatment in different subclasses NSCLC with driver EGFR or KRAS mutations, as well as SCC with PAK1 amplification. OTSSP167 also works as PAK1 inhibitor. The therapeutic effect of PAK-1 inhibitor and PKCι inhibitor was validated using OTSSP167 plus auranofin.

Keywords: lung adenorcarcinoma, Squamous cell carcinoma, combination therapy

P2.03-46 PI3K/AKT SIGNAL PATHWAY REGULATES MALIGNANT TRANSFORMATION OF MPLC WITH EGFR-SENSITIVE MUTATION

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Background: Multiple primary lung cancer (MPLC) is a presumed uncommon entity, but its true incidence, ranging from 0.2% to 8%, is increasing as the result of the widespread use of early detection tools. MPLC displays diverse clinical trajectories and genomic profiles. The in-depth study on the mechanism of malignant transformation of MPLC will provide new ideas for the future treatment of MPLC. **Method:** In this study, we analyse the genomic profiles of 25 tumors and 12 adjacent tissues from 10 patients with MPLC who underwent surgical resection through the whole-exome sequencing (WES). **Result:** Ten patients were enrolled in this study, one patient with different evolutional stages of the same disease (AAH, MIA, and IA) and one patient with completely different pathologies (adenocarcinoma and squamous cancer). Eight patients with different driver genes (EGFR exon 19 deletion,exon 21 L858R mutation and exon 21 L861Q mutation) of lung adenocarcinoma. We observed different mutational landscapes between tumors in the same patient by analyzing somatic mutations, copy number variations, clonal structures, and signal transduction pathways. Most tumors showed significant APOBEC mutant patterns, especially C→T transversions (Figure 1). Moreover, we also found that EGFR exon 19 and 21 mutations enrich different signal pathways. The PI3K/AKT signal pathway is often be enriched in tumors with EGFR exon 19 deletion, which is closely related to the early progression of the tumor. While PTEN kinase activation is associated with EGFR exon 21 L858R mutation (Figure 2). MPLCs with EGFR wild-type may be associated with abnormal regulation of signal pathways, including SOS1, JAK-STAT and others.

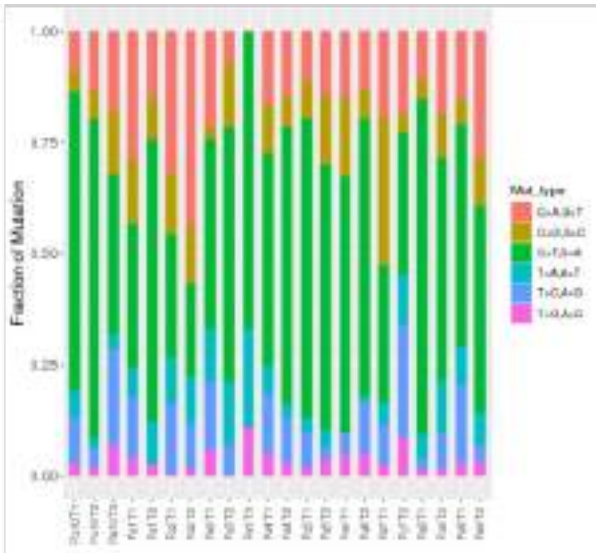

Figure 1. Mutation Spectrum

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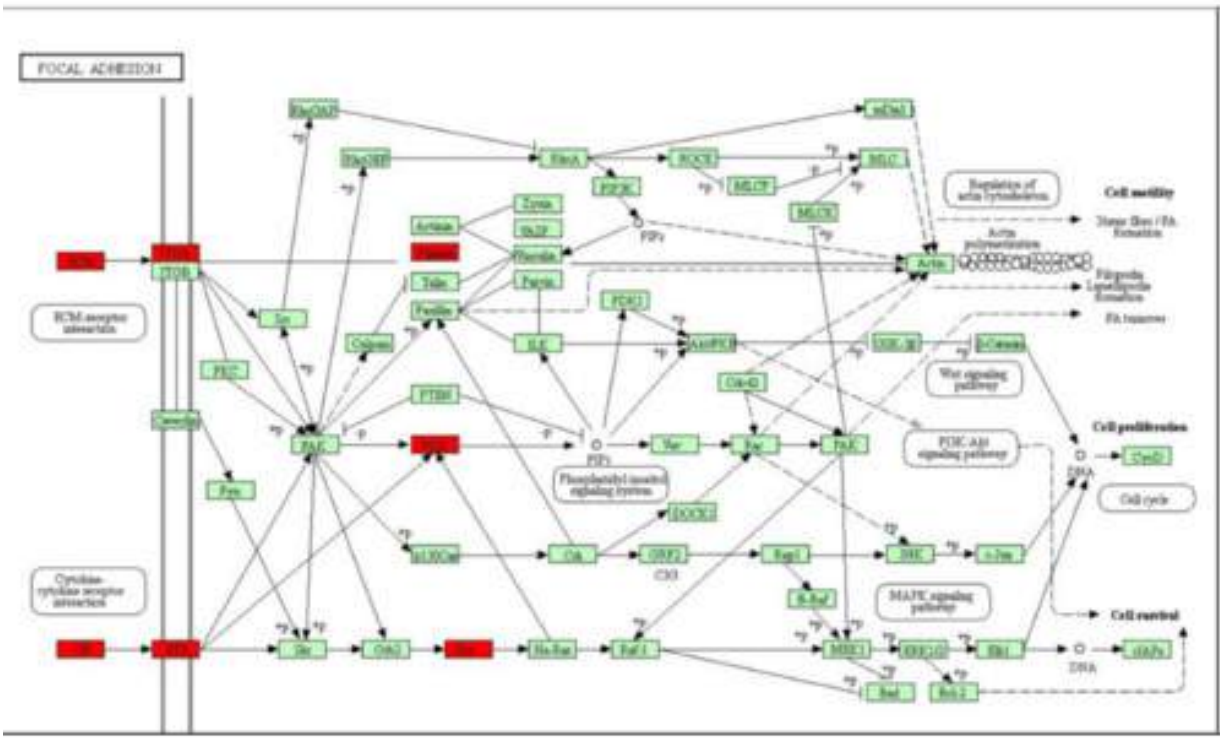
19-del

Focal adhesion



L858R

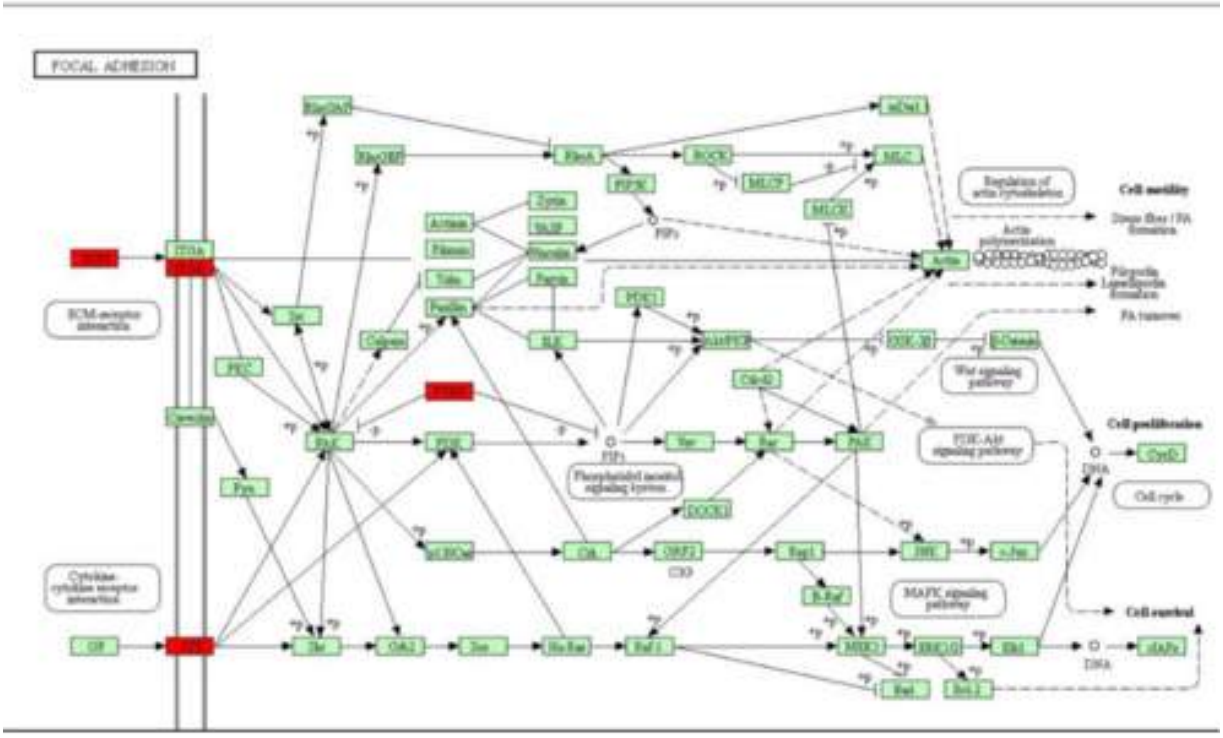


Figure 2. Signal Pathway

Conclusion: This study suggests that the different "gene mutation trajectories" of EGFR exon 19 and 21 mutations are closely related to the genetic heterogeneity of MPLC. Besides that,APOBEC mediated mutations may play an important role in the initial malignant transformation of tumors.

Keywords: signal pathway, Multiple primary lung cancer, EGFR

POSTERS

P2.03-47 DEREGULATION OF A NOVEL CIS-ACTING LNCRNA IN NON-SMALL CELL LUNG CANCER MAY CONTROL HMGA1 EXPRESSION

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Background: Since the discovery of long non-coding RNAs (lncRNAs), they have been increasingly implicated in cancer-associated phenotypes. Recently, some lncRNAs have been shown to regulate the expression of neighbouring protein-coding genes, including oncogenes and tumour suppressor genes. High mobility group A1 (HMGA1) is aberrantly expressed in several aggressive cancer types, including non-small cell lung cancer (NSCLC), where high *HMGA1* expression has been associated with poor overall survival and chemotherapy resistance. While *HMGA1* is known to be deregulated in lung cancer, the mechanisms that mediate its expression remain unknown. These lncRNAs, known as *cis*-acting, may represent undiscovered therapeutic action points in cancer driving pathways. Here we investigate the deregulation of a putative *cis*-acting lncRNA in NSCLC, and it's relationship with the oncogene *HMGA1*. **Method:** LncRNA expression was generated from RNA-sequencing data from 36 microdissected tumour and matched non-malignant tissues. Normalized sequence read counts were used to identify transcripts with significantly deregulated expression (Wilcoxon Signed-Rank Test, BH-p<0.05). Validation was performed in sequencing data obtained from The Cancer Genome Atlas (TCGA). SiRNA-mediated knockdown of lncRNA candidates were performed in a non-malignant epithelial lung cell line (BEAS-2B). Quantitative real-time PCR was used to observe the effects of lncRNA knockdown on the expression of neighbouring protein-coding genes. **Result:** Our analyses identified a lncRNA neighbour to *HMGA1*, *RP11.513I15.6*, to be significantly downregulated in 2 cohorts of LUAD samples. Conversely, we found *HMGA1* expression to be significantly overexpressed in LUAD tumours, and was found to be anticorrelated with *RP11.513I15.6.* Additionally while *RP11.513I15.6* decreased with tumour stage, HMGA1 expression increased with stage. *In vitro* experiments demonstrated siRNA-mediated inhibition of *RP11.513I15.6* in immortalized lung epithelial cells resulted in a significant increase in *HMGA1* expression. **Conclusion:** Our results suggest that *RP11.513I15.6* is a novel *cis*-acting lncRNA that negatively regulates HMGA1, and may contribute mechanistically to the maintenance of lung cancer phenotypes. Further characterization of this oncogene regulatory mechanism may uncover a novel therapeutic intervention point for tumours driven by HMGA1.

Keywords: gene regulation, Non-coding RNA

P2.03-48 TUMOR-DERIVED GRANULOCYTE CHEMOTACTIC PROTEIN 2 COOPERATES WITH PROTEASES TO DRIVE LUNG ADENOCARCINOMA

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Background: Introduction: Lung adenocarcinoma (LADC) commonly arises in the lungs of smokers that are heavily affected by chronic inflammation. Inflammatory signaling from tumor to host cells is critically involved in the pathogenesis of LADC, but the exact mechanisms by which the lung epithelium interacts with the immune system during carcinogenesis are obscure. Objectives: We discovered that murine and human LADC cell lines overexpress the inflammatory and angiogenic CXC chemokine granulocyte chemotactic protein 2 (GCP2, *CXCL6*) compared with normal epithelial cells. GCP2 is processed by immune proteases: neutrophil elastase (NE, *ELANE*), proteinase 3 (PR3, *PRTN3*) and matrix metalloproteinase 9 (MMP9, *MMP9*). We suppose that GCP2 interacts with these proteases to drive LADC and aimed at investigating its function(s). **Method:** GCP2, MMP9 and PR3 expressions were determined by ELISA and immunohistochemistry. Mouse and human microarray data were analyzed using Affymetrix Transcriptome Analysis Console. GCP2 silencing using dedicated shRNA pools (SantaCruz Biotechnology) and NE/PR3 or MMP9 compound knockout mice were used to study GCP2 interaction with immune proteases in LADC progression. **Result:** Murine and human LADC tumors and cell lines overexpress GCP2, MMP9, NE and PR3 at the mRNA and protein levels. GCP2 is sequestered to tumor cells, whereas proteases are produced by tumor-infiltrating immune cells. LADC-secreted GCP2 is incompletely processed and require MMP9, NE or PR3 for full activation and vasoactive effects. Moreover, GCP2-silenced LADC cells injected in mice show a lack in metastasis formation. **Conclusion:** Our results indicate that tumor-originated GCP2 cooperates with immune proteases to drive LADC, providing a paradigm of how the respiratory epithelium coopts the innate immune system during carcinogenesis.

P2.03-49 ROLES OF CENPU IN LUNG ADENOCARCINOMA PROGRESSION AND INVASION

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Background: Centromere protein U (CENPU), a centromere protein mediating kinetochore-microtubule interaction, is critical for proper cell cycle and mitosis. It has been implicated that CENPU promotes tumorigenesis in variant malignancies. However, roles of CENPU in lung adenocarcinoma progression and underlying mechanisms remain to be elucidated. **Method:** CENPU expression in 90 pair lung adenocarcinoma/adjacent normal lung samples was examined with immunohistochemistry (IHC). Then CENPU expression was inhibited with lentiviral-mediated shRNA strategy in human lung adenocarcinoma cell line H1299 to examine the impact of CENPU knockdown for lung adenocarcinoma progression and metastasis. Cell proliferation, colony formation, cell cycle and cell survival were analyzed by Cellomics cell counting method, colonogenesis assay, PI and Annexin V-APC staining respectively while cellular migration and invasion were determined by cell scratch and transwell test. Furthermore, expression of critical factors involved in epithelial-to-mesenchymal transition (EMT) were determined with western blot. **Result:** CENPU expression was significantly increased in lung adenocarcinomas as compared to adjacent normal lung tissues (fold change=8.54, P<0.0001) (Fig. 1A). Functionl analysis revealed that in human lung adenocarcinoma cell line H1299, CENPU knockdown impaired cell proliferation (Fig. 1B), inhibited colony formation ability (Fig. 1C) and induced cell cycle arrest (Fig. 1D). Additionally, cellular migration and invasion was also inhibited by CENPU knockdown (Fig. 1E-F). It is further shown that E-Cadherin was induced while N-Cadherin and vimentin were inhibited by CENPU knockdown (Fig. 1G), indicating that CENPU was important for EMT process and cancer metastasis.

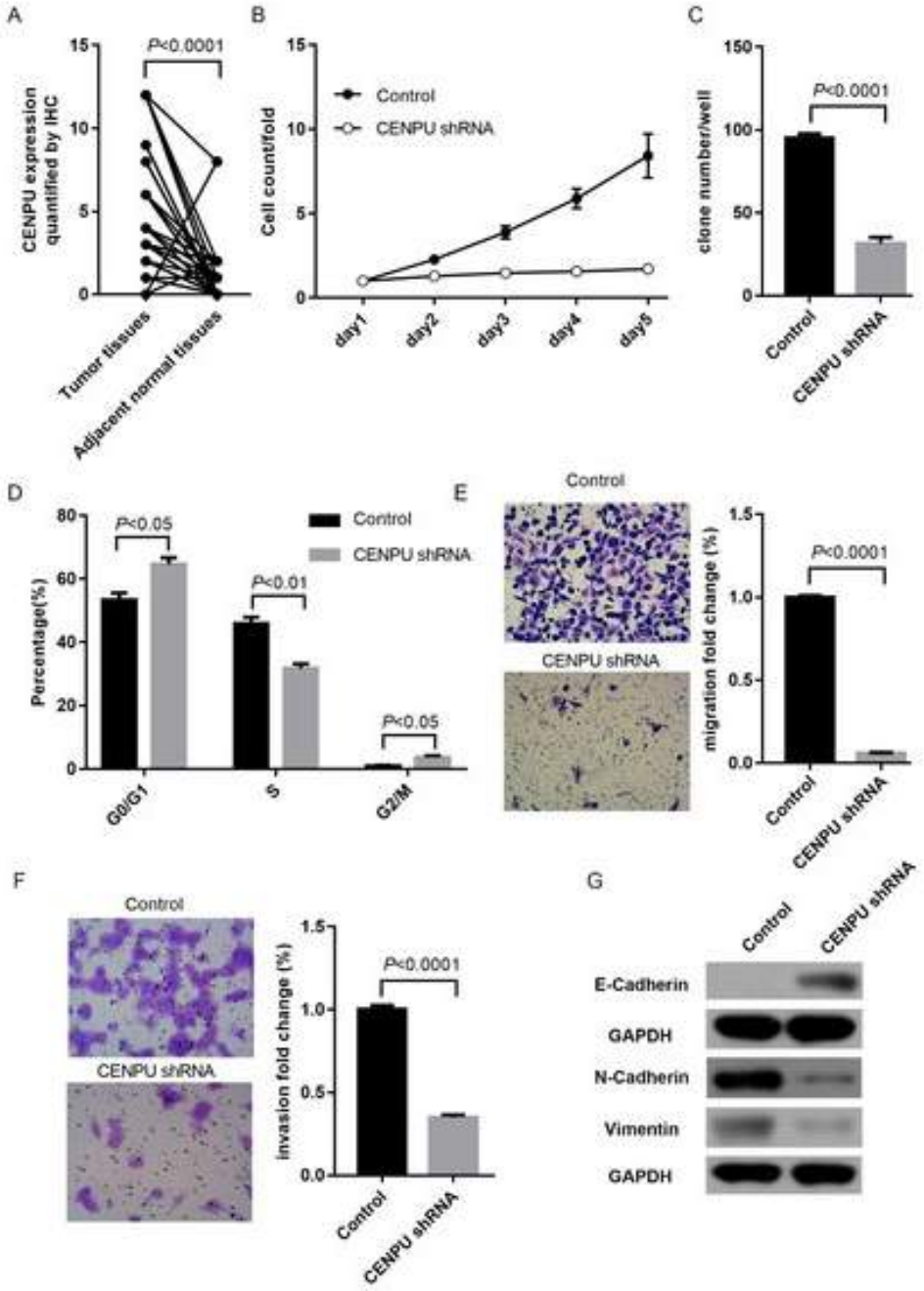

Figure 1 CENPU in lung adenocarcinoma progression and invasion

(A) CENPU status in lung adenocarcinoma and adjacent normal tissues examined through IHC.

(B) Cell proliferation status in H1299 cells with CENPU knockdown.

(C) Colony formation ability in H1299 cells with CENPU knockdown.

(D) Cell cycle status in H1299 cells with CENPU knockdown.

(E) Cell migration ability of H1299 cells with CENPU knockdown examined by transwell assay.

(F) Cell invasion ability of H1299 cells with CENPU knockdown examined by transwell assay (with Matrigel).

Conclusion: It showed that CENPU expression is significantly upregulated lung adenocarcinoma tissue. Functional analysis indicated that CENPU is critical for cell proliferation, survival, migration and metastasis in lung adenocarcinoma cell line H1299. CENPU represents a promising target for lung adenocarcinoma therapy.

Keywords: CENPU, lung adenocarcinoma, Cell invasion

POSTERS

P2.03-50 STROMAL BTK EXPRESSION PREDICTS POOR PROGNOSIS IN NSCLC PATIENTS

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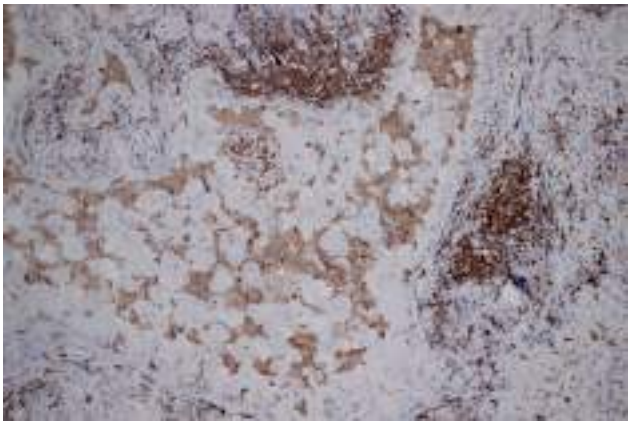
Background: Bruton's tyrosine kinase (BTK) is a kinase that plays a crucial role in B-cell development and widely involves cancer biology. We sought to explore the relationship between BTK expression and NSCLC. **Method:** We firstly used a cohort of 1,249 consecutive NSCLC patients who underwent surgical resection in our center between Apr 2018 and Sep 2018 with fresh tissue to examine the presence of BTK (cohort 1). Another cohort of 681 patients with resected NSCLC between 2009-2014 with stored paraffin sections and survival information were also retrieved to assess the prognostic value of BTK (cohort 2). All samples were stained by IHC for BTK (EPR20445) and PD-L1 (SP142). **Result:** The overall expression rates of BTK expression on tumor and stromal cells were 11.9% and 87.1% respectively in cohort 1, which did not differ across histological types or other clinical features. Both tumoral expression (Chi2=8.84, P<0.01) and stromal expression (Chi2=3.96, P=0.047) of BTK were positively correlated with tumoral PDL1 expression. In cohort 2, we found that the stromal (HR=1.49, P=0.03) but not tumoral (HR=0.74, P=0.20) BTK expression was significantly correlated with poorer prognosis, after adjusting for tumoral PDL1 expression (HR=0.58, P<0.01) and other covariates.



Conclusion: This is the first study showing the presence of BTK expression and its positive correlation with PDL1 expression in NSCLC. Stromal BTK expression predicts poor prognosis in NSCLC patients. This study shed light on the biological effect of BTK-expressing cells and treatment potential of targeting relevant pathways.

Keywords: Brutons tyrosine kinase (BTK), NSCLC, prognosis

P2.03-51 GENE VARIANTS AND EXPRESSIONS OF GALECTIN-3 IS ASSOCIATED WITH NON SMALL CELL LUNG CANCER AND VASCULAR INVASION OF THE TUMOR

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Background: Galectin-3 is a β-galactoside binding protein and known for its deregulation in cancer. In previous studies, correlations between single nucleotide polymorphisms (SNP) and cancer development have been identified in the context of genetic susceptibility to different types of cancer. However, potential phenotypic variations related to galectin-3 SNPs have not yet been evaluated in non-small cell lung cancer (NSCLC). **Method:** In this study, it was aimed to correlate expression levels of gene and protein galectin-3 with genotype and allele distribution of rs4644 and rs4652 SNPs of galectin-3 between NSCLC patients (n=65) and healthy control (n=95) individuals. SNPsrs4644 and rs4652 in galectin-3 were studied using TaqMan Real-Time PCR system. Tissue gene expression levels of galectin-3 for patients was also analysed by Real-Time PCR. Galektin-3 serum levels were measured by ELISA. **Result:** There were no significant differences in genotype and allele distribution of SNPs and galectin-3 gene expression levels between the tumor tissues compared to tumor surrounding tissues (p> 0.05); Mean serum level of galectin-3 was significantly higher in patients (26.05 ± 1.77 ng / ml) than that of controls (11.62 ± 1.30 ng/ml) (p <0.0001). The presence of angiolymphatic invasion was statistically significantly associated with AA genotype (p = 0.04). SNP rs4644 AC/CC genotype was found to be associated with higher serum galectin-3 levels in patients compared to that of controls (p<0.0001) while SNP rs4652 with AA / AC genotype was associated with lower serum galectin-3 levels in controls compared to patients (p<0.0001). Serum galectin-3 level has been shown to be statistically significantly associated with of vascular invasion among patients who had AC genotypes for both SNPs rs4644 and rs4652 (p = 0.03; p = 0.019 respectively). **Conclusion:** Galectin-3 could be defined as a possible biomarker for NSCLC and it plays a role as surrogate marker for vascular invasion in tumors.

Keywords: galectin-3, carcinogenesis, Polymorphism

P2.03-52 CORRELATION BETWEEN INFLAMMATORY MARKERS AND ONCOLOGICAL OUTCOMES IN SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

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Background: Various systemic inflammatory factors have been recognized as predictive markers of oncological outcomes in human malignant diseases. Recently, combined scores of inflammatory factors of preoperative peripheral blood have been reported as more sensitive and powerful markers for predicting oncological and survival outcomes in several solid organ malignancies. In the present study, we evaluate the predictive value of various inflammatory parameters for oncologic outcomes in non-small cell lung cancer patients. **Method:** We retrospectively reviewed patients with non-small cell lung cancer undergoing complete resection with pathological nodal evaluation between January 2016 and February 2019 in our department. We assessed the correlation between inflammatory factors including combined parameters from preoperative peripheral blood and pathologic findings expressing oncological invasiveness such as pT3/T4, solid/micropapillary subtype in adenocarcinoma, pleural invasion, lymph node metastasis, and any sort of M factors. The evaluated inflammation-related scores are follows; C-reactive protein (CRP), neutrophils, lymphocytes, albumin, platelets, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), lymphocyte-CRP ratio (LCR), CRP-albumin ratio (CAR), platelet-albumin ratio (PLR), neutrophil-lymphocyte ratio (NLR), lymphocyte-LDH ratio (LLR), albumin-ALP ratio (AAR) and LDH-albumin ratio (LAR). Preoperative carcinoembryonic antigen (CEA) level and maximum standard uptake value (SUV max) of FDG-PET on primary lesions were also evaluated as known predictive markers of oncological outcome in non-small cell lung cancer. **Result:** A total of 306 patients were enrolled in this study. The following data are clinicopathological findings of this cohort; age: 69.5±9.9, gender: male 212, female 94, histology: squamous 64, adeno 230, adenosquamous 4, other 8, solid/micropapillary in adeno 52, pT3/T4 35, positive pleural invasion 75, positive lymph node metastasis 56, positive M factor 1 (dissemination). Results of significant predictive markers are follows (p<0.05, a stronger marker is placed on left side); CRP, CEA, NLR, SUV for pT3/T4, CRP, albumin, LDH, SUV for positive pleural invasion, CRP, CEA, LAR, albumin for pN positive, respectively. No predictive markers were identified regarding histological subtype in adenocarcinoma. **Conclusion:** In non-small cell lung cancer patients, combined inflammatory scores derived from preoperative peripheral blood could predict limited oncological outcomes. Known predictive markers such as CRP, CEA and SUV max on PET-CT reflected the outcomes more strongly.

Keywords: inflammatory maker, Non-Small Cell Lung Cancer, biomaker

POSTERS

P2.03-53 IMMUNOPROTEASOME AS A POTENTIAL THERAPEUTIC TARGET IN CISPLATIN-RESISTANT SMALL AND NON-SMALL CELL LUNG CANCER

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Background: Cisplatin resistance remains a major problem in the treatment of both non-small (NSCLC) and small cell lung cancer (SCLC). Cisplatin has been reported to cause DNA damages and oxidative stress leading to numerous changes in cell physiology in transcriptional and protein levels. Thus, cisplatin-resistant (CR) cancer cells could alter the proteasome expression to eliminate abnormal proteins induced by cisplatin. Here, we examined the status of proteasomes in CR lung cancer cells and whether proteasomes could be a therapeutic target to overcome cisplatin resistance in lung cancer. **Method:** CR variants were established from three NSCLC cell lines (A549, H1299, and H1975) and two SCLC cell lines (SBC3 and SBC5) in our laboratory. The activity of 20S proteasome core enzyme, the expressions of proteasome subunits, and the sensitivity of immunoproteasome inhibitors, Carfilzomib (CFZ) and PR957, were examined in these CR cells. **Result:** The CR cells showed higher activity of 20S proteasome core enzyme compared with the parent cell counterparts. Quantitative RT-PCR and Western blot analysis revealed that all of the five CR cells had significantly higher expressions of immunoproteasomes, including PSMB8 and PSMB9, while no remarkable changes were observed in the expressions of standard proteasomes. H1299 and SBC3 cells became more sensitive to CFZ and PR957 when acquiring resistance to cisplatin. CFZ induced cell cycle G2/M arrest and apoptosis in CR variants of H1299 and SBC3. **Conclusion:** Immunoproteasome can be a therapeutic target in a portion of cisplatin-resistant both of NSCLC and SCLC.

Keywords: immunoproteasome, proteasome inhibitor, cisplatin

P2.03-54 IMPRINTED GENES PREDICT NON-SMALL CELL LUNG CANCER PROGNOSIS

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Background: Lung cancer (LC) is the leading cause of cancer mortality worldwide, Significant numbers of stage I/II patients after curative surgery present with recurrent and progressive disease. It is critical to identify additional biomarkers to predict prognosis of early stage NSCLC. In carcinogenesis, epigenetic modifications on imprinted genes are changed and lead to biallelic (loss of imprinting, LOI) and multiallelic (copy number variation, CNV) expression. We present here an epigenetic panel involved in NSCLC prognosis. **Method:** Retrospective study of 123 NSCLC cases with known 5-year survival status. Samples from diagnostic bronchoscopies are subjected to in-situ hybridization targeting non-coding regions to show the expression status of imprinted genes. Total expression (TE), LOI and CNV are counted manually. A statistical model is generated based on the expression status of a 3-imprinting gene epigenetic panel (DCN, PEG10 and SNRPN) to classify the cases. The 5-year survival is used as the only standard for good or poor prognosis. **Result:** The NSCLS cases can be classified into 4 groups by epigenetic panel. In group A with high expression of DCN, 91.2% (31/34) had poor prognosis, including 8 stage I, 6 stage II, 9 stage III and 8 stage IV. In group B with low expression of DCN and high expression of both PEG10 and SNRPN, 75% (6/8) had poor prognosis. In group C with low expression of DCN and low expression of either or both of PEG10 and SNRPN, 39.5% (30/76) had poor prognosis. In group D with no expression of DCN, PEG10 or SNRPN, 100% (5/5) had good prognosis, even when metastatic and recurrent cases are found, their average survival is more than 8 years. **Conclusion:** Imprinting Gene epigenetic panel may provide a quantitative assessment of NSCLC prognosis, and complement standard pathologic staging. This explains the poor prognosis of some early stage ca. The prognostic role may help select individual cases for adjuvant therapies. Further studies with expanded epigenetic panel and larger patient sets are planned to refine the classification algorithm, and identify potential predictive biomarkers for specific therapies to advance personalized lung cancer care.

Keyword: Imprinted Genes, Non-small Cell Lung Cancer, Prognosis

P2.03-55 HIGH INTEGRIN α3 EXPRESSION IS ASSOCIATED WITH POOR PROGNOSIS IN PATIENTS WITH NSCLC

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Background: Integrin α3β1 belongs to a family of heterodimeric transmembrane glycoprotein receptors that mediates cell adhesion and cytoskeleton function. We recently showed that integrin α3β1 is a promising novel cancer biomarker and drug target in NSCLC. While the integrin α3 unit (INTA3) mediates the binding to various ligands and substrates, the integrin β1 unit (INTB1) mainly is primarily responsible for the complex biological functions. INTA3 only binds to INTB1 as the binding partner. This study was undertaken to evaluate if INTA3 expression was correlated with clinicopathological parameters and survival in patients with non-small cell lung cancer (NSCLC). **Method:** Tissue microarrays (TMAs) were made from archival formalin-fixed and paraffin-embedded tissue blocks of 161 NSCLC patients, which included 91 adenocarcinoma (LUAD), 46 squamous carcinomas (LUSC), and 24 other histology types. TMA sections were stained for INTA3 expression using anti-integrin α3 antibody (ab131055, dilution 1:100; Abcam) by immunohistochemistry (IHC) stain. Staining intensity was graded as 0 (0-5%, negative), 1+ (6-20%, weak), 2+ (21-50%, moderate), and 3+ (51-100%, strong). Kaplan-Meier curves and log-rank test were used to compare overall survival of IHC score groups. To adjust for covariate imbalance between IHC score groups, propensity-score-weighted Kaplan-Meier curves and weighted Cox models were used. Logistic regression was used to study association between INTA3 expression and patient clinicopathological parameters. **Result:** INTA3 IHC expression was detected in 107/161 (66.5%) of the NSCLC samples. Weak (1+), moderate (2+) and strong (3+) INTA3 expression was detected in 66 (41.0%), 33 (20.5%), and 8 (5.0%) cases, respectively. Kaplan-Meier curves indicated that weak (1+) and strong (3+) INTA3 expression was significantly associated with poor overall survival in NSCLC patients ($p < 0.05$ and $p < 0.001$, respectively). Propensity-score-weighted survival analysis demonstrated that INTA3 IHC expression (1+-3+) was associated with poor prognosis (HR = 1.39, 95% CI: 1.06-1.83, p =0.02) for all NSCLC patients, as well as in subgroups of female patients (HR =1.99, 95% CI: 1.32-3.01, $p < 0.01$), smokers (HR =2.46, 95% CI: 1.66-3.65 $p < 0.01$) and differentiation grade I&II (HR =3.0, 95% CI: 1.91-4.59 $p < 0.01$), but not in LUSC patients (p=0.11), LUAD patients (p=0.07), male patients (p=0.06), non-smokers (p=0.34), differentiation grade III (p=0.98). Logistic regression indicated that high INTA3 expression is associated with no smoke history (OR=2.7, 95% CI:1.3-5.7, p=0.01). **Conclusion:** INTA3 was expressed in the majority of NSCLC by IHC and was associated with poor prognosis. Further study is warranted for targeting integrin α3(β1) in NSCLC.

Keywords: Biomarker, intergin, Non-Small Cell Lung Cancer

P2.03-56 POLYMORPHISM ICAM-1 AND BETA-3 INTEGRIN ARE ASSOCIATED WITH THE DEVELOPMENT OF NON-SMALL CELL LUNG CANCER AND THE PROGNOSTIC ROLE OF ICAM-1

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Background: Lung cancer is widespread cancer in the worldwide. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers. ICAM-1 and β3 integrin have been have been found to be associated with the angiogenesis, tumor growth and metastasis in various tumor types. Our primary aim in this study was to explore gene polymorphisms in ICAM-1 and β3 integrin molecular pathway in NSCLC patients and to clarify whether these values are effective

on the etiopathogenesis and prognosis of the disease. **Method:** Sixty-nine patients with operable (T1-4N0-1M0) NSCLC patients and 120 healthy individuals between January 2012 and June 2018 were included in the study. The tumor samples were taken after resected specimen. Blood samples of the patients were also collected before surgical resection. ICAM-1 and β3 integrin gene polymorphisms were determined by using PCR-RFLP techniques. Also serum ICAM levels were determined by ELISA method. The stages of the tumor were constructed according to 8th staging system. **Result:** There was no statistically significant difference between patient with NSCLC and healthy control groups with regard to β3 Integrin Leu33Pro gene polymorphism(p=0.182). However, in patients with NSCLC, AG genotype frequency and G allele carriers of ICAM K469E variant were found to be higher than the control group and the difference was statistically significant(OR:2,710 95%CI:1,364-5,376; p=0.005). It has been determined that having a G allele increased approximately 2,95 fold the risk of disease and also carrying of AGTC combined genotype increased(OR:2,95 95%CI:1,366-6,373;p=0.049). When patients were evaluated according to tumor stage, serum levels of ICAM-1 gene in early tumor stage was found to be significantly higher than in advanced tumor stage (p=0,013). No significant difference was found between the range of histopathological subtypes and serum ICAM levels (p>0,05). Also, no statistically significant association was found between serum ICAM levels and angiolymphatic invasion (p=0.101, perineural invasion(p=0.054), lymph node metastasis (p=0.585). **Conclusion:** ICAM-1 as an intercellular adhesion molecule seems to play an important role in lung carcinogenesis and it might play a role in the invasiveness of the tumor. However, β-3 integrin was not found to be associated with lung cancer development. The role of ICAM-1 in the genesis of lung cancer as well as immune mechanism should be further investigated.

Keywords: ICAM-1, Beta-3 integrin, Polimorphism

P2.03-57 THE ROLE OF ARL4C IN THE CARCINOGENESIS PROCESS OF LUNG ADENOCARCINOMA

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Background: The aberrant activations of EGF / Ras and Wnt / β-catenin signaling are known to be closely involved in carcinogenesis and malignant transformation of various cancers, but the mechanism in carcinogenesis is unknown in detail. The expression of ADP-ribosylation factor (ARF) -like 4c (Arl4c) is induced by the EGF / Ras and the Wnt / β-catenin signalling, and immunohistochemical analyses of tissue specimens obtained from lung adenocarcinoma patients revealed that Arl4c was not observed in non-tumor regions but was strongly expressed at high frequencies in tumor lesions. In addition, the positivity of Arl4c expression was not correlated with the tumor's T grade or N grade. These findings suggest that this protein may be involved in the process of carcinogenesis of lung adenocarcinoma. In this study, we analyzed the role of Arl4c in the carcinogenesis process of lung adenocarcinoma, using immunohistochemical analyses of tissue specimens, and normal human small airway epithelial cell (SAEC) cancer model *in vitro*. **Method:** Using the specimens resected from patients who performed lung resection, Arl4c expression was immunohistochemically examined in Atypical Adenomatous Hyperplasia (AAH), which is a pre-cancerous stage, and relationships between Arl4c expression and clinicopathological characteristics were analyzed. *In vitro*, to establish an immortalized SAEC, we introduced hTERT, CDK4 and DN-p53 to SAEC (SAEC-Triple) with retroviral vector plasmids. Then, we established cell lines stably expressing Arl4c. Using these cells, we assessed the proliferative capacity in a two-dimensional (2D) plastic dish culture and 3D Matrigel culture. In addition, to assess the cell tumorigenic ability, we performed the 2D clonogenic colony formation assay. **Result:** The expression of Arl4c was observed in 22 of 27 patients (81%) with AAH, while Arl4c-positive cells were never observed in the alveolar epithelium of non-AAH region. No significant difference in clinicopathologic characteristics between Arl4c positive and Arl4c negative groups. *In vitro*, Alr4c were transfected into SAEC-Triple and confirmed the expression of these proteins by the western blotting. In 2D culture, there was no significant difference between the cell proliferation capacity of SAEC-Triple with Arl4c and that of SAEC-Triple with control vector. In contrast, when SAEC-Triple were grown in 3D Matrigel, stable expression of Arl4c was remarkably increased sphere areas. In a 2D clonogenic colony formation assay, the number of colonies was much higher in SAEC-Triple with Arl4c compared to SAEC-Triple with control vector ($P < 0.05$). Consistent with these findings, Phosphorylation of Erk1/2 was significantly increased in SAEC-Triple with Arl4c compared with cells expressing control. **Conclusion:** Arl4c expression in AAH lesion indicated that Arl4c involved in the processes of lung carcinogenesis. Arl4c promotes proliferative capacity by activating Phosphorylation of Erk1/2.

Keywords: Arl4c, carcinogenesis, lung adenocaricnoma

P2.03-58 DOUBLE PRIMARY LUNG CANCER AND BREAST CANCER IS A DISTINCT DISEASE ENTITY

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Background: Double primary lung cancer (LC) and breast cancer (BC) is occasionally observed in clinic. Prior knowledge often attributes increased risks for second primary BC/LC in LC/BC patients to radiation exposure. Our previous study showed that in a 128-patient female Taiwanese double primary LC/BC cohort, 77 (60%) had both cancers diagnosed within 5 years of each other, suggesting the existence of other contributing risk factors. The current study aims to identify characteristics of female double primary LC/BC patients in western-based population. **Method:** The double primary LC/BC cohort was identified from the Vanderbilt BioVU database. Vanderbilt BioVU is a de-identified electronic medical record (EMR)-based biorepository that enables longitudinal EMR study and paired genetic data assessment. **Result:** A total of 65 patients were identified. Among them, 59 (90.8%) were non-Hispanic Caucasians, 5 (7.7%) were African Americans, and one (1.5%) was an Asian. Twelve (18.5%) had their BC and 5 (7.7%) had their LC diagnosed before age 50. Eleven (16.9%) patients were life-long never-smokers, and among them, 4 (36.4%) had their BC and 2 (18.2%) had their LC diagnosed before age 50. Definite disease diagnostic dates were available in 62 patients. Among these, only 18 (29.0%) received radiotherapy for either LC or BC and had two cancers diagnosed beyond 5 years from each other. Among the 50 patients with available data for BC molecular subtypes, 38 (76.0%) were ER/PR-positive and HER2-negative, 4 (8.0%) were ER/PR-positive and HER2-positive, and 6 (12.0%) were triple-negative. All of the HER2-positive patients were never-smokers; one of them had bilateral BC, another had bilateral LC, and the rest two had strong LC family history. Forty-eight (73.9%) patients in this cohort had family cancer history within their first to third-degree relatives. There were BC in 28 (43.1%), LC in 20 (30.8%), colon cancer in 9 (13.9%), hematological malignancies in 9 (13.9%), gynecological cancers in 6 (9.2%), prostate cancer in 5 (7.7%), pancreatic cancer in 4 (6.2%), gastric cancer in 3 (4.7%), esophageal cancer in 2 (3.1%), glioblastoma multiforme in 2 (3.1%) and kidney cancer in 2 (3.1%) patients, respectively. **Conclusion:** Our data showed that female double primary LC/BC is a distinct disease entity, of which hereditary genetic factors may play an important role. In line with our previous study results, radiation exposure may not be the major risk factor for double primary LC/BC. Genomic studies will be of particular importance to unravel the mystery of this unique disease entity.

Keywords: Double Primary, Lung cancer, Breast cancer

P2.03-59 THE ROLE OF RADIATION DOSE-DEPENDENT LIPID METABOLISM REPROGRAMMING ON RADIATION SURVIVAL/RESISTANCE IN LUNG CANCER CELLS

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Background: Radiotherapy plays a more and more important role in the management of lung cancer. However, radioresistance still limits the long-term control of tumors. Exploration of the dynamic changes of metabolic reprogramming in surviving/resistant lung cancer cells exposed to increased doses of radiation is helpful to elucidate the metabolic mechanism of radiation resistance in lung cancer cells, to develop new targets for the clinical intervention and the early detection of radiation resistance. **Method:** Lung cancer cells A549, H520 and H460 were treated *in vitro* with fractionated radiation (2 Gy) to a cumulative total dose of 40Gy, 60Gy or 80Gy.

Cellular radiation sensitivity was verified by colony survival assay and comet experiments. Cell proliferation was determined by EdU assay. Transcriptome sequencing and metabolomic analysis were performed to identify differentially expressed genes and metabolites in radiation-resistant cells and their parental cells. Oil Red O staining was used to detect lipid droplet content. RT-PCR and WB were used to detect the expression of genes related to lipid metabolism. **Result:** Lung cancer cell sublines that had been exposed to 20, 30 or 40 fractions of 2Gy had a significant increase in radioresistance as compared with their parental cells. Furthermore, this radioresistance of cells increased with the increase of previous radiation dose exposure. We found that lipid droplet deposition and the expression of lipid metabolism genes, such as fatty acid oxidation-related genes and glycerol metabolism-related genes, showed an increasing trend with previous radiation dose in surviving/resistant lung cancer cells exposed to radiation. Metabolomic analysis revealed that lipid metabolites such as glycerol and oxaloacetic acid also increased significantly. Inhibition of carnitine palmitoyltransferase 1A (CPT1A) by Etomoxir, a fatty acid oxidation inhibitor, significantly enhanced the radiosensitivity and decreased the DNA repair ability of various surviving/resistant lung cancer cells exposed to radiation. **Conclusion:** The surviving/resistant lung cancer cells generated by sequential irradiation provide models for future investigations of the dose-dependent mechanisms of radioresistance in a preclinical setting. Radiation dose-dependent lipid metabolism reprogramming may contribute to radiation survival/resistance in lung cancer cells. Support: 81572279, 2016J004, LC2016PY016, 2018CR033.

Keywords: Radioresistance, lipid metabolism reprogramming, CPT1A

P2.04 IMMUNO-ONCOLOGY
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.04-01 CHANGES OF BCR REPERTOIRE ARE PREDICTIVE BIOMARKER FOR THE EFFICACY OF IMMUNE CHECKPOINT INHIBITOR IN NSCLC

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Background: Clonal diversity of T cell receptor (TCR) and/or B cell receptor (BCR) repertoires might play a major role in antitumor immunity in cancer patients. Assessment of TCR and BCR repertoires might enable us to predict the efficacy of immune checkpoint inhibitors (ICI). **Method:** The study population comprised 30 patients with non-small-cell lung cancer (NSCLC), who started treatment with nivolumab (3mg/kg, every two weeks) or pembrolizumab (200mg, every three weeks) between February 2016 and August 2017. Patient blood samples were collected before and four to six weeks after the initiation of treatment. TCR and BCR chain sequences were determined by using the unbiased gene amplification method with Adaptor-Ligation PCR. The diversity of TCR and BCR repertoires was evaluated with inverse Shannon-Weaver index (iSWI). **Result:** We compared the iSWI between before and after treatment. The fold changes of iSWI in BCR repertoire after treatment in patients with PR were significantly higher than those with SD or PD. In contrast, the fold changes of iSWI in TCR repertoire after treatment were not associated with tumor responses. When the cut-off value of fold change of iSWI in BCR repertoire after treatment was determined as 0.85, 25 (83%) and 5 (17%) patients were considered as high and low fold change group, respectively. Progression free survival in the high fold change group was significantly longer compared with that in the low fold change group (182 vs 49 days; 95% confidence interval (CI);99-N.R. vs 31-168 days, respectively; P=0.01). **Conclusion:** Our findings suggest that reduced repertoire diversity in BCR, but not in TCR, might be associated with better clinical outcomes in advanced NSCLC patients treated with ICI. Assessment of the changes of BCR repertoire after treatment might be useful for predicting the efficacy of ICI. The present results require confirmation in a large-scale prospective study.

Keywords: pd-1, Biomarker, NSCLC

P2.04-02 EFFECT OF CHEMOTHERAPY, CHEMOIMMUNOTHERAPY, AND IMMUNOTHERAPY ON PARAMETERS OF T CELL EXHAUSTION IN METASTATIC NON-SMALL CELL LUNG CANCER

J. Bauml[1], D. Yoon[2], P. Yan[2], S. Katz[3], S. Jeffries[2], C. Davis[4], C. Aggarwal[1], R. Cohen[1], M. Marmarelis[1], A. Singh[1], C. Ciunci[1], E. Wherry[1], S. Albelda[1], C. Langer[1], A. Huang[1]

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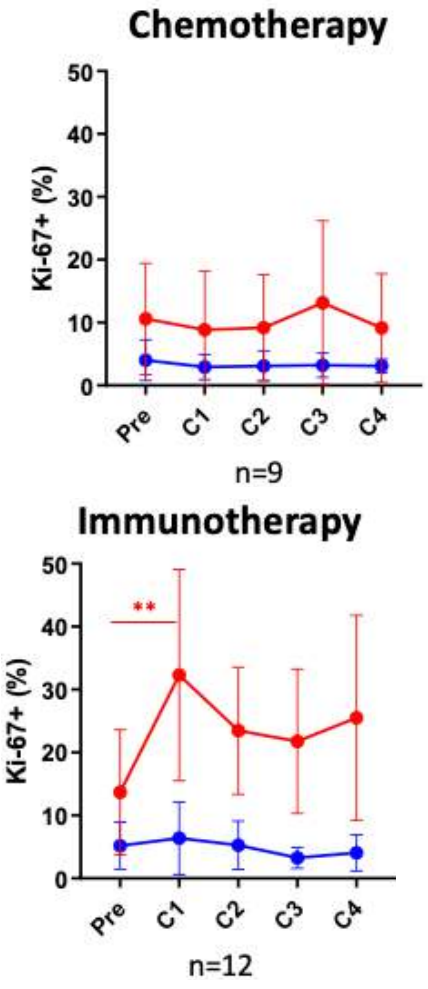
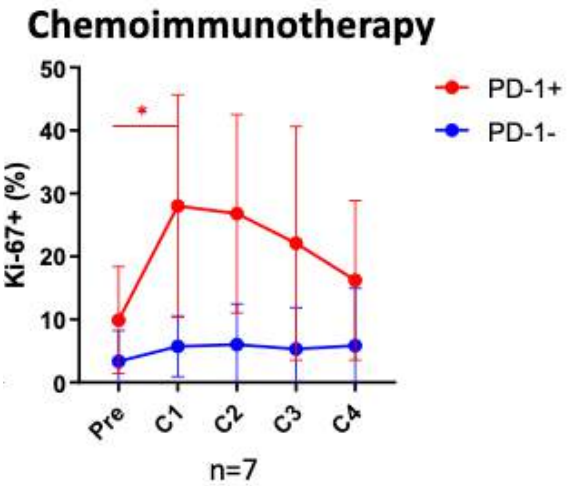
Background: The pharmacodynamic immune response to anti-PD-1 immunotherapy can be tracked in the peripheral blood of cancer patients and is associated with response to therapy. However, it is unclear how chemotherapy and chemoimmunotherapy affect T cell activity. Given the established role of these treatments in Non-Small Cell Lung Cancer (NSCLC), we sought to compare the impact of chemotherapy, chemoimmunotherapy, and immunotherapy on T cell immunity. **Method:** We prospectively collected blood samples in pts beginning chemotherapy, chemoimmunotherapy, or immunotherapy for metastatic NSCLC at baseline and with each cycle. Peripheral blood mononuclear cells were stained for immune markers and analyzed using 26 parameter flow cytometry. Immune response was characterized by increased expression of Ki67 on PD-1 expressing CD8 T cells. Statistical analysis was performed using paired t-test or Wilcoxon matched pairs analysis based on normality of data. All patients had CT scans with full RECIST 1.1 and tumor volume measurements. **Result:** We analyzed 28 pts (63% female, median age = 65.5). 9 pts received chemotherapy, 12 pts immunotherapy, and 7 pts chemoimmunotherapy. Both immunotherapy (p = 0.001) and chemoimmunotherapy (p=0.016) resulted in an immune response that peaked at 3 weeks compared to baseline (Figure). No immune response was identified with chemotherapy (p=0.734). Immune response was detected in exhausted T cells (PD1+CD39+ CD8) for both immunotherapy (p =0.007) and chemoimmunotherapy (p =0.031). In addition, chemoimmunotherapy induced activation of CD27+CCR7+ memory CD8 T cells (p=0.0313), not seen with immunotherapy (p= 0.871).





Conclusion: Chemoimmunotherapy and immunotherapy, but not chemotherapy, induced a significant immune response in the peripheral blood, peaking at 3 weeks. While immunotherapy and chemoimmunotherapy both targeted an exhausted population, chemoimmunotherapy induced an immune response in exhausted and memory T cells. We have collected more samples, and at time of the WCLC will present these data, as well as correlation with RECIST responses.

Keywords: T Cell Exhaustion, Immunotherapy biomarker, Chemoimmunotherapy biomarker

P2.04-03 NIVOLUMAB OUTCOMES IN OCTOGENARIAN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER IN FRENCH REAL-WORLD SETTING

J.-B. Assié[1], F.-E. Cotté[2], M. Giaj Levra[3], C. Calvet[2], R. Jolivel[4], B. Jouaneton[4], A.-F. Gaudin[2], V. Grumberg[5], C. Chouaid[1], R. Corre[6]

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Background: Around 10% of patients newly diagnosed non-small cell lung cancer (NSCLC) in France are octogenarian. Knowledge about nivolumab outcomes in such specific population is still limited and real-world data represent a valuable source of information. The aim of this study was to examine use and outcomes of nivolumab in elderly patients aged ≥80 years. **Method:** Based on the National hospitals database (PMSI), we built a retrospective cohort of all NSCLC patients (ICD code: C34*) initiating nivolumab in 2015-2016 in second- or later-line setting and followed them until Dec 2017. Information on patients' baseline characteristics (demographics, comorbidities, treatment history) was retrieved for elderly (≥80 years) and non-elderly (<80 years), and time to treatment discontinuation (TTD) with nivolumab and overall survival (OS) were estimated with Kaplan-Meier methodology. **Result:** Among 10,452 NSCLC patients initiating nivolumab during the inclusion period, 514 (4.9%) were 80 years or over. Mean age at baseline was 82.5 years (±2.4) in elderly and 62.8 years (±8.8) in non-elderly. Compared to non-elderly, patients were more frequently men in elderly group (p<0.001) and had more frequently prevalent hypertension and diabetes (p<0.001). Cerebral metastasis, renal failure, COPD, pulmonary insufficiency and other pulmonary chronic diseases were statistically less frequent in the elderly group (p<0.001). TTD curves showed identical median of treatment duration between both groups (2.8 months). Median OS were found similar between elderly and non-elderly patients (11.5 vs 11.6 months) and, long-term survivals were also comparable with 1-year and 2-year OS rates. Characteristics and outcomes are presented in the table.

Characteristics and outcomes	< 80 years (N=9938)	≥ 80 years (N=514)	p-value
Demographics			
Gender – Male	7019 (70.6%)	401 (78%)	< 0.001
Mean age (±SD)	62.8 y (±8.8)	82.5 y (±2.4)	< 0.001
Median age (Q1-Q3)	64 y (57-69)	82 y (81-84)	< 0.001
Comorbidities			
Hypertension	1844 (18.6%)	142 (27.6%)	< 0.001
Diabetes	871 (8.8%)	63 (12.3%)	< 0.001
Renal failure	460 (4.6 %)	19 (3.7%)	< 0.001
Chronic obstructive pulmonary disease	1298 (13.1%)	50 (9.7%)	< 0.001
Pulmonary insufficiency	149 (1.5%)	4 (0.8%)	< 0.001
Other chronic pulmonary diseases	870 (8.8%)	33 (6.4%)	< 0.001
Cerebral metastasis	1771 (17.8%)	29 (5.6%)	< 0.001
Lung cancer management care			
Diagnosis to nivolumab initiation - Median (Q1–Q3)	12.4 mo (6.7–24.0)	14.2 mo (7.9–29.9)	0.002
Nivolumab TTD - Median (Q1–Q3)	2.8 mo (1.4–6.7)	2.8 mo (1.5–6.5)	N.S.
Nivolumab discontinuation	9120 (91.8%)	473 (92.0%)	N.S.
Subsequent systemic treatment	4908 (53.8%)	210 (44.4%)	< 0.001
Overall survival (OS)			
Median OS (Q1 –Q3)	11.6 mo (4.1-26.2)	11.5 mo (5.0-25.2)	N.S.
1-year OS rate	48.8%	47.5%	N.S.
2-year OS rate	27.3%	25.8%	N.S.
N.S.: non significant ; TTD: time to discontinuation			

Conclusion: A small percentage of patients initiating nivolumab during the study period were aged 80 years or over (<5%). Elderly profile suggests a cautious selection by clinicians, which may also explain similar outcomes than ones in the non-elderly population.

POSTERS

P2.04-04 CITESEQ CHARACTERIZATION IN EARLY STAGE NSCLC PATIENTS IDENTIFIES DISTINCT PATTERNS OF IMMUNE INFILTRATE

A. Leader[1], B. Maier[1], J. Grout[1], C. Chang[1], L. Walker[1], M. Davila[1], A. Lanksy[1], T. Marron[1], R. Flores[1], M.B. Beasley[1], H. Salmon[1], A. Rahman[1], E. Kenigsberg[1], M. Merad[2]

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Background: The success of immunotherapy in late-stage lung cancer patients, together with the need for novel therapies for early-stage disease, mandates an increased understanding of the immune infiltrate in early-stage lesions. Recent advances in sequencing-based single-cell technologies have enabled an unprecedented degree of resolution in the phenotypic characterization of patient tissues. **Method:** Tumor and non-involved lung resection specimens were acquired from 23 early-stage NSCLC patients. Immune cells were isolated and analyzed by single-cell RNAseq (scRNAseq) using the 10X Chromium platform. Resulting expression signatures were clustered using an in-house pipeline. To validate populations and elucidate surface marker staining patterns for transcriptionally-defined cell clusters, we used cellular indexing of transcriptomes and epitopes by sequencing (CITEseq)—using oligonucleotide-conjugated antibodies to simultaneously measure expression of over 50 surface proteins along with transcriptomes of single cells—to analyze tumors from 8 additional patients. To identify T cell phenotypes that were differentially present and clonally expanded within tumor compared to non-involved lung, we paired scRNAseq with T cell receptor repertoire profiling in 3 patients. Finally, to validate the transcriptional phenotypes we detected and to extend our dataset, we incorporated 8 patients from a public dataset, totaling 39 patients included in the study. Immune signatures were correlated with presence of actionable mutations, smoking history, stage, and histology. **Result:** Using these single cell analyses, all major immune cell lineages were identified within tumors, including multiple distinct myeloid and lymphoid subsets, which notably were phenotypically distinct from those isolated from uninvolved lung tissue. Existing databases of ligand-receptor pairs were leveraged to construct an interactome, implicating specific axes of cell-cell communication in driving changes common to tumors. As we hypothesized, correlative analyses across tumor samples revealed a cellular module marked by exhausted T cells, plasma cells, mature dendritic cells, and monocyte-derived macrophages that was enriched in patients with significant smoking histories and *EGFR*^{WT} disease. **Conclusion:** These findings indicate that strong immune differences exist between treatment-naïve lesions, and that these differences stratify with smoking history and smoking-related driver mutations. Given existing literature indicating that positive smoking history confers improved response to immune checkpoint blockade, our data suggests that this disparity may be mediated by set differences in treatment-naïve immune microenvironments. We will now apply this analysis pipeline to tumors treated in the neoadjuvant setting in an ongoing trial (submitted to WCLC in abstract form).

Keywords: NSCLC, immune microenvironment, single cell

P2.04-05 A RETROSPECTIVE EVALUATION OF PD-L1 EXPRESSION HETEROGENEITY ON PRIMARY NON-SMALL CELL LUNG CANCER AND METASTATIC LYMPH NODES (REPLICA)

A. Bille[1], D. Nonaka[2], P. Taniere[3], E. Willis[4], A. Douiri[5], C. Flach[5], D. Curinga[6], S. Velamuri[6], E. Karapanagiotou[4]

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Background: Immunotherapies have changed the treatment landscape in lung cancer. Programmed death ligand (PD-L1) protein which is defined as membranous PD-L1 expression on tumour cells regardless of staining intensity represents a reliable biomarker. The heterogeneity of PD-L1 expression in different sites of disease is unknown; this may have implications on biopsy, staging and potentially treatment choice. The primary objective of this study is to evaluate the relationship between PD-L1 expression in the primary site (lung) and metastatic lymph node LNs N1 and/or N2, in NSCLC. **Method:** Paired samples (lung tumour and hilar/mediastinal LNs) from 300 patients who underwent lung resection and lymphadenectomy for NSCLC, between January 2013 and October 2018, have been collected and analysed for PD-L1 immunohistochemistry expression using the 22C3 pharmDx Agilent assay. PD-L1 stained slides have been reviewed by two pathologists independently, using Tumour Proportion Score in the categories of <1%, 1-49% and >=50%. The agreement between the pathologists was assessed using Kappa statistic, while cross tabulation was used to compare PD-L1 expression and assess association between the primary tumour and involved LNs. **Result:** Of the 300 paired samples 285 have been assessed by pathologist 1 and 300 by pathologist 2. The median age of the patients is 69; 55% were males, 92% had a positive smoking history and 65% had an adenocarcinoma; 50% had hilar involvement only. There was moderate agreement between the two pathologists in PD-L1 assessment in both primary tumour [k=0.40 (95%CI 0.34-0.47)] and LNs [k=0.51(95%CI 0.47-0.59)]. Pathologist 1 and 2 reported 80% and 81% overall agreement between PD-L1 expression classification in the primary tumour and involved LNs respectively. When the primary tumour showed no PD-L1 expression, both pathologists reported no PD-L1 expression in 95% of the paired LNs. When the primary tumour expressed PD-L1 >=50%, pathologist 1 reported 30% of involved LNs showed <1% and 30% showed 1-49% staining, whilst pathologist 2 reported 4 % of involved LN showed PD-L1 <1% and 39% showed 1-49% PD-L1 staining. **Conclusion:** The majority of cases show similar PD-L1 expression between the primary tumour and involved LNs while heterogeneity is present in 20% of cases. Where the PD-L1staining was >=50 in the primary tumour, the majority of involved LNs showed only 1-49% or <1% for PD-L1 expression. These findings may have implications on site of biopsy and management.

Keywords: PD-L1 heterogeneity, non-small cell lung cancer, immunotherapy

P2.04-06 BLOOD-BASED MULTIPLEX KINASE ACTIVITY PROFILING AS A PREDICTIVE MARKER FOR CLINICAL RESPONSE TO CHECKPOINT BLOCKADE IN ADVANCED NSCLC

D. Hurkmans[1], E. Verdegaal[2], R. De Wijn[3], S. Koolen[1], C. Lamers[1], D. Van Den Heuvel[3], J. Groten[3], R. Debets[1], E. Kapiteijn[2], R. Mathijssen[1], S. Van Der Burg[2], J. Aerts[1]

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Background: Only a minority of non-small-cell lung cancer (NSCLC) patients benefit from treatment with immune checkpoint inhibitors (ICIs), therefore, there is an urgent need for response prediction. Previously, the potential of using tyrosine kinase activity profiling of baseline peripheral blood mononuclear cells (PBMC) was demonstrated in an analysis with ICI treated advanced melanoma patients [1]. Here, we apply this methodology to evaluate the predictive value for response to ICIs in NSCLC. **Method:** 59 ICI naïve advanced NSCLC patients treated with PD-1 blockade were included in this exploratory analysis of the prospective immuno-monitoring study (MULTOMAB; NTR7015). PBMC were isolated from patient blood samples obtained prior to treatment with ICIs. Kinase phosphorylation signatures of PBMC lysates were measured using a micro-array, comprising of 144 different peptides derived from sites that are substrates for protein tyrosine kinases. Correlation of the profiles with progression free survival (PFS) and overall survival (OS) was analyzed using univariate cox-regression. Predictive multivariate (GLMnet) analysis was performed by binary survival grouping of patients with a cut-off at 140 days for PFS and 365 days for OS. The predictive performance of the models was estimated using cross validation. Multiplex flow cytometry, enumerating 18 immune cell subsets and assessing expression for 28 T cell markers, was performed for a selection of patients to gain additional insight in the immune profile [2]. **Result:** Univariate Cox regression showed significant correlation of phosphorylation signal with PFS for 7 peptides ($p < 0.01$, False Discovery Rate [FDR] = 10%), and with OS for 34 peptides ($p < 0.01$, FDR = 2%). Evaluation of the predictive value of GLMnet models resulted in estimates for the Correct Classification rate (CCR) of 67-70% for PFS and 67-73% for OS. When the cross validated predictions of the models were used to categorize the patients in a *predicted-high-risk* and a *predicted-low-risk group*, this resulted in a significant difference in survival between these groups. The *predicted-low-risk group* displayed significant better median PFS and OS than the *predicted-high-risk group* ([246 vs. 56 days; HR

2.3, 95%CI 1.2-4.7, p=0.02] and [488 vs. 171 days; HR 2.7, 95%CI 1.1-6.6, p=0.03], respectively). **Conclusion:** Similar to melanoma, kinase activity profiles of baseline PBMC samples of advanced NSCLC patients can predict the response to PD-1 blockade. This assay may serve as a predictive biomarker for response to anti-PD-1 therapy. Involvement of immune receptor kinases is being investigated. An independent validation study is underway.

Keywords: NSCLC, kinase activity, immune checkpoint inhibitor

P2.04-07 SURGICAL RESECTION OF ADVANCED LUNG CANCER AFTER A RESPONSE TO EGFR-TKI AND/OR IMMUNOTHERAPY: A SINGLE INSTITUTION EXPERIENCE

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European Institute of Oncology, Milan/Italy

Background: The usefulness of residual tumor resection after epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) or immunotherapy treatment remains unclear. We describe a single institutional case-series of patients who underwent residual tumor resection after responding to EGFR-TKIs and/or immunotherapy for advanced non-small cell lung cancer (NSCLC) **Method:** Using a prospective database, we reviewed clinical, surgical, pathological, and prognostic data of 15 patients who underwent surgical resection of advanced lung cancer after a response to EGFR-TKI and/or immunotherapy between January 2016 and March 2019. **Result:** There were 10 males and 5 females, all smokers; median age of 58 years (range, 43-72). All patients had T4N2 NSCLC. Five patients received only EGFR-TKI, 6 received EGFR-TKI and immunotherapy, and 4 only immunotherapy. Median time from beginning therapy to surgery was 17 months (range, 6-23). Surgery included 13 lobectomies, one right upper sleeve, and one right pneumonectomy. Lymph node dissection and vascular and bronchial isolation was extremely difficult. Intraoperative morbidity and mortality was nil. Postoperative morbidity was 20% (n=3) and included one bronchopleural fistula, one prolonged air leaks, one atrial fibrillation. Median hospital stay was 6 days (range, 5-15). Pathology showed 6 complete responses (40.0%) (2 after immunotherapy, 4 after EGFR-TKI and immunotherapy) and 9partial responses (60%). Moreover, the area of tumor clearance was characterized by (i) immune activation-dense tumor infiltrating lymphocytes; (ii) massive tumor cell death-cholesterol clefts; and (iii) tissue repair-neovascularization and proliferative fibrosis (each feature enriched in major pathologic responders versus nonresponders, $p<0.05$). With a mean follow-up of 23 months, all patients are alive. **Conclusion:** The timing and validity of a salvage surgery for residual lesions remain unclear when TKIs and/or immunotherapy are offered as first-line therapy to patients with advanced NSCLC. In our cases, surgery was performed with acceptable morbidity. Surgical resection of the residual tumor might contribute to good local control.

Keywords: Advanced lung cancer, Target therapy, Immunotherapy

P2.04-08 PRELIMINARY EXTERNAL VALIDATION OF THE CLINICAL DEFINITIONS OF RESISTANCE TO IMMUNE CHECKPOINT INHIBITORS IN NON-SMALL CELL LUNG CANCER

E. Gillaspie[1], J. Whisenant[2], L.-C. Huang[1], M. Wharton[1], Y. Shyr[1], L. Horn[2]

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Background: Immune checkpoint inhibitors (ICIs) have become an important component of treatment for patients with advanced stage non-small cell lung cancer (NSCLC). Unfortunately, the majority of patients on ICIs will eventually progress. Based on the results from a meta-analysis review of the current ICI literature, Gillaspie et al developed a clinical radiographic response criterion to classify patients as having innate, acquired resistance or durable response to ICIs. The objective of this study was to validate this categorization using prospectively collected clinical data. **Method:** The study population consisted of Stage IIIB and IV, biopsy-proven NSCLC patients from a single institution treated on or off a clinical trial with single agent ICIs in the first, second line or beyond. De-identified tumor data, stage and treatment data long with response to ICIs were collected prospectively into a database. Patients were censored at last date of follow-up if no progression had occurred. Progression-Free survival (PFS) curves and rates were estimated using the Kaplan-Meier method and then compared to the categorization established by the meta-analysis. **Result:** From April 2012 to January 2018, 231 patients met criteria for inclusion and analysis. Median age was 65 years, 61% were male and 92% white. Forty-three (18.6%) received ICI in the first line, while the remaining 188 were treated in the second line or above. Analogous to the meta-analysis, our single center data demonstrated three distinct sub-populations of response. PFS curve slopes were evaluated and compared between the proposed classification and our single center experience (Table 1). The slopes of the curves are similar for the Innate, Adaptive or Acquired Resistance and Durable Response categories established in the meta-analysis. Our single-center experience resulted in a slightly steeper slope in the innate response category compared to the clinical trial literature. This may be explained by our cohort including patients who are treated in the third line or beyond whereas most of the meta-analysis trials restricted populations to either first or second line only. A steeper PFS curve would be expected in a more heavily treated population.

Table 1

	PFS Slope Meta-Analysis	PFS Slope Validation
Innate Resistance	12.9	14.0
Aquired Resistance	3.8	3.4
Durable Response	1.2	1.1

Conclusion: This single center assessment of the proposed classification for resistance to immune checkpoint inhibitors in non-small cell lung cancer confirms the three distinct subgroups of response based on a comparison of the PFS curves. A formal statistical validation will be performed and presented. Future studies are planned to include prospectively collected data from additional comprehensive cancer centers within the validation cohort.

Keywords: Immunotherapy, classification of response

P2.04-09 IMMUNE-RELATED ADVERSE EVENTS IN ADVANCED NON-SQUAMOUS NSCLC PATIENTS TREATED WITH UPFRONT CHECKPOINT INHIBITORS COMBINATION

A. Sultan[1], K. Thein[1], S. Swarup[1], N. Jahan[1], A. Tun[2], S. Meda[1], M. Arevalo[1], T. Naing[3], T. Htut[4], N. D'Cunha[1], S. Awasthi[1], S. Rehman[1], L. Tijani[1], F. Hardwicke[1]

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Background: Immune-related adverse events (IRAE) are a unique set of adverse events caused by checkpoint inhibitors due to enhanced activation of the immune system. IRAEs can virtually affect any organ system and have been responsible for significant morbidity, treatment delay, treatment discontinuation, and even death. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of IRAEs when checkpoint inhibitors were utilized as first-line in combination with chemotherapies in non-squamous non-small cell lung cancer (NSCLC) patients. **Method:** We systematically conducted a literature search using PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019. Phase 3 RCTs that mention IRAEs as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q -statistic. Random effects model was applied. **Result:** 2785 patients with advanced non-squamous NSCLC from 5 RCTs (Keynote – 021,189, IMpower – 130, 132 and 150) were eligible. The study arm used standard chemotherapy regimens in combination with pembrolizumab or atezolizumab while control arm utilized only standard chemotherapy regimens. The randomization ratio was 2:1 in IMpower-130 and Keynote-189 studies and 1:1 in other studies. The RR of all-grade side effects were as follows: hypothyroidism, 3.82 (95% CI: 2.14 – 6.80, p < 0.0001); hyperthyroidism, 2.58 (95% CI: 1.32– 5.04; p = 0.005); pneumonitis, 2.62 (95% CI: 1.58– 4.32; p = 0.0002); hepatitis, 3.75 (95% CI: 1.23 – 11.50, p = 0.02); colitis, 4.82 (95% CI: 1.67– 13.90; p = 0.004); and pancreatitis, 2.35 (95% CI: 0.75–7.41; p =0.14). The RR of high-grade side effects were as follows: hypothyroidism, 2.93 (95% CI: 0.62 – 13.74, p = 0.17); hyperthyroidism, 2.32 (95% CI: 0.37– 14.71; p

= 0.37); pneumonitis, 1.65 (95% CI: 0.80– 3.41; p = 0.18); hepatitis, 4.14 (95% CI: 1.05 – 16.33, p = 0.04); colitis, 3.31 (95% CI: 1.02– 10.77; p = 0.05); and pancreatitis, 1.44 (95% CI: 0.29– 7.13; p = 0.65). **Conclusion:** Patients on combined chemoimmunotherapy experienced a significant increase in all grades of hepatitis and colitis with a relative risk of 4.14 for grade 3 and 4 hepatitis. They also contributed to all-grade hypothyroidism, hyperthyroidism and pneumonitis. These toxicities have significant impact on patients' quality of life, ultimately affecting patients' compliance. A timely intervention with proper supportive care is necessary.

Keyword: Check point inhibitors toxicities

P2.04-10 BIOMARKERS OF PATHOLOGICAL RESPONSE ON NEO-ADJUVANT CHEMO-IMMUNOTHERAPY TREATMENT FOR RESECTABLE STAGE IIIA NSCLC PATIENTS

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Background: PD1/PDL1 treatments have become the main therapy in advanced stages of NSCLC due to its significant increase in overall survival (OS), but recently, combination with chemotherapy in locally advanced stages is showing promising results. Many studies have described peripheral blood immune cells parameters as biomarkers of response to immunotherapy. In our study, we described the effect of neo-adjuvant chemo-immunotherapy treatment in Complete Blood Count (CBC) and Peripheral Blood Mononuclear Cells (PBMCs) phenotype, as well as, the association of these parameters with the degree of pathological response. **Method:** Immune cell populations of 46 resectable stage IIIA NSCLC patients treated with neo-adjuvant chemo-immunotherapy from NADIM clinical trial were analysed. Samples were extracted before initiating the neo-adjuvant treatment with nivolumab plus carboplatin and at the third cycle before patients underwent surgery. We classified patients in 3 subgroups of pathological response assessed in the resection specimen: complete response (pCR), major response (<10% viable tumour) and incomplete response (>10% viable tumour, pIR). Wilcoxon and Mann-Whitney U statistic test were used to evaluate differences between pre and post treatment and between pathological responses groups respectively. **Result:** From 46 patients, 5 patients did not undergo surgery, so they were excluded from the analysis. Absolute numbers of Leucocytes, Eosinophil, Monocytes, Neutrophils, Haemoglobin and Platelets from hemograms were significantly reduced after neo-adjuvant treatment. However, no changes were observed for Lymphocytes, Basophils, LDH levels or the Lung Immune Prognostic Index (LIPI). Additionally, post-treatment Neutrophil-to-Lymphocyte (NLR), Myeloid-to-Lymphoid lineage (M:L) and Platelets-to-Lymphocytes (PLR) ratios were decreased. Remarkably, from all the CBC absolute numbers and ratios, only PLR variation showed differences between pCR and pIR. On the other hand, percentages of PBMCs (T cells, B cells, NK cells and macrophages) did not vary after neo-adjuvant treatment, however activation of CD4 T cells and NK cells as well as PD-1 receptor expression on immune cells were downregulated after neo-adjuvant chemo-immunotherapy. Interestingly, these variations correlate with pCR. **Conclusion:** In our study, PLR, PD-1 expression, CD4 T cells and NK cells activation are predictive biomarkers of response to treatment. Thus, a higher decrease on PLR post neo-adjuvant treatment is associated to pCR. Moreover, a decrease of PD-1 expression in CD4, CD8 and NK cells, as well as, a reduction of CD4 T cells and NK cells activation after neo-adjuvant treatment, are associated to pCR.

Keywords: biomarkers, neo-adjuvant chemo-immunotherapy, stage IIIA NSCLC

P2.04-11 OVERCOMING RESISTANCE TO IMMUNOTHERAPY USING CVA21: INITIAL RESULTS FROM A PHASE II STUDY

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Background: Resistance develops in most non-small cell lung (NSCLC) patients treated with anti-PD-1/anti-PD-L1 based immunotherapy. CVA21 is an oncolytic coxsackie virus that targets ICAM over-expressing tumour cells. Pre-clinical models suggest that CVA21-induced tumour lysis may enhance the clinical efficacy of the anti-PD-1 antibody Pembrolizumab by inducing immune cell infiltration in patients that lack an immune cell rich tumour microenvironment. Previously, the Keynote 200 trial of CVA21 combined with Pembrolizumab reported an ORR of 23% in immunotherapy-naive NSCLC. We report the efficacy of Pembrolizumab in combination with CVA21 in a preliminary cohort of eight pre-treated NSCLC patients with secondary resistance to prior anti-PD-1/anti-PD-L1 therapy. **Method:** On progression of prior therapy, IV CVA21 ($1x10^9$ $TCID_{50}$) was administered on days 1, 3, 5, 8, then Q3W for 6 months, in combination with Pembrolizumab (200mg IV from day 8, then Q3W for up to 24 months). Repeat biopsies were mandated prior to cycle 2 of Pembrolizumab. Tumour measurements were calculated using immune-related RECIST. PD-L1 was tested on pre- and post-treatment biopsies using SP-263 (Ventana) and reported using the tumour proportion score (TPS). **Result:** The majority of patients were female (n=7, 88%), median age 65 years (range 55-75), seven (88%) current or former smokers, five (63%) with 3+ lines of prior treatment, and only 1 anti-PD-1/anti-PD-L1 naive. Two patients were KRAS mutant, the remaining were wild type for EGFR, ROS1, ALK and BRAF. Two (25%) partial responses (PR) were observed, both in anti-PD-1/anti-PD-L1 pre-treated patients. Both responders were continuing at data cut-off, 240 and 120 days since commencement. Two achieved SD (overall clinical benefit 50%) and 3 were non-evaluable (1 early non-treatment-related death, 3 awaiting first scan). Early PD at 56 days occurred in the anti-PD-1/anti-PD-L1 naive patient (n=1). In the two PRs, PD-L1 TPS was 25% and 60% respectively. Preliminary IHC staining of paired biopsies showed an increase in PD-L1% in 2 (33%) evaluable patients at 21 days. PD-L1 TPS ranged from <1% to 80% in pre-treatment biopsies, but was not predictive of response or benefit from combination therapy. An increase in PD-L1 was associated with a trend toward longer disease stability (median 147 days). Combination treatment was well-tolerated with no observed G4/5 TRAE's. **Conclusion:** Intravenous CVA21 in combination with pembrolizumab demonstrated encouraging clinical activity in patients who had progressed on prior anti-PD-1/anti-PD-L1 therapy, regardless of PD-L1 levels.

Keywords: CVA21, Pembrolizumab, NSCLC

P2.04-12 PH I TRIAL OF CONCURRENT OR SEQUENTIAL IPILIMUMAB, NIVOLUMAB, AND SBRT TO MULTIPLE SITES IN PATIENTS WITH STAGE IV NSCLC

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Background: Despite the promise of immunotherapy for the treatment of advanced NSCLC, only a fraction of patients experience significant benefit from immunotherapy alone. Previous studies have shown that SBRT can stimulate innate and adaptive immunity to potentially augment immunotherapy. In addition, SBRT is used in patients with limited metastatic disease as consolidative approach, showing an improvement overall survival when compared to systemic treatment alone. Combining immunotherapy with ablative therapy is being studied by a number of investigators. While many

of these pre-clinical and clinical studies are promising, timing of immunotherapy with SBRT has not be formally studied. Further, few of these studies have addressed treatment of multiple sites of disease and little is known about what molecular changes occur in the tumor microenvironment immediately after ablative therapy. This trial is designed to evaluate the safety and efficacy of the combination of nivolumab (N) and ipilimumab (I) plus sequential(S) or concurrent(C) SBRT in patients with stage IV NSCLC. **Method:** This is a single-center phase I, open-label, two-arm, randomized platform trial. Eligible patients include those with stage IV NSCLC with ≥2 metastatic lesions that meet criteria for SBRT (0.2 cc to 65 cc of viable tumor, larger tumors able to be partially treated up to 65 cc). Eligible patients are simultaneously accrued on arm I (S) and arm II (C) in a 1:1 ratio. Participants in arm I complete SBRT to 2-4 sites followed by initiation of N/I 1-7 days after completion of SBRT. Participants in arm II are treated with N/I within 24-48 hours of SBRT with required SBRT completion to 2-4 sites within two weeks (prior to the second dose of N). Protocol therapy consists of treatment with N 3mg/kg every 2 weeks and I 1mg/kg every 6 weeks for a maximum of 24 months. The primary endpoint is dose-limiting toxicity defined as a >33% rate of grade ≥3 toxicity. DLT is defined as any grade ≥3 toxicity possibly, likely, or definitely related to SBRT plus N/I (the combination and not the individual components). Secondary endpoints include response rate and progression free survival at 6 months, control rate of treated lesions and non-treated lesions, and comparison of efficacy and toxicity between the arms. Biopsies and blood draws performed pre- and post-SBRT will facilitate molecular correlative studies including investigation of changes in the immune microenvironment induced by the two approaches. **Result:** Current enrollment includes 27 of the 40-80 participants: 15 patients are enrolled on arm 1 (sequential) and 12 patients are enrolled on arm 2 (concurrent). SBRT safety cohorts, to which patients can contribute to more than one, include the following: central lung (n=20), peripheral lung (n=7), abdominal (n=5), osseous (n=9), and liver (n=5). All patients have paired pretreatment and posttreatment biopsies of at least one irradiated lesion. 79% of post-ablative biopsies are suitable for DNA/RNA sequencing. **Conclusion:** Section not applicable

Keyword: Immuno-oncology, SBRT

P2.04-13 INTERLEUKIN-18 AND LUNG CANCER: A MENDELIAN RANDOMIZATION STUDY

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Background: Previous studies have shown that Interleukin-18 (IL-18) suppresses the growth of lung cancer. IL-18 might restore natural killer cell-mediated immunosurveillance against MHC class I-deficient tumors and enhance the therapeutic effects of cancer immunotherapy. However, whether there is a causal influence of higher IL-18 protecting against lung cancer remains unknown. We aim to explore whether genetically predicted circulating level of IL-18 is associated with lung cancer through 2-sample Mendelian randomization (MR) analysis. **Method:** We obtained the summary data for significant single-nucleotide polymorphisms (SNPs, P<5×10−8) associated with serum IL-18 from a genome-wide association study of 8293 healthy adults. Their associations with lung cancer and its histological subtypes were evaluated in the International Lung Cancer Consortium (ILCCO, 11348 lung cancer cases, and 15861 controls) applying Inverse variance–weighted (IVW) meta-analysis, Weighted-median analysis, Mendelian randomization–Egger regression, Simple mode method, and Weighted mode method. We also performed several sensitivity analyses to evaluate the potential violation of MR assumptions. **Result:** Genetically predicted IL-18 level is associated with lower risk of lung cancer (Odds ratio [OR] per 1 standard deviation (SD) increase: 0.824, 95% confidence interval (CI) 0.762-0.890, p<0.001). Similar trends were shown in the histological subtypes of lung cancer: lung adenocarcinoma (OR per 1 SD increase: 0.816, 95%CI 0.708-0.941, p=0.005) and squamous cell lung cancer (OR per 1 SD increase: 0.883, 95%CI 0.787-0.990, p=0.034). Our sensitivity analyses also showed that there was no directional pleiotropy bias and horizontal pleiotropy bias. Table 1. Mendelian randomization estimates of associations of genetically predicted circulating IL-18 and lung cancer and its histological subtypes using different analysis methods.

Variants	Outcome	Method	OR	95%CI	*P* value	Heterogeneity *p*†	MR-Egger intercept *p*‡
IL-18	Lung cancer	IVW	0.824	0.762-0.890	<0.001*	0.868	
		MR Egger	0.964	0.750-1.239	0.787	0.976	0.251
		Weighted median	0.823	0.748-0.906	<0.001*		
		Simple mode	0.826	0.714-0.955	0.042*		
		Weighted mode	0.826	0.727-0.938	0.026*		
IL-18	Lung adeno-carcinoma	IVW	0.816	0.708-0.941	0.005*	0.216	
		MR Egger	1.137	0.752-1.720	0.568	0.372	0.159
		Weighted median	0.840	0.713-0.989	0.036*		
		Simple mode	0.807	0.622-1.046	0.156		
		Weighted mode	0.827	0.663-1.032	0.144		
IL-18	Squamous cell lung cancer	IVW	0.883	0.787-0.990	0.034*	0.809	
		MR Egger	0.791	0.557-1.123	0.247	0.765	0.545
		Weighted median	0.927	0.803-1.070	0.301		
		Simple mode	0.919	0.736-1.146	0.480		
		Weighted mode	0.939	0.765-1.153	0.572		

*: *P* value < 0.05; IVW: inversevariance weighted; OR: odds ratio; CI: confidence interval.

Conclusion: Genetically predicted higher IL-18 is causally associated with lower lung cancer risk, indicating that IL-18 might have the potential to be used clinically to protect against lung cancer. Additional work is warranted to confirm the causality and underline the potential mechanisms.

Keywords: Lung cancer, IL-18, Mendelian randomization

P2.04-14 NLR, DNLR AND PLR AS POSSIBLE PREDICTIVE MARKERS IN PATIENTS WITH NSCLC TREATED WITH ICI

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Background: Clinical evidence suggests a possible predictive role of Neutrophil-to-Lymphocyte ratio (NLR), derived Neutrophils/(leukocytes minus neutrophils) ratio (dNLR) and Platelet-to-Lymphocyte ratio (PLR) in different tumors, including non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICI). **Method:** In this Italian multicenter retrospective trial NLR, dLNR, PRL fluctuations were analyzed in patients with stage IV NSCLC treated with ICI. Those rates were assessed at baseline, before the second, third and fifth cycles. In patients still on treatment, samples were collected also at 1 and at 2 years from ICI start. The primary objective was the relationship between baseline ratios and response to ICI, through the identification of different cut-offs estimated using ROC curves. **Result:** Data of 402 patients receiving ICI (antiPD1 91%, antiPDL1 7% and antiPDL1 plus antiCTLA-4 2%) were analysed: 287 (71%) were males, median age was 65 (39-86 yrs-old), 84 patients (21%) were on first line treatment. The most common histology was adenocarcinoma (62%) and 95% of patients had an ECOG performance status of 0-1. One hundred and eleven (30%) patients were using steroids in permissive doses for ICI. Disease control rate (DCR) was observed in 228 patients (58%) with 95 (24%) reporting an immune objective response. Median progression free survival was 5,3 months and the median overall survival was 9,6 months, after a median follow-up of 9,6 months (range 4,0-13.0). Basal NLR, dNLR and PRL were predictive of response (p=0.0002, p=0.0003 and p=0.0304, respectively). Best response categories were dichotomized in Response (SD + PR + CR) versus no Response (PD). With this classification, the differences were more pronounced and statistically significant for basal NLR and dNLR (p=0,045 and p=0,004, respectively). The cut-off values for basal NLR and dNLR were defined (BLNLR=2,46; BLdNLR=1,61) to identify patients most at risk of "non Response" through the ROC curves. Confounding factors were assessed using logistic regression models (age, gender, smoking). During treatment, an increase in the values was observed at the time of progression, both for NLR (average variation: -1.57) and for dNLR (average variation + 0.32), even if the statistical significance is limited to NLR (p = 0.041). **Conclusion:** NLR, dNLR and PLR are independent factors of response to ICI. Compared to the present literature data, this study highlights that NLR ratio may predict progressive disease earlier than radiological restaging.

Keywords: predictive markers, Immune Checkpoint Inhibitors, Non-Small Cell Lung Cancer

P2.04-15 ASSOCIATION BETWEEN OPIOIDS AND OUTCOME OF 1ST LINE IMMUNOTHERAPY IN ADVANCED NSCLC PATIENTS: A RETROSPECTIVE EVALUATION

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Background: Opioids represent the pharmacological backbone of cancer-related pain treatment. However, preclinical studies suggest that opioids can cause immunosuppression. Recently, immune checkpoint inhibitors (ICIs) have become available for treatment of patients with advanced NSCLC. With this study we aimed at retrospectively evaluate the impact of chronic opioid treatment on the outcome of advanced NSCLC (aNSCLC) patients treated with first-line ICIs. **Method:** We retrospectively reviewed the records of aNSCLC patients treated with anti-programmed-death-1 (PD-1) or its ligand (PD-L1) single-agent ICIs in 2 Italian institutions. We included all patients with enough follow-up to have at least one radiological evaluation during ICIs treatment. Patients with rapid clinical progression were included in the analysis. We analyzed response rate (RR), progression-free survival (PFS), and overall survival (OS). Response was evaluated using RECIST v1.1 criteria. **Result:** 75 patients were found, 64 included in the analysis. Mean age at diagnosis was 66.5 years (range 37-84), 65% were male. Histological type were: 76.5% adenocarcinoma, 14% squamous, 9.5% others, most with high PD-L1 expression (90.5% with ≥50% TPS). 58 patients (90.6%) were stage IV at ICIs start, with mean number of metastatic sites 1.8. Most patients were current/former smokers (87.5%); ECOG performance status (PS) at ICI start was: 0 in 34 pts (53.1%), 1 in 25 (39%), 2 in 5 (7.9%). 20 patients were receiving opioids at ICIs start (31.3%), with a mean daily dose equal to 59 mg of oral controlled-release morphine. With a median follow-up of 10.9 months, the median number of ICIs cycles was 7.5 (range 1-26). RR, mPFS and mOS in the whole series were 40.6%, 9.4 months and 17.1 months, respectively. Compared to the others, patients receiving opioids had numerically lower RR (30% vs 45.5%, p=0.24), a shorter PFS (median 12.7 vs 1.7 months, Hazard Ratio [HR] 4.16, 95%CI 2.15-8.05, p<0.001) and OS (median not reached vs 3.2 months, HR 4.68, 95%CI 2.09-10.52, p<0.001). At the multivariate analysis, opioid use continued to be significantly associated with worst PFS (HR 3.19, 95%CI 1.45-7.01, p=0.004) and OS (HR 4.16, 95%CI 1.61-10.76, p=0.003), even when accounting for PS, disease stage and number of metastatic sites. **Conclusion:** Our results suggest a possible detrimental effect of opioids in aNSCLC patients treated with first line single-agent ICIs, even when correcting for other prognostic factors. However, due to the short follow-up, the small number of patients, and the lack of a control group, our results should be considered exploratory.

Keywords: Immunotherapy, NSCLC, Opioids

P2.04-16 NOVEL CT BASED RADIOMIC FEATURES ARE PROGNOSTIC AND PREDICTIVE OF BENEFIT OF CHEMOIMMUNOTHERAPY IN ADVANCED NON-SQUAMOUS NSCLC

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Background: Carboplatin, pemetrexed and pembrolizumab (C/P/P) is currently approved for patients with advanced non-squamous carcinoma of the lung (NS-NSCLC) based on superior survival outcomes noted in KEYNOTE-189. Since clinical benefit was observed across all PD-L1 expression categories, there are currently no robust predictive biomarkers that can identify subsets of patients likely to derive benefit from this regimen. We sought to evaluate whether radiomic features extracted from within and outside the nodule on pre-therapy CT scans could predict response to C/P/P. **Method:** We retrospectively identified 52 patients with stage IV NS-NSCLC who received C/P/P. Of these, 6 were excluded because of non-evaluable thoracic lesions. Lung tumors were contoured on 3D SLICER software by an expert reader. Textural and shape radiomic features were extracted from intra/peritumoral regions using MATLAB® 2018b platform (Mathworks, Natick, MA). The primary endpoint of our study was RECIST response and secondary end point was overall survival (OS). A linear discriminant analysis classifier (LDA) was used to predict response across 100 iterations of threefold cross validation in the dataset. Performance of classifier on response was measured by area under receiver operating characteristic curve (AUC). To build the multivariate radiomic signature for OS, least absolute shrinkage and selection operator (LASSO) Cox regression model was used and a risk score was computed according to a linear combination of selected features. Patients were divided into high-risk or low-risk groups based on median risk score. **Result:** The top five radiomic features (intra/peritumoral textural patterns) predictive of response to C/P/P were identified by mRMR feature selection method. LDA classifier using these features could discriminate responders from non-responders with an AUC of 0.77 ± 0.05. The radiomic risk score was calculated using a linear combination of top six selected features from LASSO with corresponding coefficients. In a multivariate Cox proportional hazards model using a combination of clinicopathologic and radiomic features, the radiomics signature

was found to be significantly associated with OS (averaged on 100 iteration of CV) (HR 10.42; 95% CI: 4.18-26; P = 4.92e-07). Kaplan-Meier survival analyses according to the radiomics signature risk-score showed significantly worse survival in the high risk category. **Conclusion:** Textural features within and outside the nodule on pre-treatment CT images of patients with NS-NSCLC treated with C/P/P were predictive of responses and OS. Additional validation of these quantitative image-based biomarkers in independent cohorts is warranted.

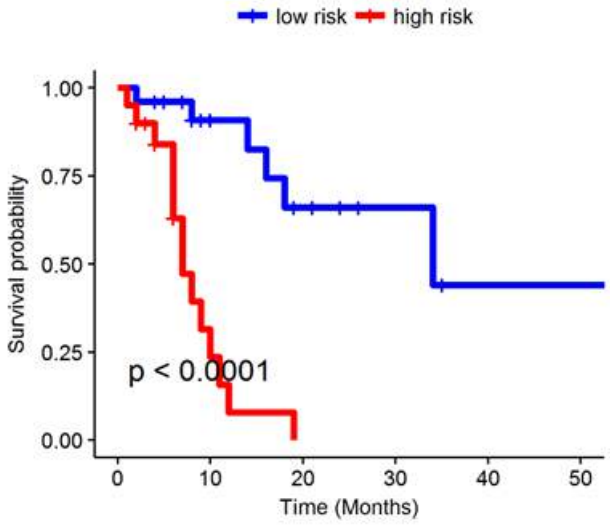

Figure: Kaplan-Meier survival analyses of patients (N = 46) with NS-NSCLC treated with C/P/P using the radiomics signature risk-score.

Keywords: chemoimmunotherapy, Radiomics, Biomarker

P2.04-17 IMMUNE REPERTOIRE IS A POTENTIAL PREDICTIVE BIOMARKER FOR EVALUATING THE EFFICACY OF MUTANT NEOANTIGEN SPECIFIC T CELL COMBINED WITH PD1 ANTIBODY

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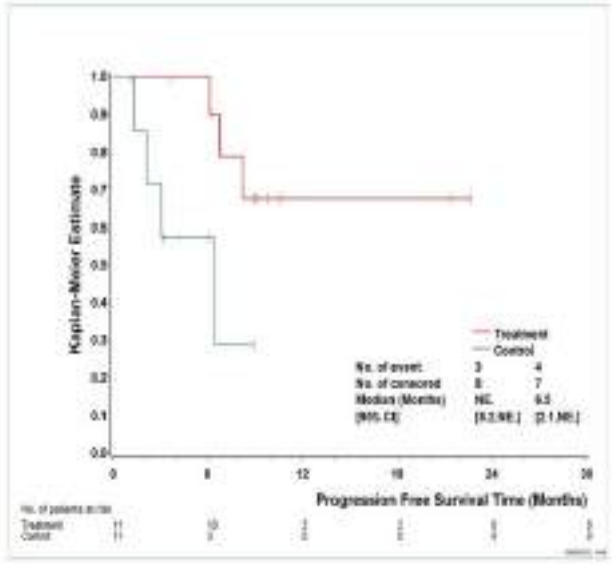
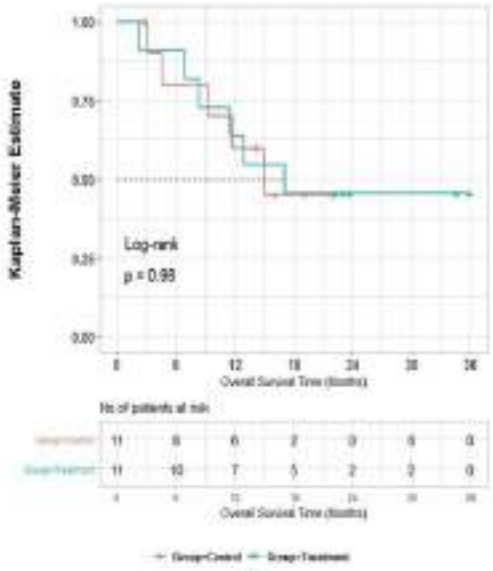
Background: The efficiency of PD1 monoclonal antibody used alone is not satisfactory. The therapeutic method of solid tumor with mutant neoantigen specific T (Nas-T) cell developed in this study is an adoptive cell therapy which is specific for each patient. Our previous research has proved that Nas-T can prolong patients' PFS with a good safety. We aim to further explore the effect of Nas-T on OS and to evaluate the characteristics of immune repertoire (IR) as a predictive biomarker. **Method:** A total number of 12 patients with advanced solid tumors who failed after multiline treatments were recruited. They were treated with Nas-T cells, PD1 antibody and BSC; other 11 patients were treated with PD1 inhibitors and BSC as control. Peripheral blood was collected at baseline and per cycle (21-28d) respectively. Immunosequencing of the CDR3 regions of human TCRβ chains was used to detect IR. T-cell diversity and clonality for each IR was calculated. To quantitatively evaluate the consistency of the infused T-cell repertoires during the therapy, we adopted the Morisita overlap index (MOI), which considers the composition and the abundance of T-cell rearrangements. MOI ranges from 0 to 1, with 1 indicating identical TCR repertoires and 0 indicating completely distinct TCR repertoires between two samples. **Result:**



PFS



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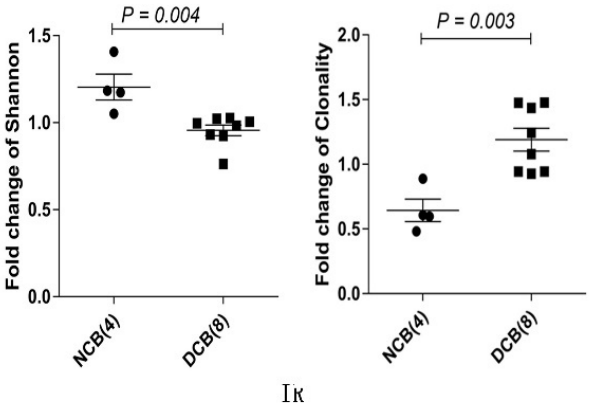

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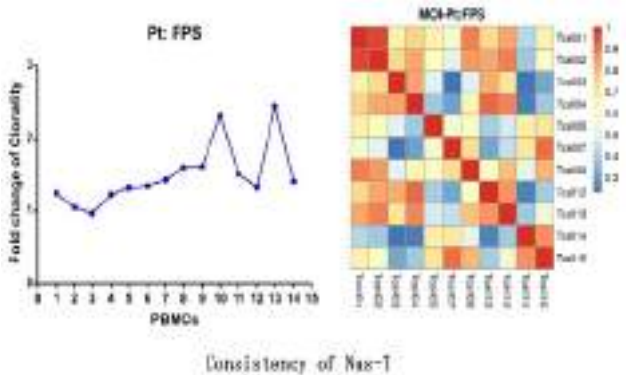

Updated data showed there was no statistical significance in OS (P>0.05), which may be related to the small sample size and short follow-up time. Compared to baseline, T-cell repertoire of NCB and DCB after 1st cycle displayed significant changes: Shannon 0.96 vs 1.20, P=0.004; Clonality 1.20 vs 0.64, P=0.003. Elevated Clonality may indicate expanded tumor-specific T-cells which could recognize mutant neoantigen specifically. MOI result for one patient, for example, exhibited a good consistency among each batch of infused Nas-T. **Conclusion:** The combined immunotherapy of mutant Nas-T cell and PD1 antibody is more effective than PD1 antibody alone in prolonging PFS, but has no effect on OS. IR Clonality change shows its potential as a predictive biomarker.

Keywords: Immunotherapy, Immune Repertoire, Solid Tumor

P2.04-18 ANALYSIS OF PATIENT MICROBIOME AND ITS CORRELATION TO IMMUNOTHERAPY RESPONSE AND TOXICITY IN LUNG CANCER

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Background: In recent years, attention has shifted to modification of tumor responses to immunotherapy, potentially via the host microbiome. The mechanisms of this association, causative or consequential, remain incompletely understood. We seek to explore this further with a longitudinal study of lung cancer patient microbiomes, outcomes and toxicities preceding and during immunotherapy. **Method:** Patients with lung cancer (LC) treated with immunotherapy (anti-PD-1/L1 agents including pembrolizumab, nivolumab, atezolizumab and durvalumab) with or without chemotherapy at the University of Iowa were consented for this ongoing study. Subjects from November 2018 – February 2019 were included in this report. Nasal and buccal swabs, as well as stool samples were obtained prior to therapy in compliance with institutional regulatory guidelines. Patients were treated and monitored per respective disease protocol; responses were recorded per RECIST 1.1 criteria, and toxicities graded per CTCAE 5.0. Samples underwent DNA extraction followed by 16S rRNA metagenomic analysis and taxonomic profiling using Divisive Amplicon Denoising Algorithm (DADA)-2 pipeline. The microbiome from all body sites were compared. LC gut microbiomes were also compared to fecal samples provided by healthy control residents (HC), as well as patients with other malignancies such as renal clear cell (RCC). This project is registered in clinicaltrial.gov (NCT03688347). **Result:** Gut microbiota was significantly different compared to oral and buccal microbiota in all patients. Gut microbiota from 16 LC patients were compared to 8 HC samples. LC patients exhibited drastically different baseline microbiota composition at both the phylum level, including dramatic increases in Firmicutes, Actinobacteria and Verrucomicrobia, and significant decreases in *Bacteroidetes*, *Proteobacteria* and *Cyanobacteria*. We noticed a clear inversion of Firmicutes/Bacteroidetes ratio between HC and LC patients, differences also reflected at the genus level. Interestingly, gut microbiome from 5 RCC patients was strikingly different from HC but exhibit high concordance with those from LC. LC patients who experienced immunotherapy-related toxicities were found to have at baseline markedly more *Anaerostipes* and *Eggerthella* relative to HC, and fewer Lachnospira. **Conclusion:** Our study found promising trends in microbiome constitution whose evaluation will benefit from a larger subject pool as we continue to accrue patients. Compared to HC, we found significant differences in baseline LC gut microbiome at phylum and genus levels, and notable differences when comparing LC patients who suffered immunotherapy-related toxicities to those with none. Our project marks an important first step in a long-term study that could shed new light on the microbiome's influence on immunotherapy treatment outcomes.

Keywords: Immunotherapy, Microbiome, Metagenomics

P2.04-19 NEOADJUVANT CHEMOTHERAPY IS ASSOCIATED WITH IMMUNOGENIC CELL DEATH AND INCREASED T CELL INFILTRATION IN EARLY-STAGE NSCLC

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Background: Recent success using immune checkpoint blockade (ICB) in the metastatic setting has raised the need to understand the immune microenvironment (IME) in early-stage disease. Moreover, pre-clinical evidence suggests that cytotoxic agents can modulate this IME. A recent study conducted by our group showed that non-small cell lung cancer (NSCLC) patients who received neoadjuvant chemotherapy followed by surgery (NCT), as compared to patients who received upfront surgery (US), had higher densities of $CD3^+$ lymphocytes and $CD68^+$ tumor-associated macrophages (TAMs). $CD3^+CD4^+$ lymphocytes and TAMs also correlated with better clinical outcomes. In this study, we explored the relationships between NCT and the IME by harvesting tumor samples of multiple surgical NSCLC cohorts. **Method:** The PROSPECT microarray database was queried in NCT (n=45) and US (n=200) patients to investigate differentially expressed genes related to immunogenic cell death (ICD), susceptibility to $CD8^+$ T cell and NK cell cytotoxicity, priming of antigen presenting cells, immunosuppressive enzymes and intra-tumoral cytokines. Available data from the ImmunogenomiC prOfiling of NSCLC (ICON) and other surgical NSCLC cohorts was evaluated to determine: 1) differential immune profiling using FACS (NCT=17; US=39) and multiplex IHC imaging (NCT=10; US=72); 2) plasma circulating cytokines (NCT=18; US=73); 3) tumor mutational burden (TMB) (NCT=40; US=61). Participants who received NCT or US were excluded according to these criteria: 1) concurrent treatment in addition to NCT; 2) sarcomatoid and small cell histologies; 3) clinical or pathological TNM Stage 4 disease; 4) synchronous malignancies other than lung. **Result:** PROSPECT NCT patients expressed increased damage-associated molecular pattern (DAMP) genes (HSPA2, HSPA4, HSPE1, and S100A2; $p<0.05$) and T cell-related chemotaxis and antigen presentation genes (CXCR7, CD1A; $p<0.05$). Concordantly, the ICON cohort FACS results showed that NCT patients display increases in: 1) infiltration of $CD8^+$ T cells ($p=0.004$); 2) proliferating $Ki67^+CD8^+$ T cells ($p=0.02$); 3) tissue resident memory $CD8^+CD103^+$ ($p=0.02$) and $CD4^+CD103^+$ non-T_{reg} cells ($p=0.01$). Trends from the ICON multiplex IHC also highlighted increases in $CD8^+$ T cells ($p=0.09$), $CD20^+$ cells ($p=0.08$), as well as $PD\text{-}L1^+$ malignant cells ($p=0.08$) and $PD\text{-}L1^+$ TAMs ($p=0.08$) in NCT patients, the latter finding being supported by increased circulating MCP-1 ($p=0.03$). TMB was similar between NCT and US groups ($p=0.912$). **Conclusion:** Our data provides the first evidence of ICD (i.e., increased DAMP gene expression) following NCT in human early-stage NSCLC. Furthermore, our data highlights the association of NCT with a favorable IME (i.e., increased T cell infiltration), supporting the rationale of NCT and ICB combinations in localized NSCLC.

Keywords: Neoadjuvant chemotherapy, early-stage NSCLC, immune microenvironment

POSTERS

P2.04-20 TP53/KMT2C CO-MUTATION AS A NOVEL BIOMARKER FOR IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Immune checkpoint inhibitors (ICIs) have shown remarkable antitumor effects in non-small cell lung cancer (NSCLC), however only a subset of patients respond. Genomic alterations (GAs) detected by targeted next-generation sequencing (NGS) is increasingly used in clinical practice, but its correlation with recognized immune biomarkers and predictive value for ICIs response in NSCLC is unclear. **Method:** FFPE tumor and matched blood samples of 637 NSCLC patients (84 squamous cell and 553 non-squamous cell) were collected for targeted NGS panel sequencing from December 2017 to January 2019. GAs including single nucleotide variations, short and long insertions/deletions, copy number variations and gene rearrangements were assessed. TMB high (TMB-H) was defined as ≥10 muts/Mb. Positive PD-L1 expression was defined as ≥1% of tumor cells with membranous staining (22C3/28-8, DAKO). Genomic data and ICIs treatment outcome from a 240 NSCLC patient cohort was derived from cBioPortal (MSKCC, J Clin Oncol 2018). **Result:** In 637 NSCLC patients, the prevalence of PD-L1≥1% was 26.5% and the median TMB was 4.6 muts/Mb (IQR, 2.3-10). Recurrent *TP53*, *KRAS*, *LRP1B* and *KEAP1* mutations were significantly correlated with higher TMB (p value). *TP53*, *KRAS* and *KEAP1* mutations were significantly enriched in the TMB-H/PD-L1+ subset while *STK11* mutations were enriched in TMB-H/PD-L1- subset (p value). *KMT2C*, also known as *MLL3*, belongs to the mixed-lineage leukemia (MLL) family of histone methyltransferases and its GAs was found in 5% of our cohort. Tumors with *KMT2C* and *TP53* co-mutations (co-MUT) had a significantly higher TMB (15.1 muts/Mb) than *TP53/KMT2C* single-MUT (8.7 muts/Mb) and *TP53/KMT2C* co-WT (3.1 muts/Mb) tumors. Moreover, TMB-H/PD-L1+ subset was enriched in *KMT2C* and *TP53* co-MUT (25%) comparing to *TP53/KMT2C* single-MUT (14.7%) and *TP53/KMT2C* co-WT (3.3%) tumors. Survival analysis from public clinical trials confirmed that patients with *TP53/KMT2C* co-MUT had remarkable clinical benefit to ICIs in both progression free survival (PFS) and durable clinical benefit (DCB). The median PFS was 7.3, 4.2 and 2.5 months for *TP53/KMT2C* co-MUT, *TP53/KMT2C* single-MUT and *TP53/KMT2C* co-WT patients, respectively (p=0.0032). *TP53/KMT2C* co-MUT was an independent variable of PFS (*TP53/KMT2C* co-MUT vs. *TP53/KMT2C* co-WT, HR: 0.47, 95%CI: 0.25-0.89, p=0.0199). Furthermore, *TP53* with *KMT2C* or *KRAS* co-MUT expanded the patient population benefiting from ICIs (mPFS = 7.2 months, p=0.00042; DCB = 51.2%, p= 0.0195). **Conclusion:** This study provides evidence that *TP53/KMT2C* co-MUT may serve as a predictive biomarker for ICIs in NSCLC. GAs detected by targeted NGS could illuminate insight for immunotherapy.

Keywords: Non-Small Cell Lung Cancer, KMT2C, Immunotherapy

P2.04-21 SERUM CRP DECREASE HAS PREDICTIVE VALUE FOR LONG-TERM DISEASE CONTROL BY PD-1/ PD-L1 INHIBITORS IN PATIENTS WITH NSCLC

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Background: Several studies showed the predictive or prognostic value of systemic inflammatory markers such as C-reactive protein (CRP) in patients with non-small cell lung cancer (NSCLC) treated with PD-1/PD-L1 inhibitors. In OAK study, serum CRP decrease at 6 weeks from baseline was associated with the favorable clinical efficacy of atezolizumab, a PD-L1 inhibitor. However, the result is not validated in the clinical practice setting including patients treated with anti PD-1 antibodies. The aim of this study is to investigate the significance of serum CRP change from baseline as a biomarker in NSCLC patients treated with PD-1/PD-L1 inhibitors. **Method:** The current study is a retrospective cohort study. NSCLC patients treated with anti-PD-1/PD-L1 inhibitors in 2nd or later line setting were reviewed at Nagoya University Hospital and Tosei General Hospital. Patients were divided into two groups by serum CRP change (Group 1; patients with serum CRP decrease at 6 weeks by >= 33% compared to the baseline, and Group 2; the others except Group 1). **Result:** From January 2016 to September 2018, 124 advanced or recurrent NSCLC patients were enrolled. 34 (27.4%) patients were divided into Group 1 and 90 (72.6%) were into group 2, respectively. Group 1 showed statistically significant higher objective response rate compared with Group 2 (38.2% vs 7.0%, p< 0.01), and longer progression-free survival (PFS) (1-year PFS rate: 34.2% vs. 11.7%, HR of group 1 to group 2: 0.63 (95%CI: 0.39-0.98), p=0.04). Multivariate analysis also identified the CRP decrease as an independent favorable factor of PFS (adjusted HR of group 1 to group 2: 0.45 (95%CI: 0.26-0.77), p< 0.01). In contrast, PFS and OS were similar between the patients treated with PD-1 and PD-L1 inhibitors. **Conclusion:** Serum CRP decrease at 6 weeks from baseline would have predictive value for long-term disease control by PD-1/PD-L1 inhibitors for NSCLC in the clinical practice setting.

Keywords: Serum CRP decrease, long-term disease control, PD-1/ PD-L1 inhibitors

P2.04-22 PROGRAMMED DEATH 1-MRNA EXPRESSION PREDICTS BENEFIT TO ANTI-PD1 MONOTHERAPY IN A PROSPECTIVE COHORT OF ADVANCED NSCLC

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Background: Immunotherapy (IO) targeting PD1 or PD-L1 represents a new treatment option for patients (pts) with advanced non-small cell lung cancer (NSCLC). Besides PD-L1 IHC, other predictive biomarkers are being explored as potential predictors of outcomes. Our group has recently described an association between *PD1*-mRNA expression and response to IO in a retrospective multi-tumor dataset (*Annals Oncol 2018*). We aimed to corroborate these results in a prospective cohort of advanced NSCLC. **Method:** We prospectively evaluated the expression of 7 immune-related genes (*CD4, CD8, PD1, PDL1, IFNG, GZMM* and*FOXP3*) and 5 housekeeping genes in formalin-fixed paraffin-embedded tumor samples obtained before anti-PD1 therapy using the nCounter platform (Nanostring Technologies). The study cohort included consecutive pts with advanced NSCLC, ECOG/PS 0-1, no targetable oncogenes, treated in the first or second-line setting with anti-PD1 monotherapy from June 2017 to January 2019. Associations between the expression of *PD1* mRNA (as a continuous variable and using a previously defined pre-specified cutpoint) and response (complete and partial response) were assessed using logistic regression analysis. Kaplan-Meier method was used for survival analysis. PD-L1 IHC tumor cell expression was assessed using the 22C3 clone. Pearson correlation between PD-L1 IHC and *PD1* mRNA was explored. **Result:** A total of 43 pts were included (men 79%; adenocarcinoma 53%; nivolumab 55%; pembrolizumab 45%; first-line 30%; second-line 70%). Response occurred in 23% of pts and was significantly associated with *PD1* (p=0.029) and *FOXP3* (p=0.035) expression. Using the pre-established *PD1* cutoff (*Annals Oncol 2018*), 37% and 63% samples were *PD1*-high and *PD1*-low, respectively. *PD1*-high was significantly associated with increased overall response rate (ORR) (43% *vs* 11%, OR=6.22 [CI=1.31-29.44], p=0.021) and progression-free survival (HR 0.36 [CI= 0.14-0.90], p=0.028) but not with overall survival (p=0.117). PD-L1 IHC expression was available in 35 cases, of which 46% had high (>=50%) expression levels. A moderate concordance (0.49) was observed between PD-L1 IHC and *PD1*-mRNA. In this subset analysis, high PD-L1 IHC was significantly associated with response (50% *vs* 11%, OR=8.50 [CI= 1.45-49.53], p=0.043). Importantly, when combining predefined high/low-sets for both biomarkers (PD-L1 IHC/*PD1*-mRNA), response was significantly increased in PD-L1-high/*PD1*-high compared to PD-L1-low/*PD1*-low (ORR 58% *vs* 0%, p=0.019). **Conclusion:** *PD1*-mRNA expression is associated with response to anti-PD1 monotherapy and can increase the predictive ability of PD-L1 IHC. Further validation of these findings in pivotal clinical trials evaluating IO in advanced NSCLC pts seems warranted.

Keywords: nCounter, PD1, Immunotherapy

P2.04-23 TUMOR-STROMA INTERACTIONS PROMOTE CGAS-STING DRIVEN INFLAMMATION IN LUNG TUMOR MICROENVIRONMENT

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Background: The tumor stroma is an essential component of the tumor microenvironment (TME) and has critical roles in promoting resistance to immunotherapies. Most anticancer therapies target cancer cells specifically, however, it is important to also study signaling contributions from the TME. The recruitment of immune cells following intratumoral administration of Stimulation of Interferon Genes (STING) agonists in the TME is a critical event in the cGAS-STING-driven antitumor immune response, a pathway with great relevance in the context of cancer immunotherapy. Towards this, the infiltration of immune cells rely on functional vasculature to infiltrate into the tumor tissue. We have previously demonstrated that LKB1 mutation is associated with suppression of tumor cell STING levels due to mitochondrial dysfunction and reduced production of T-cell chemoattractants such as CXCL10 in KRAS-driven non-small cell lung cancer (NSCLC). Consistently, immunohistochemical staining of patient samples showed poor infiltration of CD3, CD4, and CD8 T cells into LKB1 negative versus LKB1 intact cancer epithelium, and instead, retention of T-cells in stroma. **Method:** 3-D microfluidic device was fabricated using cyclic olefin polymer (COP) at AIM BIOTECH. NCI-H1355 cells were cultured for 24h in ultra low-attachment culture plates for spheroid formation. To form the 3D tumor microvascular model, cancer spheroids, human lung fibroblasts (hLFBs) and human umbilical vein endothelial cells (HUVECs) were resuspended in an extracellular matrix-like fibrin/collagen gel and loaded into the central channel and cultured for 7 days and hydrated with culture medium (Vasculife, lifeline). Cytokine profiling (Human Cytokine 40-plex panel) was performed with media collected from 3D culture. **Result:** To examine how LKB1 alters immune cell recruitment, we used a 3-D microfluidic co-culture system to study interactions between vasculature and tumor spheroids derived from a KRAS/LKB1 mutated (KL) cell line with LKB1 reconstitution +/- STING deletion. Co-culturing tumor spheroids and vasculature, we identified changes in morphology, cytokine production, and gene expression that occur during the co-culture. We found that co-culture induced cooperative production of multiple immune cell chemo-attractants such as CXCL10, CCL2, CCL5, and G-CSF (Fig.1b,c). Interestingly, this more physiologic ex vivo tumor model of LKB1 reconstitution revealed particularly strong cooperative production of STING-dependent cytokines such as CXCL10 in the vasculature. Moreover, knocking down STING in the LKB1-reconstituted cancer cells did not significantly attenuate production of CXCL10 and other cytokines in co-culture, suggesting that tumor/vasculature interaction may promote STING activation in the vasculature regardless of cancer cell-intrinsic STING function. Furthermore, although there was no appreciable response after treatment of KL cancer cells with cGAMP based STING agonists, treatment of isolated 3-D vascular networks with cGAMP enhanced vascular permeability and increased production of CXCL10 and CCL5, possibly contributing to defective chemokine gradients that retain T cells near the vasculature. **Conclusion:** Developing these more complex models that incorporate 3-dimensional tumor and self-assembled microvasculature may elucidate important aspects of cGAS-STING biology in KL lung cancer microenvironment, and may ultimately aid further development of effective immunotherapies targeting this signaling pathway.

Keywords: cGAS-STING, KRAS/LKB1 lung cancer, tumor-vascular interactions

P2.04-24 TRANSCRIPTIONAL PROFILING OF NEOANTIGEN SPECIFIC T CELLS IN RESECTABLE NSCLC TREATED WITH NEOADJUVANT ANTI-PD-1

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Background: Neoadjuvant nivolumab has a manageable safety profile and can be effective in patients with resectable non-small cell lung cancer (NSCLC). To characterize the immune response in these patients, we sought to evaluate the existence and dynamics of neoantigen specific tumor-infiltrating T cells and identify their molecular phenotype including co-inhibitory checkpoint expression. **Method:** We evaluated peripheral blood and tumor infiltrating lymphocytes from seven patients treated with nivolumab. To identify neoantigen-specific T cell responses, we used MANAFEST (Mutation Associated Neoantigen Functional Expansion of Specific T cells), an assay we developed that links antigen specificity with unique CD8+ TCR Vβ CDR3 identities. We then carried out single cell TCRseq/RNAseq of tumor infiltrating T lymphocytes (TIL) to enumerate the genome wide digital gene expression and T cell clonotypic identity of each single cell (VDJ+DGE analysis), and particularly those with Vβ CDR3 regions identical to those identified as neoantigen-specific by MANAFEST. **Result:** Neoantigen-specific TCRs were detected in peripheral blood in all 3 patients with major pathologic response (MPR) and in 3 of 4 patients without MPR. Several of these clonotypes were found in the resected tumor and underwent peripheral expansions upon PD-1 blockade. In one notable patient, MD043-011, MANAFEST detected a T cell clonotype specific for a *CARM1* R208W mutation, despite this patient having no evidence of pathologic response. This neoantigen-specific clonotype represented 3.4% of TIL. Two years later, this patient recurred with a solitary brain metastasis. Single cell analyses of TIL in the primary lung lesion and brain metastasis revealed the same neoantigen-specific T cell clonotype was detected in the metastatic lesion. Strikingly, this clonotype exhibited a differential expression profile in the primary and recurrent lesion, with the clonotype in the primary tumor having an enrichment and upregulation of heat shock proteins indicating molecular stress and the clone in the metastatic lesion having an upregulation of checkpoint molecules, including CTLA4, TIM3, and LAG3. T cell cloning and validation experiments, as well as identification of transcriptional programs associated with MPR, are ongoing. **Conclusion:** The coupling of MANAFEST with single cell VDJ+ DGE analysis enabled us to characterize antigen specific clonotypes after differential expansion using the TCR as a molecular barcode. The presence of alternate co-inhibitory immune checkpoints on neoantigen-specific TIL from non-responding tumors suggests a potential driver of resistance to anti-PD-1 in early stage NSCLC. Ultimately, this integrative approach may provide key insights in predicting and understanding clinical response to neoadjuvant PD-1 blockade in NSCLC.

Keywords: NSCLC, neoantigens, tcells

P2.04-25 GUT MYCOBIOME AND METABOLIC INTERACTIONS WITH BACTERIA IN LUNG CANCER PATIENTS REVEALS POTENTIAL THERAPEUTIC VULNERABILITIES

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Background: There is a lack in our understanding of pathogenesis and mechanisms accounting for large variability in response to systemic therapy. Recent data suggest that the gut-lung axis regulates systemic immune function. Moreover, in vivo and clinical studies, mainly in melanoma and mixed epithelial tumors, suggest the role of gut bacteria and response to systemic therapy. However, the presence and potential theranostic role of gastrointestinal (GI) mycobiome in lung cancer has not been explored. Here, we aimed to evaluate

the associations of GI bacteria and Candida species in lung cancer patients. **Method:** We included 124 stool samples from 98 lung cancer patients (adenocarcinoma (n=48), squamous cell (n=24), small cell lung cancer (n=15) and other (n=11). Patients underwent lung resection surgery (n=20) or treated with first line chemotherapy CHT (n=78). We analyzed the gut microbiome according clinicopathological variables using Internal transcribed spacer (ITS) and shotgun metagenomic sequencing technique. We performed Spearman correlation between gut microbial species and continuous variables and random forest model (RF) for feature selection. Pathway analysis was done using HUmann2 pipeline, bacterial species annotation was performed with Metaphaln2 pipeline and for fungi ITS, we used PIPITS pipeline. We compared Candida diversity with healthy controls from the Human Microbiome Project. **Result:** We identified Candida species in 65% (71 of 124) of the stool samples. Of these, 48 were baseline 23 were follow-up samples (treatment). 77% of the patients included were diagnosed with advanced stage disease. There were significant differences in Candida abundance in healthy controls vs. cancer patients. In contrast, there were no significant differences in alpha and beta diversity between baseline and follow-up samples (treatment). In total 46 significant species and 140 pathways were significant different and fed into RF. Species belonging to Actinobacteria, Bacteroidetes and Firmicutes phyla are important features in RF and found to be negatively correlated ($r <= -0.3$, and $p < 0.05$) with Candida species. Certain bacteria pathways were significantly different according to the presence of Candida. **Conclusion:** Candida is present in stool samples in the majority of lung cancer patients both at diagnosis and during systemic therapy. There were associations with certain gut bacteria and Candida species that may have potential future therapeutic implications. Further biomarker studies in well-defined homogenous subgroups are ongoing in order to identify the exact biomarker role of the mycobiome in lung cancer.

Keyword: Mycobiome, Microbiome, Chemotherapy,

P2.04-26 SINGLE CELL PROTEOMICS PROFILING OF LIVE T-CELLS IN KRAS+ AND MET-AMP NSCLC TO PREDICT IMMUNE CHECKPOINT INHIBITOR RESPONSE

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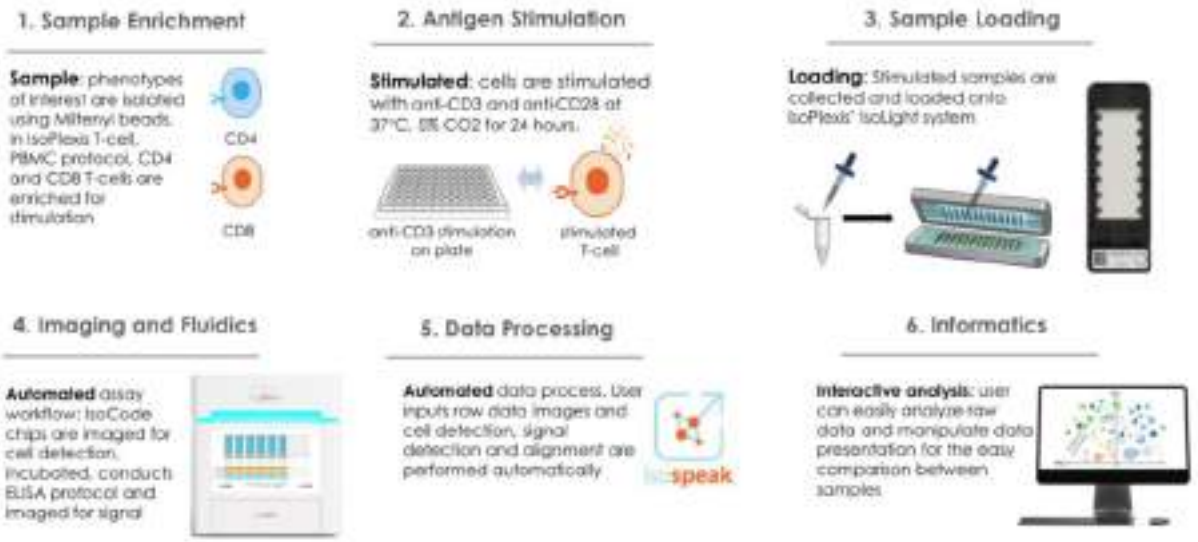
Background: Immune checkpoint inhibitors (CPI), alone or in combination with chemotherapeutics, have been approved for first-line treatment in non-small cell lung cancers (NSCLCs) and have therapeutic efficacy across many cancer types. While these new cancer immunotherapeutic agents (e.g. pembrolizumab, nivolumab, atezolizumab) represent exciting additions to the treatment paradigm of a large array of genomics-guided precision medicine strategies for oncogene-addicted lung cancers, emerging clinical data raises doubts about the efficacy and the role of immune checkpoint inhibition in oncogene-addicted lung cancers driven by EGFR mutation, ALK-rearrangement, and MET amplification (MET-Amp) or MET exon-14 skipping mutations, regardless of the expression level of PD-L1. Moreover, clinically relevant and reliable predictive biomarkers of CPI response remain inadequate, despite the currently used PD-L1 expression, tumor mutational burden and microsatellite instability (MSI) status. **Method:** We longitudinally profiled more than 32 cytokines released by peripheral T-lymphocytes from patients under CPI therapy using a novel live single-cell microfluidics-based liquid biopsy platform. Paired pretreatment and post-2 cycles of treatment peripheral blood samples from each subject were analyzed to delineate early biomarkers correlative to CPI treatment response in a pilot cohort of four representative patients with advanced NSCLC.



Result: CD8(+) T-cells have stronger polyfunctional response than CD4(+) T-cells in all patients, demonstrating considerable heterogeneity among different patients and different T-cell types [CD4(+) vs. CD8(+)]. To compare overall polyfunctional upregulation by cytokines grouped by function, we adopted a novel polyfunctional strength index (PSI) in our biomarker bioinformatics analysis. Post-treatment CD4(+)/CD8(+) T-cells across patients showed overall higher PSI than pretreatment cells except in one patient. The polyfunctional profiles are largely composed of effector proteins associated with antitumor immunity and, to a lesser extent, chemoattractive and regulatory cytokines in CD8(+) T-cells. Upon anti-CD3/CD28 stimulation, the combinations of secreted cytokines in post-treatment samples are markedly distinct from pretreatment samples in both CD4(+) and CD8(+) cell subsets. The PSI analysis data presented highlight a patient with stage IVB KRAS-mutated (KRAS+)(PD-L1=60%) lung adenocarcinoma and another one with MET-amplified lung adenocarcinoma (PD-L1=85%-95%), who demonstrated excellent tumor response to anti-PD1 CPI, providing an immune single cell proteomics biomarker measure of response in oncogene-addictive tumor treated under CPI. **Conclusion:** Our study nominated an early association between single-cell immune cytokine profiling and CPI clinical treatment outcome in advanced oncogene-driven NSCLC. Further studies with larger cohorts are warranted for validating PSI as predictive biomarker of CPI response, especially in patients with addictive oncogene-driven lung cancer.

Keywords: immune checkpoint therapy, single cell, proteomics profiling

POSTERS

P2.04-27 CLINICAL IMPLEMENTATION OF MULTIPLEX IMMUNOFLUORESCENCE TO CHARACTERIZE TUMOR IMMUNE STATUS IN LUNG CANCER PATIENTS

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Background: Tumor cell PD-L1 positivity by immunohistochemistry (IHC) enriches for response with PD-(L)1 inhibitors in patients with non-small cell lung carcinoma (NSCLC). However, PD-L1 IHC has limited positive and negative predictive value and does not provide information about the immune effector cell population in the tumor environment. Multiplex immunofluorescence (MIF) can be used to simultaneously characterize checkpoint proteins and immune cell infiltrates on a single tumor slide. MIF is not, however, routinely used in clinical practice. We operationalized and launched prospective MIF for lung cancer patients. **Method:** Patients were consented to an institutional protocol for tumor sequencing and immunoprofiling. Samples were submitted for MIF reflexively following a diagnosis of lung cancer on any in-house core biopsy or resection specimen. Slides were reviewed by a pathologist and imaging scientist to confirm tumor adequacy and three to six representative 20X fields of view that included tumor and tumor-stroma interface were selected for scoring. Automated staining for AE1/AE3, PD-L1, PD-1, CD8, FoxP3 and DAPI was carried out on a Leica BOND RX Autostainer and imaged using the Polaris imaging system (PerkinElmer). Under pathologist supervision, biomarkers were quantified in each region at a single cell level using the Inform Advanced Image Analysis Software (PerkinElmer). An automated reporting system calculated a PD-L1 tumor proportion score (TPS) and immune cell density across the analyzed regions. **Result:** To date, 80 samples have been received for analysis (40% biopsies and 60% resections), of which 78 (98%) were imaged successfully. Average turnaround time from receipt of specimen to complete reporting was 25 days. PD-L1 was considered positive (TPS >50%) in 4 (5%), low positive (1-49%) in 42 (55%), and negative (<1%) in 32 (41%). CD8+/PD1+ density ranged from 0 to >800/mm2 (median 59) and FOXP3+ cells from 2 to >700/mm2 (median 59); both showed a broad standard deviation, consistent with heterogeneity in the tumor and adjacent stroma. Nine (11%) tumors showed a pattern of adaptive immune resistance (so-called "hot" tumors), defined as CD8+/PD1+ density greater than the median and at least low positive PD-L1 TPS. **Conclusion:** Multiplex immunofluorescence and pathologist-guided image analysis of fixed tissue specimens can be integrated into clinical practice with a low rate of failure and acceptable turn-around time to identify unique immunologic subsets of lung cancer. Limitations of data storage and analysis speed require focused field selection, therefore optimization of the scored area(s) is essential to ensure accurate tumor immune classification. Studies to determine the feasibility of use of MIF for selection of patients for immunotherapy are ongoing.

Keywords: NSCLC, immunofluorescence, PD-L1

P2.04-28 NEOCOAST: NEOADJUVANT DURVALUMAB ALONE OR WITH NOVEL AGENTS FOR RESECTABLE, EARLY-STAGE (I–IIIA) NONSMALL CELL LUNG CANCER

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Background: Resectable, earlystage nonsmall cell lung cancer (NSCLC) is a potentially curable disease.The current standard of care is surgery with or without adjuvant or neoadjuvant platinumbased doublet chemotherapy. However, over half of patients eventually relapse after surgery and die from NSCLC. Clinical studies have shown that neoadjuvant programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) checkpoint inhibitors may yield clinically meaningful pathological responses in patients with resectable NSCLC.[1–3] The NeoCOAST trial is a multidrug platform study to assess the PD-L1 checkpoint inhibitor durvalumab alone or in combination with novel agents, with the goal of identifying new treatment strategies to improve clinical outcomes of patients with resectable, early-stage NSCLC. **Method:** NeoCOAST (NCT03794544) is a phase 2, open-label, randomized trial that will initially evaluate the clinical activity and safety of neoadjuvant durvalumab alone or in combination with the novel agents oleclumab (MEDI9447), monalizumab (IPH2201) and danvatirsen (AZD9150), in patients with resectable, stage I (>2 cm) to IIIA NSCLC. New treatment arms evaluating other durvalumab combinations may be added based on emerging preclinical and clinical data. The primary endpoint is major pathological response rate in the resected tumor specimen after treatment with neoadjuvant durvalumab alone or in combination with novel agents. Secondary objectives include feasibility of tumor resection surgery within 14 days of the end of the 4-week treatment period, safety, pathological complete response rate, pharmacokinetics and immunogenicity. Correlative translational analyses include tumor genomics, changes in the tumor microenvironment, and T cell populations. NeoCOAST is open for accrual with an estimated total target enrollment of up to 40 patients per treatment arm. References [1]Forde PM, et al. N Engl J Med. 2018;378:1976–86. [2]Rusch V, et al. MA04.09. Presented at IASLC 19th World Conference on Lung Cancer, 23–26 September 2018, Toronto, Canada. [3]Cascone T, et al. LBA49. Presented at European Society of Medical Oncology Congress, 19–23 October 2018, Munich, Germany 2018. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: early-stage NSCLC, neoadjuvant treatment, checkpoint inhibition

P2.04-29 ASSOCIATION OF INFLAMMATION RELATED GENES WITH LUNG CANCER RISK IN MOROCCAN POPULATION

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Background: Lung cancer is known to be a complex multifactorial disease involving both genetic and environmental factors. The study of different signaling pathways and identification of the genes involved, will contribute to further understanding the pathogenesis of the disease, thus allowing the development of appropriate targeted treatments and even a prevention strategies. The inflammation caused by immune system activation is likely linked to carcinogenesis by promoting angiogenesis and proliferation of tumour cells, according to the cytokine profile in the tumour microenvironment. Previous studies have suggested that key cytokines in inflammation pathways may have an important roles in the etiology of lung cancer. The aim of this study was to investigate whether common inflammation related genes influence lung cancer risk in Moroccan population. **Method:** Single nucleotide polymorphisms (SNPs) in IL-6, IL6-R and IL6-ST, IL6, IL17-A, IL17-F, IL-8, MIF and STAT3 genes were assessed in 150 controls and 150 lung cancer patients. Genotyping was performed with the TaqMan® allelic discrimination technology and RFLP-PCR. Gene expression of cytokines was evaluated in the peripheral blood samples of lung cancer patients and healty controls. Total RNA of the blood cells were extracted and reverse transcribed to cDNA. Screenings of deferentially expressed genes associated with inflammation were performed using real-time PCR. **Result:** Among the studied SNPs, we found a significant association for the IL-6 (rs2069840), IL-6 (rs1800795), IL-6 (rs1800796), IL-17F (rs763780), IL-17F (rs763780), IL-8 and the MIF (rs755622). No significant association was observed for the remaining SNPs of IL-6R (rs2228145) IL-6ST (rs2228044), IL-17A (rs2275913), IL17A (rs7747909) and STAT3 (rs2293152) genes. Cytokines genes expression revealed significant association with lung cancer. Genes expression were increased in lung cancer patients comparing to healty subjects. **Conclusion:** Our results suggest the important role of inflammation related genes in the occurrence of lung cancer and cytokines genes associated may be considered as a genetic marker for predisposition to Lung cancer in Moroccan population.

Keyword: Lung cancer, inflammation, cytokines, polymorphisms, genes expression, risk, Moroccan population

P2.04-30 SEQ-ING A BETTER WAY TO DETECT PD-L1 IN NSCLC

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Background: Immunotherapies targeted against PD-L1 and PD-1 have caused a paradigm shift in the treatment of NSCLC, and PD-L1 protein expression has emerged as a standard diagnostic biomarker that predicts which patients are more likely to respond to immunotherapy. However, the use of PD-L1 protein expression as a biomarker is complicated by differences in PD-L1 antibodies, immunohistochemistry methods and platforms, pathologist scoring, and positivity cut-points. We propose that using RNA-sequencing (RNA-seq) methodologies will be an equally reliable approach to determine PD-L1 expression within a tumour and will yield a greater depth of biomarker information than PD-L1 IHC alone. **Method:** We performed quantitative immunohistochemistry (qIHC) on 262 resected stage I-III formalin-fixed paraffin-embedded (FFPE) NSCLC patient samples registered in the Glans-Look Lung Cancer Research (GLR) database using the commercially available E1L3N PD-L1 antibody (Cell Signalling Technologies). Staining intensity was quantified and used to establish a positivity threshold that was subsequently used to define positivity cut-points of <1%, 1%-49%, and >50% (as used for determining treatment eligibility for Pembrolizumab). We performed single-end RNA-sequencing on FFPE samples from the same GLR patient cohort. Raw counts were normalized to counts-per-million for use in our analyses. **Result:** We compared the PD-L1 mRNA expression to the PD-L1 protein staining intensity across the tissue core and found a significant correlation (p<0.001, Spearman's rho=0.538). We also found significant correlation between PD-L1 mRNA expression and the percent-positivity score determined by qIHC (p<0.001, Spearman's rho=0.605), which was particularly apparent when comparing PD-L1 mRNA expression between cut-point groups where expression was significantly higher in the 1%-49% and >50% groups. Interestingly, we also found moderate, yet significant correlation between PD-1 mRNA expression and both PD-L1 protein staining intensity and percent positivity (p<0.001, Spearman's rho=0.437 and 0.415 respectively), and we were able to identify several differentially expressed genes between the PD-L1 positive and negative groups. **Conclusion:** Given the high degree of correlation between PD-L1 mRNA expression and PD-L1 protein staining and positivity, RNA-seq can be a viable option for assessing candidacy for immunotherapy. In addition to the wealth of supplementary data on important biomarkers, RNA-seq offers the possibility for using non-invasive procedures such as liquid biopsy to measure PD-L1 levels in a sequential, objective fashion.

Keywords: Immunotherapy, RNA-sequencing, PD-L1

P2.04-31 IMMUNE PHENOTYPIC BIOMARKERS IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH DEFINITIVE CHEMORADIATION AND ATEZOLIZUMAB

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Background: Consolidation durvalumab is the current standard of care for locally advanced non-small cell lung cancer (LA-NSCLC) after chemoradiation (CRT). However, predictive and prognostic biomarkers of response to immunotherapy are still poorly characterized. In particular, minimally-invasive blood-based biomarkers that can be sequentially assessed during therapy may prove useful in understanding the characteristics of response and optimal sequencing of therapy. We report serial blood immune-phenotyping of patients undergoing concurrent chemoradiation therapy (CRT) with PD-L1 blockade with atezolizumab. **Method:** Between February 2016 and October 2018, 40 LA-NSCLC patients were evaluated in conjunction with the single-institution DETERRED trial. The first 10 patients were treated with carboplatin/paclitaxel chemotherapy and atezolizumab for two cycles followed by maintenance atezolizumab for 1 year after completing CRT, followed by 30 patients treated with atezolizumab concurrent with CRT followed by chemotherapy/atezolizumab and maintenance atezolizumab. In all, 38 patients were evaluable. Peripheral blood was drawn at the beginning (baseline), midway through CRT (2-4 weeks), and at the end of CRT, with periodic follow up samples for up to two and a half years. Immune phenotyping was performed by flow cytometry on fresh, whole blood within 24 hours of phlebotomy. Cox regression was preformed to assess biomarker correlations with survival. **Result:** At the second blood sample midway through CRT, patients who eventually progressed had a larger increase from baseline in the percentage of peripheral blood CD4 T helper cells expressing PD-1 (p = 0.042) and this change was associated with both progression-free (PFS, p = 0.039) and overall survival (OS, p = 0.042). Progressors had a mean increase of 2.5 percentage points while non-progressors had a mean drop of 1.9. At the first post-CRT follow-up, an increase in the percentage of CD8 cytotoxic T lymphocytes expressing PD-1 was negatively associated with survival (PFS p = 0.0015, OS p = 0.023) as well as the percentage of granulocytic myeloid suppressor cells (PFS p = 0.0089, OS p = 0.034). These comparisons were not significant when corrected for multiple testing. However, the change in CD4 PD1 after 2-4 weeks of CRT was an independent prognostic indicator of PFS in multivariate cox regression analysis including age, stage, and histology (p = 0.02, hazard ratio 1.2, 95% CI 1.03 to 1.4). **Conclusion:** Increases in peripheral blood lymphocytes expressing PD1 and myeloid suppressor cells may be prognostic for locally advanced patients treated with CRT and immune checkpoint blockade but additional studies are needed to verify these markers in immunotherapy resistance.

Keywords: Immunotherapy, NSLCS, biomarkers

P2.04-32 COMPARISON OF CLINICOPATHOLOGICAL AND GENOMIC CHARACTERISTICS BETWEEN NSCLCS WITH A PD-L1 TUMOR PROPORTION SCORE OF ≥90% VS <1%

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Background: Determinants of PD-L1 expression in non-small cell lung cancer (NSCLC) are poorly defined. To identify characteristics associated with high vs. absent PD-L1 expression, we compared clinicopathologic and genomic features of NSCLCs at the two ends of PD-L1 expression spectrum: a PD-L1 tumor proportion score (TPS) of ≥90% or a PD-L1 TPS of <1%. **Method:** We retrospectively collected clinicopathologic and genomic data (via targeted NGS) from consecutive NSCLC patients who had consented to an IRB-approved correlative research study and whose tumor PD-L1 TPS was either ≥90% or <1%. Single nucleotide variations, insertions/deletions, and copy number alterations were compared using Fisher's exact test. Tumor mutational burden (TMB) was compared using Mann-Whitney test. **Result:** 421 NSCLCs with PD-L1 TPS ≥90% (N=133) or <1% (N=288) and successfully performed NGS were identified. There was no difference in age, sex, histology, or stage at diagnosis between the two groups. Patients with a PD-L1 TPS of ≥90% were more likely to be smokers (86.5% vs 76.4%; P=0.02) compared to patients with a PD-L1 TPS of <1%, and tumors in the PD-L1 TPS ≥90% group had higher TMB (10.89 vs 8.47 mutations/megabase; P=0.004) than those in the PD-L1 TPS <1% group. Tumors in the PD-L1 TPS ≥90% group were more likely to have *KRAS* (47.3% vs 31.3%; P=0.002), *MET* exon 14 (9.6% vs 2.1%; P=0.003), and *TP53* mutations (71.0% vs 49.7%; P<0.001) than those in the PD-L1 TPS <1% group. Compared to the PD-L1 TPS ≥90% group, the PD-L1 TPS <1% group was more likely to have *EGFR* (23.6% vs 8.2%; P<0.001) and STK11 (23.4% vs 5.0%; P<0.001) mutations, as well as the absence of known oncogenic driver mutations (35.2% vs 24.8%; P=0.04). Chromosomal gain alterations (amplification or copy number gain) of the 9p24.1 locus, where the *PD-L1*, *PD-L2*, and *JAK2* genes are located, were more common in the PD-L1 TPS ≥90% group than in the PD-L1 TPS <1% group (11.4% vs 2.8%, respectively; P<0.001). Chromosomal loss alterations (copy loss or deletion) of the 9p24.1 locus were more common in the PD-L1 TPS <1% than in the PD-L1 TPS ≥90% group (27.5% vs 3.8%, respectively; P<0.001). A repeated biopsy case showed acquired loss PD-L1 expression (PD-L1 TPS changed from 90% to 0%) with concomitant acquired loss of the 9p24.1 locus. **Conclusion:** High PD-L1 expression in NSCLC is associated with tobacco use, high TMB, gain of the 9p24.1 locus and mutations in *KRAS*, *MET* exon 14, and *TP53*. PD-L1 negativity is associated with never smoking status, low TMB, loss of the 9p24.1 locus, mutations in *EGFR* and *STK11*, and the absence of oncogenic driver mutations.

Keywords: PD-L1, Non-Small Cell Lung Cancer, NGS

POSTERS

P2.04-33 SINGLE-AGENT TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY: RESULTS FROM A PHASE 1 EXPANSION COHORT IN NSCLC PATIENTS

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Background: Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1. Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Previous reports from this first-in-human study (NCT02407990), and other early phase studies, suggested tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors. **Method:** Patients in nine dose-expansion cohorts received tislelizumab administered at a dose of 5 mg/kg Q3W, including a NSCLC cohort. Adverse events (AEs) were assessed per NCI-CTCAE 4.03 and tumor assessments were performed Q9W (RECIST v1.1). PD-L1 was retrospectively assessed with the VENTANA PD-L1 (SP263) assay; PD-L1-positive (PD-L1$^+$) NSCLC was defined as ≥25% tumor cells expressing PD-L1 by immunohistochemistry. **Result:** A total of 49 patients with NSCLC (median age 62 years [39–78]) received tislelizumab. Twenty-three patients were Caucasian and 21 were Asian; 34 patients were current/former smokers. Forty-four patients had received prior systemic chemotherapy (1 line, n=24; 2 lines, n=10; ≥3 lines, n=10). As of 27 Oct 2018, median study follow-up was 11.2 months (0.5–27.7) and 46 patients were evaluable for response. Confirmed partial responses (PRs; n=6) and stable disease (n=23) were observed. The objective response rate was 13% (95% CI: 4.9–26.3) and the disease control rate was 63% (95% CI: 47.6, 76.8). Of the 37 patients with PD-L1 evaluable samples, PRs were seen in three of 16 patients (19%) with PD-L1$^+$ NSCLC and two of 21 patients (10%) with PD-L1$^-$ NSCLC. Across all patients, median overall survival (OS) was 11.5 months (95% CI: 9.3, not reached [NR]). Median OS was 15.1 months (95% CI: 4.2, NR) for patients with PD-L1$^+$ NSCLC and 11.2 months (95% CI: 6.1, NR) for patients with PD-L1$^-$ NSCLC. Hypothyroidism was the most commonly reported treatment-related AE (TRAE; n=6), followed by hyperthyroidism, fatigue, and pneumonitis (n=5 each). Eight grade ≥3 TRAEs were reported in six patients: pneumonitis (n=3), autoimmune colitis, vomiting, elevated ALT, elevated AST, and macular rash (n=1 each). A single treatment-related death due to pneumonitis occurred in a patient with compromised pulmonary capacity at baseline. **Conclusion:** Tislelizumab was generally well tolerated and demonstrated antitumor activity in NSCLC patients. Tislelizumab is being evaluated as a single agent or with chemotherapy in phase 3 studies in NSCLC patients (NCT03358875, NCT03594747, and NCT03663205).

Keywords: tislelizumab, NSCLC, Anti-PD-1

P2.04-34 FCGR2B EXPRESSION AS A REGULATOR OF IMMUNITY IN NON-SMALL CELL LUNG CANCER PATIENTS

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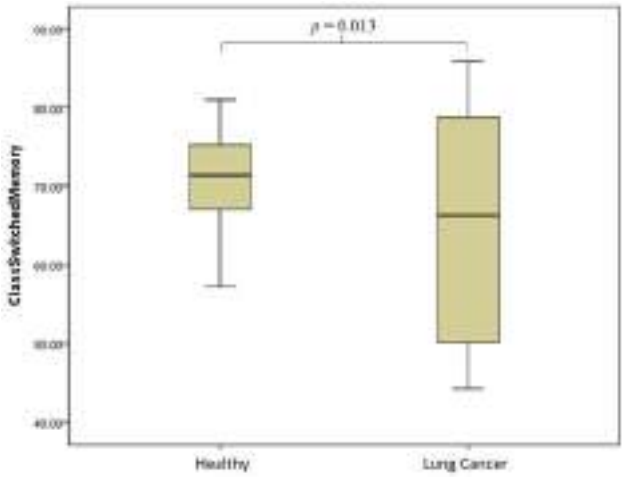
Background: FCGR2B (CD32B), a receptor on the B cell membrane, induces the production of inhibitory messages to maintain the homeostasis of the immune system and prevent excessive activation of B cells to attack their own antigens. Therefore, FCGR2B may cause immune cells to not effectively search and kill for cancer cells.This study examined the level of FCGR2B expression on B cells associated with immunity in non-small cell lung cancer (NSCLC) patients. **Method:** Healthy volunteers and lung cancer patients were recruited. All control donors' and patients' peripheral blood were collected. 200ul blood with appropriate amount of antibody was incubated for 10-15 min at room temperature in the dark and then lysed with 1ml VersaLyse Lysing Solution for 10-15 min at room temperature in the dark. Resuspend in 1ml PBS+ 1% fix solution then were counted by cytoflex flow cytometer (Beckman Coulter). For surface marker analysis, B cells were collected assessing the levels of CD19, CD32, CD21, CD24, CD27, CD38, and IgM/IgD by flow cytometric assay. T cells subtypes including CD3, CD4, CD8, CD27, CD28, CD45, CD45RA, CD57, CCR7 and PD1 were counted by cytoflex flow cytometer. **Result:** In this study, healthy volunteers (n=9) were compared with NSCLC patients (n=17) to detect the expression of FCGR2B on B cell. We found that Class Switched Memory Cell in NSCLC patients had lower performance than healthy subjects (NSCLC patients v.s. healthy subjects: 65.10 ± 15.72 v.s. 70.76 ± 7.26, p = 0.013). Class Switched Memory Cell was significant lower in advanced stage than that in early stage NSCLC patients (advanced stage v.s. early stage: 54.68 ± 27.21 v.s. 77.73 ± 7.12, p = 0.044). The expression of FCGR2B (CD19CD32) in NSCLC patients was slightly lower than that in healthy subjects (NSCLC patients v.s. healthy subjects: 19.68 ± 10.07 v.s. 32.98 ± 23.92, p = 0.099), but did not reach statistically significant differences. The expression of FCGR2B (CD19CD32) was significantly positively correlated with CD4 Naïve T cell (R = 0.789; B = 0.291; p < 0.001) and CD3CD4CD45RA (R = 0.765; B = 0.301; p = 0.001).



Conclusion: NSCLC patients with reduced numbers of Class Switched Memory B Cell are more prone to progress lung cancer disease. The positive correlation between FCGR2 B cells and naive T cells in blood is also observed. Future studies focusing on the presence of these B cell subtypes, antigen specificity and interaction with T cells are necessary to further elucidate in NSCLC patients.

Keywords: immuno-oncology, FCGR2B, Lung cancer

P2.04-35 IMMUNE RELATED ADVERSE EVENTS IN NSCLC PATIENTS TREATED WITH IMMUNE CHECKPOINT THERAPY WHO RECEIVED THE INFLUENZA VACCINATION VS NO VACCINATION

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Background: The influenza vaccination is recommended by the CDC for cancer patients to reduce the risk of influenza-related complications. There is concern that the incidence of immune-related adverse events (irAEs) may be greater in vaccinated patients receiving immune checkpoint inhibitors (ICPI). We sought to interrogate if influenza vaccination in patients with NSCLC receiving ICPI therapy had an increased incidence of iRAEs compared to non-vaccinated patients using data from our single-center experience. **Method:** We conducted a single-center retrospective analysis of patients with advanced NSCLC who received PD-1 or PD-L1 inhibitor monotherapy between March 2015 – December 2018. Influenza immunization records from both institutional and state-wide immunization registries were obtained for each patient identified between 2014 -2019. Comparisons of adverse event incidence between flu vaccinated vs control patients were tested using chi-square statistics. **Result:** 117 patients were included in our analysis, 33 patients (28%) were vaccinated during ICPI therapy, 19 (58%) received quadrivalent influenza vaccine, 13 (39%) patients received trivalent influenza vaccine and 1 (3%) was unable to be determined. 22 (67%) of vaccinated patients had an irAE vs 53 (63%) of patients who were not vaccinated during ICPI therapy (p = 0.720). Eight (24%) vaccinated patients had irAE leading to discontinuation of therapy vs 12 (14%) patients who were not vaccinated during ICPI therapy (p = 0.198). The most frequent irAE in both groups was fatigue 16 (48%) vs 28 (33%) (p=0.128). Notable irAEs included colitis (0), pneumonitis (3), hepatitis (1) with vaccination vs. colitis (1), pneumonitis (3), hepatitis (4) without vaccination. There were

no statistically significant differences in baseline demographics between both groups including age, race, gender, tumor histology or ECOG performance status. **Conclusion:** Our retrospective study suggests that in general, irAEs are not significantly increased with vaccination for influenza during treatment with immune checkpoint inhibitors. However, there is a slight trend toward increased incidence of irAE warranting ICPI discontinuation and further investigation is warranted. Limitations of this study include a small sample size and inability to grade irAE retrospectively.

Keywords: Immunotherapy, Immune related adverse events, Influenza Vaccination

P2.04-36 IMMUNE CHECKPOINT INHIBITION FOR NON-SMALL CELL LUNG CANCER (NSCLC) IN PATIENTS WITH PULMONARY TUBERCULOSIS OR HEPATITIS B

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Background: Pulmonary tuberculosis (pTB) and Hepatitis B (HepB) are endemic in Asia. Multiple trials have shown a survival benefit of immune-checkpoint inhibitors (ICI), either as monotherapy or in combination with chemotherapy over chemotherapy in the treatment of NSCLC in first or second-line setting. However, patients with chronic infections are routinely excluded from such studies, and the safety and efficacy of ICI in this population is scarce. **Method:** A retrospective review of clinical records of patients with advanced NSCLC with pTB and/or HepB, treated with ICI from January 2014 to March 2019 at a single Asian centre was conducted. The diagnosis of pTB was based on isolation of m. tuberculosis from sputum culture or nuclei acid amplification. **Result:** 13 patients were analysed. 12 (92.3%) were male, with a median age of 67 years (range 41 – 86) and 10 (76.9%) patients had an Eastern Cooperative Oncology Group performance status of 0-1. Nine (69.2%) patients received anti-PD-1/PD-L1 monotherapy, and four received ICI in combination with chemotherapy. Seven (53.8%) patients were treatment-naïve and six received ICI in the second-line and beyond. Seven patients had a history of pTB and ten patients had HepB. Four patients had a history of both HepB and pTB. The median progression-free survival (PFS) of the entire cohort was 6.7 months (95% CI: 3.3 – 10.2 months). The median overall survival (OS) was 13.3 months (95% CI: 0.0 – 31.2 months). Five patients had an objective response, and nine patients had disease control (complete/partial response or disease control). Immune-related adverse events (irAE) occurred in four patients – one patient each with endocrinopathy (G2), pneumonitis (G3), arthritis (G3) and hepatitis (G3). There were no treatment-related deaths. Four patients had pTB prior to initiation of ICI, and three patients developed pTB after. Two patients received anti-TB therapy on ICI and developed G3 transaminases which resolved after omission of anti-TB therapy. For all the patients who had completed treatment for pTB, none experienced re-activation. Of the 10 patients with HepB, four were chronic carriers (HepB surface-antigen (HBsAg) positive and detectable viral load), and six were previously exposed (HBsAg negative, anti-hepB core-antibody positive). Only one of the patients who had previous exposure to HepB received anti-viral prophylaxis and there were no incidences of re-activation. **Conclusion:** Based on our findings, the risks of ICI therapy do not appear to be increased in patients with pTB or HepB. Further studies identifying those who are at risk of reactivation are essential.

Keywords: Immune-checkpoint inhibitors, Tuberculosis, Hepatitis B

P2.04-37 PHASE I/II TRIAL OF DURVALUMAB AND TREMELIMUMAB WITH CONTINUOUS OR INTERMITTENT MEK INHIBITOR SELUMETINIB IN ADVANCED NSCLC

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Background: Despite therapeutic progress in other molecular subsets of non-small cell lung cancer (NSCLC), little progress has been made for KRAS-mutant NSCLC. Because RAS remains an elusive pharmacological target, agents targeting downstream elements of the MAPK signaling pathway have been developed, including MEK inhibitors. However, substantial benefits have not been achieved due to the development of drug resistance. Current strategies to improve outcomes in this population include MEK inhibitors and PD-1 / PD-L1 immune checkpoint blockade (ICB) combinations (e.g., NCT03225664). On the other hand, combined anti-CTLA-4 and PD-1 / PD-L1 axis ICB improves response rates in melanoma, but similar benefits remain to be seen in NSCLC: MYSTIC trial updates failed to show a progression-free survival (PFS) advantage over standard of care, and CheckMate 227 reported significantly longer PFS with first-line double ICB in the high tumor mutational burden subgroup only. Thus, the objectives of this study are: 1) to determine the safety and efficacy of combined MEK inhibition, anti-PD-L1 and anti-CTLA-4 and; 2) to unveil mechanistic insights for response and resistance. **Method:** This is a single center, Phase I/II study comparing two combination schedules of selumetinib (AZD6244, ARRY-142886), tremelimumab and durvalumab with historical controls in patients with previously treated, unresectable NSCLC. Forty patients will be accrued at the University of Texas MD Anderson Cancer Center. In the first arm, participants receive selumetinib PO BID on days 1-7 and 15-21 and durvalumab IV on day 1. Participants also receive tremelimumab IV on day 1 for courses 1-4 (courses repeat every 28 days in the absence of disease progression or unacceptable toxicity). The second arm differs by the continuous selumetinib schedule: PO BID on days 1-28. Primary objectives include the maximum tolerated dose (MTD; dose-escalation phase) and PFS (dose expansion phase). Standard 3+3 design will be applied to determine the MTD among the three pre-defined dose levels. Estimated PFS will be provided with 95% confidence interval. Secondary objectives include: 1) response rate by RECIST 1.1; 2) disease control rate (complete response + partial response + stable disease); 3) overall survival; 4) safety and; 5) duration of response. Exploratory objectives will assess biomarkers of response and resistance in pre- and on-treatment biopsies as well as peripheral blood using immune profiling, transcriptome and protein readouts. **Result:** Section not applicable (Clinical Trial in Progress) **Conclusion:** The estimated start date for this trial (NCT03581487) is April 15th, 2019, and the estimated study completion is scheduled for April 2021.

Keywords: MEK inhibitor, Immune checkpoint blockade, advanced NSCLC

P2.04-38 TUMOR-ASSOCIATED NEUTROPHILS AS A POTENTIAL PREDICTOR FOR EARLY RECURRENCE IN RESECTABLE I-IIIA LUNG ADENOCARCINOMA

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Background: A recurrence of the early-stage non-small cell lung cancer (NSCLC) is usually unpredictable by clinical features alone. It has been appreciated that the high degree of infiltrated neutrophils is significantly associated with poor patient outcome in NSCLC. **Method:** Transcriptional profiles and clinical information of 484 primary lung adenocarcinoma (ADC) subjects were retrieved from Gene Expression Omnibus (GEO). An additional cohort of mRNA expression, somatic mutations, and clinical data of 398 ADC were obtained from The Cancer Genome Atlas (TCGA). CIBERSORT algorithm was employed to infer the relative proportions of 22 sorts of leukocytes in each tumor using gene-expression profiles. Patients were stratified into two groups by the fraction of neutrophils using an optimal cutoff value (0.01) obtained with the "survminer" algorithm in R. We further investigated comprehensively the molecular differences between the high- and low-neutrophils patients. **Result:** A significantly higher rate of 1-year recurrence was found in the high-neutrophils compared with the low-neutrophils group in both training (GEO,19.5% vs 6.1%) and validation (TCGA, 27.3% vs 19.0%) cohorts. However only in training cohort the patients with high neutrophils experienced a poorer recurrence-free survival (HR 1.95, 95% CI 1.47-2.51, P< 0.0001). The two groups were not only distinguished by clinical behaviors, but presented characteristic mutation genes and mutation patterns. *EGFR* and *BRAF* were more frequently mutated in low-neutrophils patients, whereas in high-neutrophils patients the most common mutation was found in *STK11*. Yet such molecular distinction was more pronounced in ADC with high tumor mutation load (TMB >=10). Gene Set Enrichment Analysis (GSEA) suggested that the common mutant genes in high-neutrophils patients were involved in the TP53 signaling, cell cycle pathways or associated with molecular functions including chemokine production and CD4 activation, while the common mutant genes in low-neutrophils patients were linked to RAS signaling pathway. Interestingly, we

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observed immune scene accompanied with good prognosis of ADC and concordant with limited infiltration of neutrophils, for instance high infiltration of B memory cells, resting memory CD4+T cells, resting mast cells and CD8+T cells. **Conclusion:** Our findings suggested that local neutrophils are one of important components which are determinant for early recurrence of ADC, and it might serve as a simple predictor. Further research is warranted to identify the molecular mechanisms that neutrophils employed to exert, directly or indirectly, the regulatory effect on ADC progression.

Keywords: Neutrophils, NSCLC, Microenvironment

P2.04-39 CLINICAL CHARACTERISTICS OF LONG-TERM SURVIVORS WITH NIVOLUMAB IN PREVIOUSLY TREATED ADVANCED NSCLC FROM REAL WORLD DATA

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Background: Nivolumab, a programmed death-1 immune checkpoint inhibitor antibody, has become one of the new standard therapies for previously treated advanced non-small cell lung cancer (NSCLC). However, there is limited information about the long-term survival of real-world patients treated with nivolumab in Japan. **Method:** We performed a retrospective study of previously treated patients with advanced NSCLC who received nivolumab at 3 mg/kg every 2 weeks outside clinical trials from our institution in Saitama (Japan) between January 2016 and February 2017. We used real-world data (RWD) to analyze the clinical characteristics of patients who were alive 2 years after initiating nivolumab treatment. **Result:** A total of 129 patients fulfilled the inclusion criteria. Thirty-eight patients (30%) were alive 2 years after receiving the first dose of nivolumab. The median age at initial nivolumab treatment was 65 years (38–79). Twenty-nine (76%) patients were male, 12 (32%) were never-smokers, 37 (97%) had performance status (PS) 0 and 1, and 30 (79%) had adenocarcinoma histology. Twenty-five (66%) patients received nivolumab as second-line therapy, and 9 (24%) had genetic abnormalities including 7 with epidermal growth factor receptor (*EGFR*) mutations. Thirty-four cases of programmed death-ligand 1 expression in tumor samples were not quantifiable. The best responses to nivolumab per the Response Evaluation Criteria in Solid Tumors version 1.1 included 12 partial responses (32%) and 6 complete responses (16%). Eleven 2-year survivors (29%) received nivolumab for more than two years, three (8%) discontinued nivolumab because of immune-related adverse effects, and four (11%) were retreated. Fourteen 2-year survivors (37%) received only nivolumab without subsequent therapy and did not display evidence of progressive disease at the last follow-up. These survivors exhibited significantly good PS, were male, had a history of smoking, and did not harbour somatic genetic abnormalities. Multivariate analysis identified only good PS as an independent positive predictor of survival of two years or more. **Conclusion:** In our RWD experience, nivolumab resulted in a 2-year survival rate of 30% in previously treated patients with advanced NSCLC. The 2-year survival rate in a real-world clinical setting was slightly lower than that in a Japanese phase II study (ONO4538-05/06 study). Clinical characteristics associated with a positive treatment response were comparable to those observed in previous studies.

Keywords: nivolumab, Non-Small Cell Lung Cancer, long-term survival

P2.04-40 TUMOR MUTATION SCORE IS MORE POWERFUL THAN TUMOR MUTATION BURDEN IN PREDICTING RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Tumor mutation burden (TMB) and PD-L1 expression are the two important biomarkers for immune checkpoint inhibitors (ICIs) in lung cancer. However, growing evidences are showing that not all mutations, such as EGFR mutation, are favorable factors in predicting clinical outcome of ICIs and the power of TMB, which is unselective, might be attenuated. Therefore, we developed tumor mutation score (TMS) as better biomarker for response of ICIs in non-small cell lung cancer (NSCLC). **Method:** TMS was defined as the number of genes with nonsynonymous somatic mutations. Mutations were detected by targeted next-generation sequencing (NGS) in 240 NSCLC patients treated with anti-PD-(L)1 monotherapy or in combination with anti-CTLA4. Durable clinical benefit (DCB) was defined as complete response (CR)/partial response (PR)/stable disease (SD) that lasted 6 months. TMS, TMB and PD-L1 expression were compared among DCB and no durable benefit (NDB) NSCLC patients. **Result:** The total TMS was significantly correlated with TMB (R=0.98, P<0.001) and performed almost equally to TMB in the analysis. 12 genes and 11 genes (5 sharing genes) were significantly associated with longer progression-free survival (PFS) and response (DCB vs NDB), respectively. The number of mutated genes within these 18 genes were defined as TMS18. In the survival analysis of PFS, the HRs of the high group were TMS19 (HR=0.307, P<0.001), TMB (HR=0.455, P<0.001), and PD-L1 expression (HR= 0.403, P=0.02), separately. Moreover, patients with DCB had significantly higher TMS18 (P<0.001), TMB (P=0.006), and PD-L1 expression (P=0.032). High TMS18 group had highest proportion of CR/PR/SD patients, which was 74.1% (CR/PR/SD: 3/17/20), especially in distinguishing CR patients. Taken together, TMS18 was more powerful than TMB and PD-L1 in predicting response of ICIs in NSCLC. **Conclusion:** Simple transformation from unselective TMB to selective TMS greatly enhanced the power of mutations-based biomarkers. TMS in combination with PD-L1 expression might yield better efficiency in predicting response of ICIs in NSCLC with future validation in larger cohorts.

Keywords: Tumor Mutation Score, Tumor Mutation Burden, PD-L1

P2.04-41 CLINICAL AND IMMUNOLOGICAL FACTORS ASSOCIATED WITH MUTATION BURDEN IN NON-SMALL CELL LUNG CANCER

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Background: It is unclear whether factors including clinical and immune microenvironment (IME) are associated with tumor mutation burden (TMB) in patients with non-small cell lung cancer (NSCLC). We aimed to develop a prediction model to identify the association between these factors and TMB in patients with NSCLC. **Method:** We assessed somatic mutation burden in surgical tumor specimens with whole exome sequencing (WES) using an ion torrent proton platform (Thermo Fisher Scientific). The IME profiles including PD-L1 tumor proportion score (TPS), stromal CD8 tumor infiltrating T cell (TIL) density, and stromal Foxp3 TIL were quantified by digital pathology using a machine learning algorithm. To detect factors associated with TMB, factors including clinical and IME were assessed using a multipul regression model. Two hundred NSCLC patients, for whom both WES and clinical data from Project HOPE (High-Tech-Omics-based Patient Evaluation) were available, excluding those with low tumor purity (less than 20%), were assessed in this study. **Result:** Out of 250 NSCLC patients with tumors surgically resected between September 2014 and September 2015, we analyzed tumors from 200 patients. Patient **background:** median age (range) 70 (39-87), male 37.5%, smoker 27.5%, pathological stage (p-stage) (I/ II/ III) 63.5/22.5/14.0% respectively, histological type (Ad/Sq) 77.0/23.0%, primary tumor location (upper/lower) 58.5/41.5%, median standardized uptake value (SUV) 7.5 (0.86-29.8), median serum CEA level (range) 3.4 ng/ml (0.5-144.3), median serum CYFRA 21-1 level 1.2 ng/ml (1.0-38.0), median TMB 2.19/ Mb (0.12-64.38), median PD-L1 TPS 15.1% (0.09-77.4), median stromal CD8 TIL 582.1/mm^2 (120.0-4967.6), and median stromal Foxp3 TIL 183.7/mm^2 (6.3-544.0). In simple regression analysis, gender (male/female), smoking status (yes/no), p-stage (I/II,III,IV), age (< 70, ≥70), primary tumor location (lower/upper), serum CEA level (low [< 5.0ng/ml], high [≥ 5.0 ng/ml]), serum CYFRA level (low [< 3.5ng/ml], high [≥3.5 ng/ml]), and actionable mutation status (Mt+/Mt-) were favorable prognostic factors (p < .0001, p = .0001, p = .072, p = .027, p = .045, p = .002, p = .009, and p = .069 respectively). Multiple regression analysis identified five factors [smoking status:

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smoker, age: less than 70, primary tumor location: lower, serum CEA level (greater than 5ng/ml), and serum CYFRA level (greater than 3.5ng/ml)] associated with higher TMB (p = .002, p = .045, p = .03, p = .046 and p = .016 respectively). **Conclusion:** IME factors did not associate with tumor mutation burden. However, along with smoking, lower primary location, elevated CEA and CYFRA level may be independent predictors of high TMB.

Keywords: Tumor Mutation Burden, immune microenvironment, machine learning

P2.04-42 PD-L1-MEDIATED ENHANCEMENT OF HEXOKINASE 2 EXPRESSION IS INVERSELY RELATED TO T-CELL EFFECTOR GENE EXPRESSION IN NON-SMALL-CELL LUNG CANCER

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Background: The PD-1/PD-L1 pathway contributes to the metabolic reprogramming of immune cells and tumor cells. However, the mechanism by which PD-L1 regulates glycolysis in human cancer and the relationship between PD-L1 expression, glycose metabolism and anti-tumor immune response remain unclear. We addressed these issues in human non-small-cell lung cancer (NSCLC). **Method:** Changes in glycolysis-related molecules and glycolytic activity were evaluated in PD-L1^{low} and PD-L1^{high} NSCLC cells after transfection or knockdown of *PD-L1*, respectively. RNA seq and gene set enrichment analyses (GSEA) was also performed. The association between PD-L1 and immune response-related molecules or glycolysis were analyzed in patients with NSCLC and The Cancer Genome Atlas (TCGA). **Result:** Transfecting *PD-L1* in PD-L1^{low} cells enhanced hexokinase-2 (HK2) expression, lactate production, and extracellular acidification rates, but minimally altered GLUT1 and PKM2 expression and oxygen consumption rates. Consistently, GSEA revealed that the glycolytic pathway was enhanced in PD-L1^{low} cells after PD-L1 transfection. By contrast, knocking-down *PD-L1* in PD-L1^{high} cells decreased HK2 expression and glycolysis by suppressing PI3K/Akt and Erk pathways. Immunohistochemistry revealed that PD-L1 expression was positively correlated with HK2 expression in NSCLC tissues from patients (p<0.001). In TCGA analyses, *HK2* exhibited a positive linear association with *CD274* (PD-L1) expression (p<0.001) but an inverse correlation with the expression of *CD4*, *CD8A*, and T-cell effector function-related genes in the *CD274*^{high} rather than *CD274*^{low} group. Consistent with this, there were fewer CD8$^+$ T-cells in PD-L1^{positive}/HK2^{high} tumors compared to PD-L1^{positive}/HK2^{low} tumors in squamous cell carcinoma. **Conclusion:** PD-L1 enhances glycolysis in NSCLC by upregulating HK2, which might dampen anti-tumor immunity. PD-L1 may contribute to NSCLC oncogenesis by inducing metabolic reprogramming and immune checkpoint pathway.

Keywords: Programmed cell death-ligand-1, Hexokinase 2, Glycolysis

P2.04-43 HIGH OCCURRENCE OF LINE-1 RETROTRANSPOSITION IS CORRELATED WITH SMOKING HISTORY, LOCAL IMMUNOSUPPRESSION AND POOR PROGNOSIS IN LUSC

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Background: Somatic Long Interspersed element-1 (LINE-1) retrotransposition (RT) is a genomic process that relates to gene disruption and tumor occurrence. However, the expression and function of LINE-1 RT in lung squamous cell carcinoma (LUSC) remains unclear. **Method:** We analyzed the transcriptomes of paired LUSC samples in The Cancer Genome Atlas (TCGA), to characterize the most common somatic LINE-1 RTs in LUSC, followed by validation in an independent Chinese LUSC cohort and several cancer cell lines. We also analyzed the association between these LINE-1 RTs and clinico-pathology features, as well as the immunocyte content in local LUSC tumor tissues. **Result:** We observed LINE-1 RT occurred within 90% of tumor samples in TCGA, among which thirteen LINE-1 RTs were filtered for high occurrence in LUSC. In Chinese cohort, the expression of 13 LINE-1 RTs in LUSC tissues was significantly higher than those in matched adjacent normal tissues. Furthermore, 11 of 13 LINE-1 RTs were exclusively detected in LUSC cell lines rather than normal lung epithelial cells. Further analysis showed 3 LINE-1 RTs, including L1-FGGY, L1-ATP8B1 and L1-SVEP1 were correlated with smoking history, large tumor size, central tumor location, and poorer prognosis. The immunohistochemical staining (IHC) analysis showed that less CD3$^+$ T cells, more CD68$^+$ macrophages and CD33$^+$ myeloid-derived suppressive cells (MDSCs) were detected in LINE-1 RT positive tissues which implied that LINE-1 RT might induce significant immunosuppression *in situ*. **Conclusion:** In conclusion, LINE-1 RT is a frequent genomic event that correlates with smoking-related LUSC development and LUSC immune evasion which might be a promising predictive biomarker of poor prognosis in LUSC.

Keywords: Retrotransposition, LUSC, Immunosuppression

P2.04-44 COMBINED IMMUNE CHECKPOINT BLOCKADE IN MESOTHELIOMA: IN VIVO INVESTIGATION OF IN VITRO DATA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer that is causally associated with asbestos exposure. Due to its aggressive nature and despite the effectiveness of conventional anti-cancer treatment, the prognosis of patients diagnosed with MPM remains dismal, highlighting the urgent need for new therapeutic strategies. Our group and others have recently demonstrated PD-1 and PD-L1 expression in MPM patients, providing rationale to evaluate their suitability as immunotherapeutic targets in MPM. **Method:** Tree human cell lines representative for the epithelioid and sarcomatoid subtypes of MPM were placed in allogeneic co-cultures with healthy donor peripheral blood mononuclear cells. The co-cultures were treated with the following immune checkpoint blocking antibodies: anti PD-1 (Nivolumab®, BMS) or anti PD-L1 (Durvalumab®, AstraZeneca) in combination with anti TIM-3 or anti LAG-3. Supernatant was collected and enzyme-linked immunosorbent assays and multiplex electrochemo-luminescence were used to look at the secretion of 7 cytokines, being IFNγ, IL-2/5/6/10, IL-1band TNF-α, as well as the enzyme granzyme B. **Result:** Significant differences were found for the secretion of IFNγ, granzyme B, IL-2, IL-5 and IL-10. Though the differences were not always significant for the 3 MPM cell lines, the same trends were observed among them. Interestingly, highest concentrations of the aforementioned cytokines were all noticed for monotherapy treatment with anti PD-1, anti PD-L1 or or their combination with anti TIM-3. In vivo investigation of PD-1, PD-L1 and TIM-3 blockade, alone or in combination is required for validation of our *in vitro* results and is currently ongoing. **Conclusion:** Our data show that treatment with anti PD-1, anti PD-L1 or their respective combination with anti TIM-3 resulted in the highest secretion of cytokines and granzyme B, suggesting that these treatments stimulate the antitumor response the most. Results of our in vivo validation are awaited in order to confirm our *in vitro* findings.

Keywords: Immune checkpoint blockade, Mesothelioma

P2.04-45 A PHASE 1B DOSE-ESCALATION STUDY OF CAROTUXIMAB IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH METASTATIC NSCLC

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Background: Nivolumab has demostrated clinical benefit in advanced non-small cell lung cancer (NSCLC) patients who have progressed following platinum-based chemotherapy.Carotuximab (TRC105) is an antibody to endoglin, a receptor expressed on

proliferating endothelial cells and myeloid derived suppressor cell (MDSCs), which potently complements the activity of antibody targeting the programmed death receptor (PD-1) in preclinical models. By targeting MDSCs, carotuximab has the potential to complement nivolumab in patients with refractory metastatic NSCLC. **Method:** Patients with refractory metastatic NSCLC were enrolled regardless of baseline PD-L1 tumor expression and treated with 8 mg/kg or 10 mg/kg of carotuximab weekly for four doses and then 15 mg/kg every two weeks, in combination with the approved dose of nivolumab of 240 mg every two weeks using a standard "3+3" dose escalation design. Expansion cohorts were then opened to further assess the safety, tolerability, and preliminary efficacy by iRECIST of the recommended Phase 2 dose (RP2D) of carotuximab with standard dose nivolumab. **Result:** The combination of carotuximab and nivolumab was well-tolerated without dose limiting toxicitiy in 6 patients treated as part of dose escalation. One of these 6 patients, whose archival tumor did not express PD-L1 and who had not received prior PD-1/PD-L1 checkpoint inhibition treatment, developed a partial response and remains on study after 14 months. Two of the other 5 patients, one of whom who progressed following prior nivolumab treatment, achieved stable disease, one of whom remains on study at 7 months. Common adverse events regardless of relationship included low grade headache, vomiting, anemia, dyspnea, fatigue, cutaneous telangectasia, nausea, bleeding gums, diarrhea, and migraine. Target concentrations of carotuximab were achieved in all patients and anti-drug antibody was not detected. Enrollment is continuing in two parallel 12 patient expansion cohorts, one in patients who relapsed following prior PD-1/PD-L1 checkpoint inhibition and one in patients naive to PD-1/PD-L1 checkpoint inhibition. **Conclusion:** Carotuximab at its RP2D of 10 mg/kg weekly x 4 and then 15 mg/kg every 2 weeks was tolerable with nivolumab in patients with NSCLC, and demonstrated preliminary signs of efficacy

Keywords: immuno-oncology, metastatic NSCLC, Phase I trial

P2.04-46 TOLERABILITY AND TREATMENT-RELATED ADVERSE EVENTS OF UPFRONT PEMBROLIZUMAB COMBINATION REGIMENS IN ADVANCED NSCLC PATIENTS

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Background: Non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases diagnosed with lung cancer. Pembrolizumab is a humanized IgG4 subtype antibody that targets programmed death receptor (PD-1) of lymphocytes. Recent studies have shown that addition of pembrolizumab to traditional chemotherapy regimens improves survival in advanced NSCLC. Nevertheless, there are considerable safety concerns, ultimately leading to significant morbidity affecting patients' quality of life, and treatment discontinuation. We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of treatment-related adverse events (TRAE) and treatment discontinuation due to TRAE. **Method:** PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019 were queried. RCTs utilizing first-line pembrolizumab chemoimmunotherapy in patients with advanced NSCLC were incorporated in the analysis. The primary meta-analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q-test. **Result:** 3 RCTs (Keynote – 021,189 and 407) including 1298 patients with advanced NSCLC were included in the analysis. The study arm used standard chemotherapy regimens in combination with pembrolizumab while control arm utilized only standard chemotherapy regimens. The randomization ratio was 2:1 in Keynote-189 study and 1:1 in other studies. The pooled RR of any-grade TRAE was not significant at 1.01 (95% CI: 0.99–1.02, P = 0.29) and RR of high-grade TRAE was 1.03 (95% CI: 0.95–1.12, P = 0.47). Yet, the relative risk of treatment discontinuation due to any-grade TRAE was statistically significant at 1.75 (95% CI: 1.26–2.45, P = 0.001) and RR of treatment discontinuation due to high-grade TRAE was 1.85 (95% CI: 1.38–2.49, P < 0.0001). Treatment-related deaths were reported as 51 (6.87%) in study arm vs 32 (5.88%) in control arm. The pooled RR was not significant at 1.18 (95% CI: 0.76–1.82, P = 0.46). **Conclusion:** All grades of TRAE and treatment related deaths were not significantly increased in first-line pembrolizumab chemoimmunotherapy. However, patients on the study arm experienced significant drop-out due to TRAE, despite showing survival benefits in the studies. Proper supportive care may reduce unwanted treatment discontinuations and enhance patients' compliance.

Keywords: Pembrolizumab, Non-Small Cell Lung Cancer

P2.04-47 TUMOR MUTATIONAL LOAD, CD8+ T CELLS, EXPRESSION OF PD-L1 AND HLA CLASS I TO GUIDE IMMUNOTHERAPY DECISIONS

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Background: A minority of NSCLC patients benefit from anti-PD1 immune checkpoint inhibitor therapy. A rational combination of biomarkers is needed. The value of using a series of mechanism-of-action based parameters was studied for response prediction of immunotherapy: tumor mutational load (TML), $CD8^+$ T cell infiltration, HLA class I expression and the currently used PD-L1 tumor proportion score. **Method:** Patients were prospectively included between April 2016 and August 2017, and retrospectively analyzed. Metastatic NSCLC patients (n=30) with sufficient archival tissue, obtained prior to the first nivolumab administration, were selected. Response was assessed by RECIST v1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier methodology. TML was determined using a next-genome sequencing panel (409 cancer-related genes). Immunohistochemistry was performed to score PD-L1, total $CD8^+$ T cell infiltration and HLA class I. **Result:** In 30 patients with adenocarcinoma (67%) or squamous cell carcinoma (33%), high TML was significantly associated with better PFS (p=0.004) and OS (p=0.025). Interaction analyses revealed that patients with both high TML and high total $CD8^+$ T cell infiltrate (p=0.023) or no loss of HLA class I (p=0.026), patients with high total $CD8^+$ T cell infiltrate and no loss of HLA class I (p=0.041) or patients with both high PD-L1 and high TML (p=0.003) or no loss of HLA class I (p=0.032) were significantly associated with better PFS. Unsupervised cluster analysis based on the four markers revealed three sub-clusters, of which cluster 1A was overrepresented by patients with progressive disease (15 out of 16), with significant effect on PFS (p=0.007). **Conclusion:** This proof-of-concept study suggests that a combination of PD-L1 expression, TML, $CD8^+$ T cell infiltration and HLA class I expression function as a better predictive biomarker for the response to anti-PD-1 immunotherapy and PFS. Consequently, refinement of this proposed set of biomarkers and validation in a larger set of patients is warranted.

Keywords: immune checkpoint inhibitor, NSCLC, predictive biomarkers

P2.04-48 USE OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED LUNG CANCER AND PRE-EXISTING AUTOIMMUNE DISEASES

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Background: The prevalence of autoimmune diseases (AIDs) in patients with lung cancer is approximately 14%. However, patients with pre-existing AIDs have been excluded from trials of immune checkpoint inhibitors (ICIs) known to cause immune activation and lead to immune related adverse events (irAEs) limiting the data on safety and efficacy of these agents. Oncologists are therefore wary to use them in this at-risk population. **Method:** We conducted a single institution IRB-approved retrospective study to evaluate the safety and efficacy of combination and single agent ICI therapy in patients with pre-existing AIDs and concomitant advanced lung cancer that were treated with ICI from 2011 to 2018. Primary endpoints were incidence of irAEs and AID flares. The secondary endpoint was overall survival (OS). **Result:** We evaluated records from 29 patients with

lung cancer of which 17 (59%) had adenocarcinoma, 10 (34%) had squamous cell carcinoma, two (7%) had small cell cancer, and one (3%) had undifferentiated non-small cell lung cancer. AIDs included rheumatic (72%), gastrointestinal (10%), endocrine (10%) and neurologic (7%). 34% of patients experienced an irAE, though only 7% were severe (grade 3-4 colitis and hepatitis). 66% of patients reported no irAEs at all. The most common irAEs were dermatitis (14%) and colitis (10%). 10% of patients had to permanently discontinue ICIs due to an irAE while 17% temporarily held their ICI. 96% of patients with AIDs were either stable or in remission. AID flares were observed in 28% of patients with 24% requiring treatment. None of the AID flares resulted in permanent discontinuation of ICI therapy. 21% of patients were on immunomodulatory therapies at start of ICI treatment. The use of immunomodulatory medications was not associated with an increased incidence of either irAEs or AID flares. Median OS from ICI initiation was 8.5 months and median PFS was 6 months. There was no statistically significant difference for OS or PFS by presence of irAE or presence of immunomodulatory therapy at start of ICI use. **Conclusion:** In this cohort, patients with pre-existing AIDs and advanced lung cancer reported fewer AID flares (28%) than has been cited in the literature (approximately 50%). IrAEs were seen at an incidence similar to that observed in patients without AIDs. In our cohort, the majority of adverse reactions were manageable and did not require permanent discontinuation of ICI therapy. Furthermore, the presence of irAEs did not detrimentally affect patients' OS or PFS. Based on these findings, we would consider ICI therapy as an option in select patients with pre-existing autoimmunity.

Keywords: pre-existing autoimmune disease, Immunotherapy, toxicity

P2.04-49 NIVOLUMAB PLUS IPILIMUMAB (NI) VERSUS CHEMOTHERAPY PLUS NIVOLUMAB (CN) IN SQUAMOUS CELL LUNG CANCER (SQCLC): THE SQUINT TRIAL

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Background: Treatment landscape for patients with advanced NSCLC is rapidly evolving, with recent randomized phase III trials demonstrating superiority of chemo-immuno combinations versus chemotherapy alone. Role of chemo-free combinations, including NI, is under investigation with limited available data. Aim of the present trial is to investigate outcome of SqCLC patients when treated with NI or CN. **Method:** SQUINT (NCT03823625) is an open-label, randomized, parallel, non-comparative phase II study designed to assess the efficacy of NI (Arm A) or CN (Arm B) in patients with advanced, metastatic SqCLC. Eligibility requires age ≥ 18 years, histologically confirmed stage IV or recurrent stage IIIB SqCLC, $p63^+$/$p40^+$ and TTF^- tumour tissue, availability of PD-L1 status, no prior systemic therapy, ECOG performance status 0-1, adequate organ functions. Key exclusion criteria include concomitant radiotherapy or chemotherapy, prior treatment with immune checkpoint inhibitors, untreated brain metastases, other serious illness or medical condition potentially interfering with the study or with NI administration. Patients are randomly assigned 1:1 to receive N 360 mg Q3W plus I 1 mg/kg Q6W (Arm A) or plus platinum-based chemotherapy up to 6 cycles plus nivolumab 360 mg Q3W (Arm B), and stratified by PD-L1 expression (<1% versus ≥1%), presence of bone metastases (yes/no) and liver metastases (yes/no). In both arms, immunotherapy is given until disease progression, unacceptable toxicity, patient refusal and in any case for up to 24 months. Primary endpoint is 1-year overall survival (OS) rate in Arm A and B. Secondary endpoints include: response rate (RR), duration of response (DoR), median progression free survival (PFS) and median OS in Arm A and B, and according to predefined stratification factors. Sample size has been calculated assuming for each arm a minimum acceptable 1-year OS rate of 40% and an auspicated 1-year OS rate of 60%, a power of 90% and a one side significant level of 0.05. Based on such premises, the total number of patients required for the study is 112. **Result:** At the time of this analysis a total of 11 Italian Centers are recruiting and 25 subjects have been enrolled. **Conclusion:** We expect to conclude enrolment by January 2020.

Keywords: SqCLC, nivolumab, ipilimumab

P2.04-50 ADVANCED STATISTICAL APPROACH TELLS THE DIFFERENCE: TAYLOR-EXPANSION ADJUSTMENT FOR SURVIVAL ANALYSES IN IMMUNOTHERAPY TRIALS

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Background: The success in immune checkpoint inhibitors (ICIs) has again revolutionized the paradigm in lung cancer therapy, especially among patients without druggable driver mutations. Landmark studies, such as Keynote 010/042 and Checkmate 017/057, showed that patients in the ICI study arm had a better overall survival compared to patients receiving standard chemotherapy. Furthermore, most of the Kaplan-Meier (KM) survival curves crossed within the first 3 to 6 months and the survival curve for ICI study arm showed a long-tail, suggesting the existence of a subgroup that truly respond to ICIs. However, the traditional Cox proportional hazards model does not provide adjustment for treatment responses between true-responders and poor-responders. We hypothesize that hazard ratios (HRs) between the treatments differ from these two subgroups and adjustment is required for survival evaluation in ICI trials. **Method:** Overall survivals in Keynote 010, 042, 189, 407 and Checkmate 017/057 three-year updated data served as the real data illustrations in the current study. The Taylor expansion was applied to the adjustment of HRs derived from the traditional Cox model. Comparisons between the adjusted and the crude HRs were made and the differences in the proportion of patients with long-term survival obtained by the adjustment approach were also inferred. **Result:** Our results showed that when the adjustment approach was applied, the adjusted HRs for the ICI poor-responders compared to the chemotherapy control became statistically non-significant. Furthermore, the proportion of patients with long-term survival differed significantly between ICI true-responders and chemotherapy control. The pattern was observed in all four ICI monotherapy studies with crossing survival curves in the initial 3-6 months (Table 1).

Table 1. Changes in hazard ratio before and after Taylor-expansion adjustment.

ICI Trials	Cox model	Taylor-expansion adjustment	
	Hazard Ratio	Hazard Ratio	Differences in long-tail proportion
Checkmate 017/057 3-yr updated (2018, Annals of Oncology)	**0.70 (0.61, 0.81)**	0.89 (0.77, 1.03)	**0.10 (0.05, 0.15)**
Keynote 010 (2015, NEJM)			
Pembrolizumab 2mg/kg	**0.71 (0.58, 0.88)**	0.95 (0.77, 1.17)	**0.16 (0.04, 0.27)**
Pembrolizumab 10mg/kg	**0.61 (0.49, 0.75)**	0.92 (0.74, 1.13)	**0.23 (0.12, 0.36)**
Keynote 042 (2019, Lancet)			
PD-L1> 50%	**0.69 (0.56, 0.85)**	0.84 (0.68, 1.03)	**0.13 (0.01, 0.25)**
PD-L1> 20%	**0.77 (0.64, 0.92)**	0.88 (0.73, 1.06)	**0.10 (0.01, 0.20)**
PD-L1> 1%	**0.81 (0.71, 0.93)**	0.91 (0.80, 1.05)	**0.09 (0.01, 0.16)**
PD-L1= 1-49%	0.92 (0.77, 1.11)	0.94 (0.79, 1.14)	0.04 (-0.06, 0.13)
Keynote 189 (2018, NEJM)	**0.49 (0.38, 0.64)**	**0.67 (0.52, 0.88)**	**0.20 (0.04, 0.35)**
Keynote 407 (2018, NEJM)	**0.64 (0.49, 0.85)**	**0.71 (0.54, 0.94)**	0.08 (-0.13, 0.27)

Conclusion: The results suggested that the traditional Cox model might not be the optimal method for survival analyses in ICI trials and adjustment is necessary. The differences between the adjusted and the crude HRs may be very significant.

Keywords: Cox proportional hazards model, long-term survival, Immune Checkpoint Inhibitors

P2.04-51 A 6-GENE IMMUNE GENOMIC SIGNATURE (IGS) PREDICTS RESISTANCE TO NIVOLUMAB [NIV] IN ADVANCED PRETREATED NSCLC: RESULTS OF PRINCIPE TRIAL

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Background: Genomic abnormalities detected in immune-escape/editing-related genes may promote immunotherapy resistance. In the light of this hypothesis, we designed the PRINCiPe (Predictors of Resistance to Immunotherapy with NIV) study in APNSCLC. **Method:** FFPE-tumor blocks of APNSCLC pts undergone NIV were retrospectively sequenced for Somatic Mutations/Copy Number Variations (SM/CNV) (Ampliseq 17-genes customized panel: *APLNR*, *B2M*, *IFNAR1*, *IFNAR2*, *IFNGR1*, *IFNGR2*, *IRF9*, *JAK1*, *JAK2*, *JAK3*, *PIAS4*, *PTPN2*, *SOCS1*, *STAT1*, *STAT2*, *STAT3*, *TYK2*). End-points of the PRINCiPe study were overall-, progression-free-survival (OS/PFS) and objective response rate (ORR). **Result:** Forty-four APNSCLC pts were gathered (median age 69.5 yrs, median number of previous lines 3 [2-5], 2nd line NIV [75.0%], male/female 77.3/22.7%, squamous/non-squamous 31.8/68.2%, *EGFR* mutant 5 [11.4%], median follow-up 6.8 months [range 1-23], deaths 24 [54.5%]). *JAK3/JAK2* (7/3 pts, 15.9/6.8%) CNV and *IFNAR2* SM (4 pts, 9.1%) were the most frequent (>1 pts) abnormalities. Pts (n=15) with *JAK3*, *PIAS4*, *PTPN2*, *STAT3*, *IFNAR2* SM and/or *JAK2/3* CNV (IGS+) had a significantly lower PFS than those without (IGS-) (median PFS 2.8 vs. 6.6 months; *p=0.006*), while a trend towards significance was observed in terms of OS (median OS 5.1 vs. 13.0 months for IGS+ and IGS-, respectively; *p=0.06* log-rank, *p=0.05* Tarone-Ware). At multivariate analysis, IGS+ was independently associated with a shorter PFS (HR 2.64, 95% CI 1.3-5.4, *p=0.008*). IGS+ pts were significantly more probable to be affected by liver metastases than those without (*p=0.01*). **Conclusion:** The identified IGS appears to select APNSCLC pts with a significant lower chance to benefit from NIV, supporting intrinsic resistance. A prospective larger and external validation is ongoing, as well as the comprehensive transcriptome analysis.

Keywords: signature, genomic analysis, immunotherapy resistance

P2.04-52 IMPACT OF CORTICOSTEROIDS AND ANTIBIOTICS ON EFFICACY OF IMMUNE-CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune-checkpoint inhibitors (ICIs) are a standard-of-care in advanced non-small cell lung cancer (NSCLC). Corticosteroids are frequently used in symptomatic advanced NSCLC patients, but their immunosuppressive effect may reduce the efficacy of ICIs. Here we report our experience in patients with NSCLC and the potential impact of on-treatment use of corticosteroids and antibiotics. **Method:** Medical records of 267 patients with advanced NSCLC receiving ICIs from March 2013 to August 2018 were reviewed. Corticosteroid usage at the time of initiation or during ICIs treatment and administration of antibiotics from three months before the initiation of ICIs to 3 months after treatment end were collected. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survival (OS). A multivariable analysis was performed to study the influence of clinical characteristics on treatment efficacy. **Result:** 146 patients (55%) received corticosteroids: 63 (43%) for the treatment of irAEs and 83 (57%) for the management of baseline conditions. Prednisone (40%) and dexamethasone (35%) were the most commonly used types of corticosteroids. Median dose of prednisone equivalent was 50mg daily [5-1250mg], 92% patients received ≥10mg of prednisone equivalent daily. Median duration of corticosteroids was 59 days [0.5-83.0]. OS was longer in the group of patients that did not receive corticosteroids or received <10mg prednisone equivalent daily: 14.7 months (95%CI, 11.1-18.3) vs 8.3 months (95%CI, 6.9-9.8) (p = 0.009). No differences in PFS were observed: 4.6 months (95%CI, 2.9-6.3) vs 4.2 months (95%CI, 2.5-5.9) (p = 0.359). Patients receiving corticosteroids for baseline condition presented shorter median overall survival than the rest of the study population: 6.5 months (95%CI, 4.6-8.3) vs 16.5 months (95%CI, 12.1-20.8) (p <0.001). Multivariable analysis identified corticosteroids usage as an independent variable related to poorer outcomes. 141 patients (52.8%) received antibiotics. Quinolone (37%) and penicillin (33%) were the most commonly used groups of antibiotics. No correlation between the usage of antibiotics and efficacy of ICIs was found, with median OS of 10.2 months (95%CI, 6.4-13.9) vs 12.5 months (95%CI, 9.9-15.0) (p = 0.924). **Conclusion:** In our series, corticosteroid use of ≥10mg of prednisone equivalent daily was associated with significantly poorer outcomes, especially when given for baseline condition. No correlation was found between antibiotics and survival. It is important to underline that the use of

corticosteroids may simply identify a population with higher volume and aggressive tumors. Prudent use of corticosteroids needs to be warranted.

Keywords: corticosteroids, antibiotics, Immune-checkpoint inhibitors

P2.04-53 SERIAL ULTRA-DEEP SEQUENCING OF CTDNA REVEALS THE CLONAL EVOLUTION IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH PEMBROLIZUMAB

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Background: Immune-therapy with anti-PD1 inhibitors, such as pembrolizumab, is revolutionizing the treatment of non-small cell lung cancers (NSCLC). However, identifying patients for the potential therapeutic response and predicting therapy resistance and early relapse remains a challenge. **Method:** Between 2016 and 2018, 60 patients were treated with pembrolizumab, among who 12 NSCLC patients had both baseline (before treatment) and serial (on treatment) periodical circulating tumor DNA (ctDNA) samples. Those samples were sequenced on a 329 pan cancer-related gene panel. Analyses of tumor burden, blood tumor mutational burden (bTMB), maximum somatic allele frequency (MSAF), and tumor clonal structure were performed in association with clinical response. Resistance mutations involved in relapse and metastases were further investigated. **Result:** ctDNA was detected and mutational profiling was performed for each patient. Those with a high baseline bTMBlevel showed significantly improved progression-freesurvival (PFS) after pembrolizumab treatment. Tumor burden and therapeutic response significantly correlated with the MSAF instead of the bTMB. Clone analysis detected tumor progression about 2-4 months ahead of computedtomography (CT) scan. One mutation in gene *PTCH1* (Protein patched homolog 1) and two acquired anti-PD1 resistance mutations of gene *B2M* (β2 microglobulin) were identified in association with distant metastasis. The evolutionary tree of a representative patient was also described. **Conclusion:** This pilot study showed thatMSAF could be another good indicator of therapeutic response, and clonal analysis could be clinically useful in monitoring clonal dynamics, and detecting resistance and early relapse.

Keywords: Pembrolizumab, ctDNA, maximum somatic allele frequency

P2.04-54 CHARACTERISTIC OF MSI-H LUNG CANCER PATIENTS IDENTIFIED WITH TARGETED NEXT-GENERATION SEQUENCING

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Background: MSI-H/dMMR predicts response to immune oncology (IO) agents and is an approved biomarker for pembrolizumab therapy irrespective of histologic diagnosis. In this study, we retrospectively analyzed a large cohort of lung cancer patients using targeted next generation sequencing to examine the prevalence and clinicopathologic associations of MSI-H in lung cancers. **Method:** MSI and TMB status was derived from a 1021 gene targeted next generation sequencing panel. MSI was analyzed using MSIsensor 0.5, that relies on an empirically defined cutoff of MSI score>10%, as MSI-H. TMB analysis interrogated single nucleotide variants, small insertion and deletion, with VAF ≥3 %. TMB-H pts were identified with ≥9 mut/MB (upper quartile of data from geneplus). **Result:** 5592 lung cancer patients were interrogated in the study, with 4753 lung adenocarcinoma, 559 lung squamous cell carcinoma, 112 small cell lung carcinomas (SCLC), and 168 rare lung cancer types including pulmonary sarcomatoid carcinoma, carcinoid and so on. A total of 12 lung tumors were identified as MSI-H (0.21%), and 5 were lung adenocarcinoma (0.1%), 3 were small cell lung cancer (2.7%), 1 was lung squamous cell carcinoma (0.18%), 2 were pulmonary sarcomatoid carcinomas, and 1 was pulmonary carcinoid (1.8%). The incidence was higher in small cell lung cancer and rare lung cancer subtypes. The average diagnosis age of the 12 patients were 53 years (range: 16-74). All the patients were TMB-H, with the TMB averaged 51.23 mut/Mb (range: 10-70 mut/Mb). Two of the 5 lung adenocarcinoma patients carried *EGFR* L858R or 19del mutation. One patient who had both *NRAS* G12V and *EGFR* Ex20 mutation had tried nivolumab (120mg) for one cycle with deteriorating of cough and progression of disease. **Conclusion:** MSI-H is very rare in lung tumors, where it appears to enrich in small cell lung cancer and rare lung cancer subtypes. MSI-H lung cancer patients tend to have a younger diagnosis age. MSI-H may coexist with other driver alterations, including those negatively associated with IO response. Additional investigation is needed to determine efficacy of IO in these patients.

Keywords: MSI-H, TMB-H, Next generation sequencing

P2.04-55 TUMOR SPREAD THROUGH AIR SPACES IS ASSOCIATED WITH THE NON-INFLAMED IMMUNE MICROENVIRONMENT IN LUNG SQUAMOUS CELL CARCINOMA

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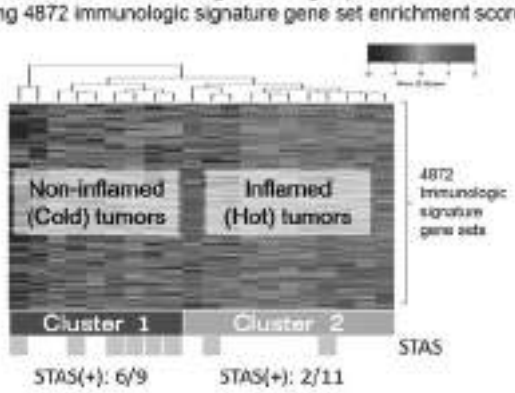
Background: Tumor spread through air spaces (STAS) is reportedly a poor prognostic factor in non-small cell lung cancer. However, little is known about the molecular background and tumor microenvironment associated with STAS. This study assessed the relationship between STAS and tumor microenvironment in lung squamous cell carcinoma using next generation sequencing data. **Method:** RNA-sequencing and whole-exome sequencing were performed in 20 surgically resected lung squamous cell carcinoma cases. Pathological specimens were reviewed to determine the existence of STAS. Somatic mutations, gene expression and gene set enrichment were analyzed and compared between STAS positive and negative tumors. **Result:** Among 20 patients, nine were pathological stage I, six stage II and five stage III. In all, eight tumors were positive for STAS and 12 were negative. While STAS was not associated with tumor size, all N2 tumors were positive for STAS. Tumor mutational burden was not associated with STAS. Hierarchical clustering using the single sample Gene Set Enrichment Analysis score of 4872 immunologic signature gene sets revealed two clusters (Figure 1). Cluster 1 revealed lower expression of immune-related genes, forming a cluster of non-inflamed (cold) tumors. The cluster of non-inflamed tumors showed a tendency to higher STAS positivity (Cluster 1, 67%; Cluster 2, 18%; p=0.065). Next, we performed Gene Set Enrichment Analysis between STAS positive and negative tumors. Using 50 Hallmark gene sets in the Molecular Signatures Database, gene sets of allograft rejection, IL2-STAT5 signaling, inflammatory response and complement were found to have a significantly lower expression in STAS positive tumors (q <0.05). We further investigated the expression of each immune-related gene and compared them between STAS positive and negative tumors, which showed that PD-L1 gene expression was significantly lower in STAS positive tumors (p=0.023).

Figure1. Hieralchical clustering of 20 lung Squamous cell carcinoma using 4872 immunologic signature gene set enrichment scores



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Conclusion: STAS positivity was associated with the non-inflamed tumor-immune microenvironment in lung squamous cell carcinoma. Our findings might partly explain the aggressive behavior of STAS positive tumors. Since the efficacy of immunotherapy might differ between STAS positive and negative tumors, further investigation of immunological and molecular aspects of STAS positive tumors is needed.

Keywords: STAS, Squamous cell carcinoma

P2.04-56 IMPROVED SURVIVAL OF NSCLC FILIPINO PATIENTS GIVEN AUTOLOGOUS DENDRITIC CELL VACCINE: CASE SERIES WITH CTC UPGRADE AND IL15

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Background: Lung cancer remains to be a major malignancy among Filipinos with a fatality rate of 19.2 for every 100,000 in 2018. The Molecular Diagnostics and Cellular Therapeutics Laboratory of the Lung Center of the Philippines has developed a complimentary therapy using autologous dendritic cell vaccine for lung adenocarcinoma, the preliminary result of which was reported in this Conference in 2013. From then onwards, a number of modifications has been incorporated in the protocol as part of the continuing research and development program of the Center. Herein, reported is the comparative performance of the vaccination protocol in the period 2009-2013 and 2014-2018 and the modifications introduced that accounted for the improved survival. **Method:** Chart data of sixteen lung adenocarcinoma patients in 2009-2013 and five patients in 2014-2018 who have undergone the immune cell therapy as part of their treatment regimen, were retrieved and compared in terms of their survival in 3, 6 and 9 month timepoints. Protocol for immune cell therapy in the same period were also retrieved and compared. The patients have executed corresponding informed consent and their therapy has undergone ethics review and approval of the Stem Cell Ethics Committee of the Center. **Result:** Patients in 2009-2013 included 1 stage1, 1 stage 2, 6 stage 3 and 8 stage 4, while patients in 2014-2018 included 1 stage 1 and 4 stage 4. For stage 1, there was a 100% survival in the 3, 6 and 9 month timepoints in both periods. For stage 4 there was a 87.5%, 50% and 12.5% survival respectively in the 3, 6 and 9 month timepoints for the 2009-2013 period while a 100%, 75% and75% survival for 2014-2018 period. Protocol evaluation showed an increase in circulating tumor gene targets used for peptide priming (i.e. from 15 to 22 targets) and the use of IL15. The additional targets included were: BRACHURY, CD133, hTERT, p53, NRAS, S100A14, and CA125 **Conclusion:** Although preliminary, the additional targets and the use of IL15 could be attributed to the improved survival rate of patients, especially for stage 4 patients.

Keyword: autologous dendritic cell vaccine, lung adenocarcinoma, circulating tumor gene targets

P2.04-57 PREDICTIVE AND PROGNOSTIC VALUE OF CTC MONITORING IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint inhibitors (ICI) have recently emerged as a treatment option for selected patients with advanced non-small-cell lung cancer (NSCLC). However, there is a lack of effective biomarker to predict the treatment response and monitor disease progression. In this prospective observational study, we aimed to investigate the predictive and prognostic value of folate receptor-positive circulating tumor cell (FR+CTC), a well-established lung cancer biomarker, in advanced NSCLC patients treated with ICIs. **Method:** Advanced NSCLC patients with at least one measurable lesion and expected to undergo ICIs treatment were recruited. Peripheral blood samples were collected from each participant at baseline, after each cycle of ICI treatment, and on disease progression. FR+CTCs were enumerated by using negative enrichment and ligand-targeted polymerase chain reaction methods. Treatment efficacy was analyzed according to the iRECIST criteria. The correlation of FR+CTC level and its dynamic changes with radiological responses was evaluated. **Result:** Of the 35 patients, 17 received first-line treatment, 10 received second-line treatment, and 8 received third-line treatment or above. CTCs were detected (≥8.7FU/3ml) in 80.0% of patients at baseline. The baseline CTC of first-line/second-line therapy patients was significantly higher than that of third-line and above therapy patients (median values 16.68 vs 8.36, P=0.017). Meanwhile, there was no significant difference in baseline CTC values between different pathological subtypes and whether PD-L1 was expressed or not. For the radiological responses, after at least two cycles of ICI treatment, PR, SD, and PD were found in 10, 8, and 4 patients, respectively. The CTC count in the PD group at baseline was significant higher than that of the disease control (PR+SD) group (P=0.033). Similarly, the CTC value after two cycles of ICI treatment in PD group (17.84 ± 7.03) was higher than SD/PR group (12.50 ± 4.94), but not statistically significant (P=0.081). However, the changes of CTCs after one or two cycles of immunotherapy were poorly related to the treatment response (P>0.05), perhaps because of the polarization trend of CTC changes in the PR group after treatment. **Conclusion:** In sum, these data confirm the predictive significance of CTCs in advanced NSCLC patients treated with immune checkpoint inhibitors. The baseline CTCs value correlated significantly with radiological response. Further studies are needed to confirm whether CTCs can be used as a prognostic factor for advanced non-small cell lung cancer.

Keywords: circulating tumor cell, immune checkpoint inhibitor, non-small-cell lung cancer

P2.04-58 THE CORRELATION BETWEEN TMB AND CLINICAL FACTORS IN EAST ASIAN LUNG CANCER PATIENTS WITH NO TKI-RELATED DRIVER GENE-MUTATIONS

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Background: Clinical factors, such as stage, metastasis, pathological type, age, smoking, gender and tumor mutational burden (TMB), have been reported to correlate with the prognosis of lung cancer (LC). However, it is still unclear how these factors influence the outcomes of patients with no TKI-related driver gene-mutations, and how these factors inter-correlate with each other. The aim of this study was to investigate the inter-correlation of these clinical variables in East Asian LC patients with no TKI-related driver gene-mutations to provide suggestions for patient selection and prognosis prediction. **Method:** 122 primary lung cancer patients without TKI-related driver gene (EGFR, ALK, ROS1, RET, BRAF, C-MET, HER2) mutations were recruited, in which 67 patients were confirmed with stage IV LC. Gene variations were determined in tumor tissue by whole-exome sequencing (WES). SPSS 20 software were used for statistics analysis, and P-values < 0.05 were considered significant. **Result:** In 122 enrolled patients, 110 (90.2%) were male, 87 (71.3%) had smoking history and 95 (77.9%) were older than 60 years old. Significant differences in TMB were observed between male and female (P <0.05), but not between patients with or without smoking history (P >0.05). Patients older than 60 years old had dramatically higher TMB than those younger than 60 (P <0.05). Gender, smoking history, age, lung cancer subtype were not associated with the occurrence of brain or bone metastases (P >0.05). The mean TMB measured by WES was 4.5 mutations/Mb for all lung cancer patients. It was notable that the ratio of patients with TMB ≤4.5 was 68.2% (15/22) and 41.7% (5/12) for bone and brain metastatic patients, respectively. .Although the difference was not significant (P=0.163), the trend suggests that there may be a metastasis-specific difference in TMB. **Conclusion:** Result from this exploratory study confirmed the gender preference in patients without TKI-related driver gene mutations. Male and elder patients with higher TMB may be the population that benefits more in immunotherapy. Although clinical the factors were not found to correlate with metastatic sites in this study, larger cohorts may find significant correlation, which could lead to the identification of novel biomarker for patient stratification or selection in therapies.

Keywords: Lung cancer, TMB, clinical factors

P2.04-59 PATIENT SURVIVAL IN NSCLC BASED ON PDL1 EXPRESSION AND TISSUE ORIGIN

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Background: Patients with NSCLC who have high PDL-1 expression have favourable outcomes when treated with checkpoint blockade compared to those who don't. Here we consider patient outcomes based on the origin of tumour biopsy and PDL-1 expression. This has not been widely considered or published. **Method:** Patient tissues which were assessed for PDL-1 expression between 2013 and 2017 were identified using a central electronic pathology database. In addition, patients who were treated and tested locally between August 2015 and December 2017 were selected using an electronic chemotherapy database. A total of 422 patients were identified. Duplicates and patients who did not have enough cells for analysis (less than 100) were excluded from analysis. Individuals treated on clinical trials were included. Tissues were grouped into lung, lymphoid, pleural or other. Other included sites such as bone, cerebral or adrenal metastasis. Analysis was carried out using SPSS 25. **Result:** Lung tissue: Patients with negative PDL-1 expression (n= 67) median OS was 619 days (95% Confidence Interval 428 -809 days). This included patients who were treated with EGFR and ALK inhibitors. In contrast, those who were PDL-1 positive (n= 106) and exposed to check point blockade, median OS was 511 days (95% Confidence Interval 373- 648 days). Lymph tissue: Patients who had negative PDL-1 expression (n= 21) median OS was 284 days (95% Confidence Interval 196 -361 days), compared to those who had high PDL-1 expression and managed with immunotherapy (n= 46) whose median OS was 546 days (95% Confidence Interval 128 -963 days). Pleural tissue: Tissues which were negative for PDL-1 expression (n= 6) median OS was 90 days (95% Confidence Interval 122- 477 days). Individuals who expressed high levels of PDL-1 (n= 15) median OS was 1253 days (95% Confidence Interval 642- 1864 days) for those who were exposed to immunotherapy. Other: In those with negative PDL-1 expression (n= 8) median OS was 1013 days (95% confidence interval 112- 1913 days). Patients with high PDL-1 expression and treated with immunotherapy had a median OS of 337 days (95% Confidence Interval 12- 661 days). **Conclusion:** OS was highest in patients who had high PDL-1 expression assessed in pleural tissues. In patients where PDL-1 expression was assessed in other tissues the worst outcomes were observed, possibly due to patient and disease factors. Some tissues may be PDL-1 rich or sparse based on origin. This may affect PDL-1 expression and subsequently patient outcomes. This warrants further investigation.

Keywords: PDL1 expression, overall survival, NSCLC

P2.04-60 PEMBROLIZUMAB-BASED REGIMENS ADMINISTERED AT NON-STANDARD FREQUENCY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Pembrolizumab (P) administered every 3 weeks ± chemotherapy is a standard treatment option for advanced NSCLC. However, other than modeling and simulation-based analysis, there have been no post-approval studies to determine the optimal administration frequency or if longer intervals between administrations are effective. **Method:** We retrospectively reviewed medical charts of 81 patients with advanced NSCLC treated with P for at least 4 cycles at a single academic center (02/2016-3/2019). 2 patients groups were selected: those who received 3 or more P-based regimens at non-standard frequency intervals between cycles longer than 3 weeks ± 3 days (group A), or those who received P-based regimens at standard frequency or up to 2 non-standard cycles (group B). Descriptive tables of demographic details, tumor characteristics, treatment details, and immune-related adverse events (irAEs) were generated. Kaplan-Meier survival analysis and Cox proportional hazards model for multivariable regression analysis were utilized. **Result:** Of 81 P-treated patients, 47 (58%) had received at least 4 cycles (group A: 14, B: 33). There were no significant differences between groups in sex, stage at diagnosis, smoking status, driver oncogene mutations, PD-L1 expression, tumor mutation burden, line of therapy, performance status or grade 3 irAEs. Patients in group B were more likely to receive P + chemotherapy (group A: 0%, B: 33.3%, p = 0.02). Patients in group A were more likely to have any grade irAEs (groups A: 78.6%, B: 33.3%, p = 0.024). The reasons for any non-standard cycles in group A were: irAEs (14.3% patients), non-irAE medical issues (35.7% patients) and solely non-medical patient-physician preference (50% patients). Median time to treatment discontinuation (TTD) was significantly longer in group A than group B (24 months vs 5 months, p <0.0001), as was median overall survival (OS) (Not reached vs 14 months, p=0.0029). Patients in group A continued to show significantly longer overall survival when adjusted for confounding variables (Hazard Ratio 5.6, p=0.029). **Conclusion:** Our data, though limited by sample size and single institution design, shows that a significant proportion of patients receive P at extended intervals in routine clinical practice and with no worse outcomes than would be expected for those with advanced NSCLC receiving P at label-specified 3-week intervals. Given the durability of benefit seen in such patients, this requires confirmation in larger datasets and prospective trials so as to maximize patient experience and clinical outcomes while minimizing financial toxicity.

	Group A (≥ 3 Non-standard cycles)	Group B (Standard or ≤ 2 non-standard cycles)	p-value chi-square log-rank test)
	N = 14	N = 33	
Median OS, months (95% CI)	Not reached (14 - not reached)	14 (8 - not reached)	0.0029
Median TTD, months (95% CI)	24 (17 - not reached)	5 (4-6)	<0.0001

Keywords: Pembrolizumab, Non-standard frequency, advanced non-small cell lung cancer

P2.04-61 PRELIMINARY REPORT OF A MULTIDISCIPLINARY TASK GROUP FOR THE STUDY OF IMMUNE-MEDIATED PULMONARY TOXICITY

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Background: Immunotherapy (IO) is now the standard of care for many tumor types. However, it is not free of risks, being pulmonary toxicity one of the most relevant immune-related adverse event due to its severity. Differential diagnosis with other pulmonary complications such as infections or tumor dissemination further complicates its management. **Method:** In order to raise awareness, gather information, and to discuss early management strategies in patients (pts) with immune-related interstitial lung disease (irILD), in 2017 we created a multidisciplinary task group comprised of pneumologists, pathologists, oncologists and radiologists. We herein report the main features of the first series of pts treated with IO who subsequently developed ILD, prospectively identified from a tertiary University Hospital over a period of two years (2017-2019), focusing on clinical presentation, radiological patterns, outcomes and therapeutic intervention. **Result:** We identified a total of 23 pts with suspicion of irILD. Patients mainly received programmed cell death-1 (PD-L1) inhibitors (61%). Main characteristics are summarized in Table 1. ILD occurred more often in males, and former or current smokers (91%), with a median age of 62 years. The most common radiological pattern was the presence of ground-glass opacities (87%), followed by consolidations (61%). Forty-eight percent of the cases had grade 3 severity according to the Common Terminology Criteria for Adverse Events (CTCAE). Thirteen of the patients (57%) underwent a fibrobronchoscopy during the diagnostic period and a specific microorganism was isolated from BAL in three cases (13%) (*Aspergillus fumigatus*, cytomegalovirus and herpes type 1 virus). Ten pts (43%) underwent transbronchial biopsies being focal organizing pneumonia and desquamative changes the most

common pathological patterns observed. Twenty patients (87%) received prednisone (1mg/kg/day) and thirteen of them (57%) also received antibiotic treatment.

		Patients (%)
Mean age (years)		
		61.63 ± 12.35
Gender		
Male		19 (83%)
Female		4 (17%)
Smoking history		
Current		2 (9%)
Never		7 (30%)
Former		14 (61%)
Type of cancer		
Lung		8 (35%)
Kidney		5 (22%)
Skin		4 (17%)
Others*		6 (26%)
*** Others: haemathologic, bladder, liver, sigma, urothelial, timic.**		
Immunotherapy		
Nivolumab		8 (35%)
Pembrolizumab		6 (26%)
Durvalumab		2 (9%)
Others*		7 (30%)
* Others: Atezolizumab, Nivolumab+Ipilimumab, Atezolizumab+Daratumumab, Atezolumab+Bevacizumab, CX-072, Nivolumab/Nivolumab+Ipilipumab, Avelumab.		

Conclusion: Immuno-mediated pulmonary toxicity is a rare but severe complication that carries a significant mortality. Due to their complexity, multidisciplinary approach is required to provide an adequate treatment and to guarantee early intervention.

Keywords: Pulmonary toxicity, Immunotherapy

P2.04-62 TCR REPERTOIRE ANALYSIS OF PERIPHERAL CD8+PD-1+ T CELLS IS EFFECTIVE AS A PREDICTIVE BIOMARKER FOR RESPONSE TO THE IMMUNE CHECKPOINT INHIBITOR

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Background: Immune checkpoint inhibitors are effective in NSCLC patients. As patient selection is important, many biomarkers have been studied. We developed a method to predict the effect of immune checkpoint inhibitors using peripheral blood. Tumor infiltrating lymphocyte (TIL) sensitizes to neoantigens, some of them migrate to peripheral blood. We measured tumor mutation burden (TMB) of resected specimen and T-cell receptors (TCRs) diversity of peripheral CD8+PD-1+ T cells, examined response rate and prognosis. **Method:** The study included NSCLC patients who relapsed after surgery and chemotherapy failed. Peripheral blood mononuclear cells (PBMC) was collected from patients before 1st administration of nivolumab. CD8+PD-1+ T cells were subjected to FACS sorting, NGS-based TCR repertoire analysis was performed by Repertoire Genesis Inc., and TCR diversity was evaluated statistically. **Result:** There were no differences in the proportion of PD-1+ in CD8+ T cells between responders and non-responders. TCR α diversity based on DE50 was significantly higher among responders than non-responders ($P < 0.01$). TCR β diversity was also significantly higher among responders than non-responders ($P < 0.01$). Progression-free survival (PFS) and Overall survival (OS) were better in TCR diversity high group than that TCR diversity low group (P=0.01). TMB was not significantly different between responder and non-responder. PFS and OS were not significantly different between TMB high (≧10) group and TMB low (<10) group. **Conclusion:** Significant therapeutic effect of nivolumab was observed in NSCLC patients whose peripheral CD8+ PD-1+ T cells had highly diverse TCR. This study suggests the TCR diversity of peripheral CD8+PD-1+ T cells is effective as a predictive biomarker for response to the immune checkpoint inhibitor.

Keywords: TCR repertoire, Immune Checkpoint Inhibitors, Biomarker

P2.04-63 EVALUATION OF COMBINED BIOMARKERS FOR TUMOR RESPONSE TO IMMUNOTHERAPY (I/O) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Immune checkpoint inhibitors have revolutionized NSCLC treatment. At present, the only established predictive biomarker for I/O-therapy stratification are PD-L1 expression and MSI status. However, the expression of PD-L1 is limited by heterogeneous expression and even high expressors not always respond to I/O therapy. The aim of the study is to evaluate the value of combinations of positive (Tumor Mutational Burden, PD-L1) and negative (a.o. CD73 expression and inactivating STK11 mutations) predictive markers in patients (pts) with advanced NSCLC on I/O therapy. **Method:** A retrospective study was performed on a cohort of 54 pts with advanced NSCLC that have been treated with I/O between 2015 and 2018. Pts were selected by the availability of tumor tissue and based on tumor response evaluated by RECIST v1.1 criteria: only patients with durable tumor response (CR,PR ≥ 6 months) and patients with no tumor response (PD as best response) were analyzed for biomarkers: hybrid capture NGS assay for TMB (New Oncology) including STK11 mutations and IHC tests for PD-L1, CD73 and VISTA. Adjusted Cox regression and ROC analysis will be performed to evaluate the predictive value of the different biomarkers. **Result:** 43/54 pts received nivolumab, 11/54 pembrolizumab in different therapy lines (from 1st to 5th line). 24 pts were defined as having a durable tumor response (median PFS 20 months, median OS not reached) 30 pts as primary progressors (median PFS 2 months, $p<0.0001$), median OS 12 months, $p<0.0001$). In 30/54 pts enough material was available for TMB testing. The median TMB-value is 11.42 mutations/Mb. In 13 durable responders median TMB-value was 13.28 mutations/Mb versus 11.00 mutations/Mb in 17 primary non-responders. STK11 mutations were observed in 3/17 primary non-responders (10%) vs. 0/13 in durable responders (0%). Additional analyses of PD-L1, CD73, and VISTA will be presented at the meeting as well as correlative data of the parameters analysed. **Conclusion:** Our results suggest that integrating several biomarkers including positive and negative predictive markers may correlate better with responses to I/O than PD-L1 and TMB alone.

Keywords: NSCLC, Immune Checkpoint Inhibitors, tumor mutational burden

P2.04-64 222 NSCLC'S CLASSIFIED BY PAM50: LUMINAL A NSCLC IS A DISTINCT SUBTYPE WITH LOW TMB AND IMMUNE SUPPRESSIVE TME

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Background: Breast Cancer (BC) and NSCLC are heterogeneous diseases with distinct disease subtypes. A 50-gene qPCR assay (PAM50) identifies 5 intrinsic biological subtypes: luminal A, luminal B, HER2-enriched, basal-like, and normal-like breast cancer. NSCLC subtypes are often divided by driver oncogene mutations. We assessed the association of genomic and transcriptomic patterns in molecular NSCLC subtypes using a 50-gene breast cancer classifier. **Method:** Retrospective analysis on Whole exome (WES) DNA and deep whole transcriptomic sequencing (RNA-Seq) (~200x10^6 reads per tumor) data from NantHealth was done. BC intrinsic subtype sorting based on RNAseq assay was used to classify breast tumors into luminal A, luminal B, HER2-enriched, basal-like, or normal-like. Immune Checkpoint therapy (ICT) gene expression was measured for PDL1,CTLA4,LAG3, IDO,TIM3,OX40,FOXP3,TIGIT, and PDL2. **Result:**

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A total of 222 NSCLC patients were classifiable using RNAseq. The molecular BC subtype distribution was 38.74% Luminal A, 32.88% Luminal B, 14.41% HER2-enriched, 9.46% basal-like, and 4.50% normal-like. Using a TMB cutoff of 200 Non-synonymous variants (Rizvi et al), there was a significant difference between LumA and LumB (OR 0.39, p=0.0014) for TMB high v low, which is similar in BC, with LumA v LumB (OR 0.46, p=0.014). In the TMB low LumA group there was a 23% EGFR mut+ rate, with 0 EGFR mut+ in the LumA TMB high group. ICT gene expression showed no difference in PDL1 expression between subgroups, but TIM3 was significantly higher in LumA and lower in Basal. ICT co-expression patterns in LumA suggest TME suppression via TIM3, IDO, and OX40 expression. Gender difference did not affect subtype classification distribution. **Conclusion:** In this retrospective analysis of NSCLC using PAM50 classification we found similar subtype distributions as BC with both LumA BC and LumA NSCLC subtype as a distinct subgroup characterized by low TMB, and LumA NSCLC with high EGFR mutation frequency, and ICT suppressive TME, suggesting potential uses of the 50 gene BC classifier in NSCLC trial design and treatment for checkpoint inhibitor eligible patients.

Keyword: PAM50, RNAseq, TMB

P2.04-65 PEPTIDE-BASED CANCER VACCINE SHORTENED THE OVERALL SURVIVAL OF A LARGE PORTION, BUT NOT ALL, OF ADVANCED CANCER PATIENTS

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Background: We have been promoting clinical trials of peptide-based cancer vaccination for various cancers, mainly at Kurume University School of Medicine. **Method:** Objective: To determine biomarkers predictive of overall survival (OS) in advanced cancer patients treated with a peptide-based cancer vaccine. Patients: The samples from two randomized, double-blind, placebo-controlled, phase III trials of personalized peptide vaccine (PPV) for advanced prostate cancer patients (n=306) and recurrent glioblastoma (n=88) patients, those from one single arm phase II trial of PPV for various types of advanced cancer patients (n=2588), and those from one randomized placebo-controlled non-personalized phase II trial (n=51) for advanced prostate cancer patients were provided for this retrospective biomarker study. **Result:** No significant differences in clinical benefit (overall survival, OS) were found between the patients receiving PPV and those receiving placebo in each of the two randomized, double-blind, placebo-controlled, phase III trials. The neutrophil or lymphocyte proportion in advanced prostate cancer patients prior to study entry was a biomarker discriminating the PPV patients (70%) who showed significantly shorter OS relative to placebo patients from the remaining PPV patients who showed significantly longer OS relative to placebo patients. The C-C motif chemokine 2 (CCL2) level prior to the study entry in recurrent glioblastoma patients was the other biomarker discriminating the PPV patients (40%) who showed significantly shorter OS relative to placebo patients from the remaining PPV patients who showed significantly longer OS relative to placebo patients. The neutrophil or lymphocyte proportion prior to the phase II study entry (n=2588) was also a biomarker discriminating the PPV patients (60%) with significantly shorter OS from the remaining PPV patients entered in the single arm phase II study in all the advanced cancer patients other than gastric cancer or glioblastoma patients. Notably, the median OS for the 250 of 399 lung cancer patients (62 %) who met either or both the cutoffs of neutrophils ^{3}64% and lymphocytes <26% was significantly shorter than that of the remaining 149 patients (38%) (9.5 month,95% confidence interval: 7.6-11.9 vs 20.0 month,13.0-25.3, p<0.001). The CCL2 level, however, prior to the study entry was not a biomarker in these lung cancer patients receiving PPV. This biomarker was also predictive of OS in a randomized placebo-controlled non-personalized phase II trial of peptide-based vaccine. **Conclusion:** Peptide-based cancer vaccine shortened the OS of a large portion, but not all, of advanced cancer patients with various types of cancer. Prospective clinical studies of peptide-based cancer vaccines using the newly defined prognostic markers may be warranted.

Keywords: peptide-based cancer vaccine, Biomarker, overall survival

P2.04-66 IMMUNOTHERAPY FOR ALL? REPRESENTATION OF MINORITIES AND THE ELDERLY IN LUNG CANCER IMMUNOTHERAPY TRIALS

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Background: Minority groups have been historically underrepresented in oncology clinical trials (CT). Disparities also exist among patients with lung cancer (LC), with Black males having the highest mortality rates of all subgroups. In 2015 the first immune checkpoint inhibitor was FDA approved for the treatment of LC, since then these agents have become a cornerstone of LC treatment. We aimed to determine the representation of ethnic minorities and elderly patients in immunotherapy LC trials. **Method:** Enrollment data from therapeutic immunotherapy LC trials with published results in ClinicalTrials.gov or individual trial publications from 2008 to 2019 was analyzed. Clinical trials that were terminated early or those that did not report race/ethnicity were excluded. Enrollment fraction (EF) was calculated as the number of trial enrollees divided by the 2015 SEER LC prevalence. **Result:** We identified 29 CT of which 22 (76%) reported race/ethnicity with a total of 11,149 CT enrollees. Majority of CT were phase 3 (54%), international trials (95%), for advanced stage NSCLC (82%). Distribution by sex, age, race/ethnicity and comparison with LC prevalence and US census are described in table 1. Clinical trials participation varied significantly across ethnic groups, Whites (EF 2.4%) and Asians (EF 12.4%) were more likely to be enrolled compared to Blacks (EF 0.46%) and Hispanics (EF 0.85%). Younger patients (<65 years-old) were more likely to be enrolled when compared to older adults, despite the national median age of LC diagnosis being 70 years-old.

	Trial Participants		Enrollment Fraction	Lung Cancer Incidence*‡	Lung Cancer Prevalence*^	2010 US Census
Characteristic	N	%	%	%	%	%
Total	11149		2.1			
Sex						
Male	7275	65.0	3.0	57.2	44.2	49.2
Female	3859	35.0	1.3	42.8	55.8	50.8
Age†						
< 65 years-old	4733	55.2	3.9	4.8	28.2	87.0
≥ 65 years-old	3835	44.8	1.2	95.2	71.8	13.0
Race/Ethnic group						
White	8531	76.5	2.4	68.1	84.5	72.4
Black	209	1.9	0.5	13.4	10.8	12.6
Hispanic	136	1.2	0.9	11.8	3.8	16.3
Asian/Pacific Islander	2027	18.2	14.2	6.0	3.4	5.0
American Indian/ Alaska Native	35	0.3	-‡	0.7	-‡	0.9
Other	163	1.5				6.2
Unknown	132	1.2				

*Age adjusted; ‡Data from 2015 SEER 18; ^Data from 2015 SEER 13; †Subgroup analysis of 15 trials; ‡2015 SEER did not report prevalence for American Indian/Alaskan Native.

Conclusion: Minority and elderly patients were less likely to be enrolled in immunotherapy LC trials from 2008 to 2019. The underrepresentation of these groups leaves knowledge gaps regarding their response and tolerability to immunotherapy, leading to the extrapolation of data from other populations to treat minority and elderly patients. Future CT should take measures to recruit participants that adequately represent our LC population and increase minority recruitment.

Keywords: Immunotherapy, clinical trials, Minorities

P2.04-67 COMPARATIVE ANALYSIS OF TMB AND MUTATIONS BY COMPREHENSIVE GENOMIC PROFILING (TSO500) IN FFPE NSCLC SAMPLES

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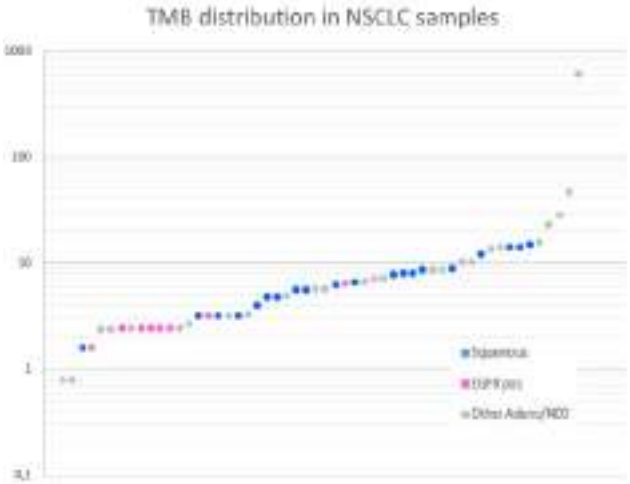
Background: Precision oncology for NSCLC involves an increasing number of targeted drugs and immunotherapy options. Comprehensive genetic profiling has been used in clinical studies to assess predictive biomarkers and mutation patterns, i.e. tumor mutation burden (TMB) associated with checkpoint therapy response. However, limited access to broader sequencing approaches, associated complex bioinformatic pipelines and issues with cross-platform reproducibility remain important hurdles for routine molecular pathology. **Method:** Here we have used the novel TSO500 gene panel (523 genes, 1.95 Mb) on the NextSeq platform (Illumina) to analyze representative surgical FFPE NSCLC specimens (n=50). Detected mutations were evaluated in comparison to matched results from routine diagnostic sequencing based on a custom 18-gene HaloPlex panel (Agilent). Obtained TMB-scores will be compared to data from analysis with the FoundationOne CDx assay (work in progress). **Result:** All 50 samples passed the pre-set QC filters. We found a wide range of TMB-values (0.79 to 610 non-synonymous mutations per Mb) with a median score of 5.6 mut/Mb (Figure 1). EGFR positive cases were found in the lower TMB range, while the remaining adenocarcinoma and squamous cell carcinomas were evenly distributed across the TMB spectrum. All known variants (n=105) from routine sequencing could be detected in the TSO500 data set (Illumina and in-house bioinformatic pipeline) with similar variant allele frequencies (r= 0.76). **Conclusion:** Variant calling with regard to NSCLC hot-spot mutations seems to be robust, but the precision and performance of TSO500 outside clinical hot-spot regions remain to be established. The distribution of TMB scores in our series of NSCLC seems to be consistent with previously published data and concordance to results with FoundationOne CDx will be presented.



Keywords: Immune oncology, Tumor Mutation Burden, Next generation sequencing

POSTERS

P2.04-68 RETROSPECTIVE ANALYSIS OF IMMUNE CHECKPOINT INHIBITORS IN NSCLC: IMMUNE-RELATED ADVERSE EVENTS AND OUTCOMES

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Background: In the United Kingdom, immune check-point inhibitors (ICPi) including pembrolizumab, atezolizumab and nivolumab are routinely used in advanced NSCLC. These agents are associated with immune-related adverse events (irAE). We present a single centre experience of a tertiary lung cancer centre on the incidence and severity of irAE, with hospitalisation episodes and duration. Patient outcomes were compared with radiological assessment of response, Neutrophil to Lymphocyte ratio (NLR) and Platelet to Lymphocyte ratio (PLR). High NLR and PLR may predict for poorer outcomes following ICPi treatment. **Method:** This was a single-centre retrospective analysis of the electronic records of NSCLC patients who received treatment with an ICPi between January 2017 and December 2018. Patients on clinical trials were excluded. NLR and PLR were derived from the most recent pre-treatment peripheral blood sampling. The subjective response as recorded in radiological reports of cross-sectional imaging was noted. The first response was defined as the response reported in the first scan after initiation of treatment and the best response was defined as best recorded response across all scans following treatment. Kaplan Meier survival analyses were performed. **Result:**

Patient characteristics and response		
Patient Characteristics	**N=46**	**%**
Median age	64.8 (range 48.1 to 81.9)	
Male	28	60.9
Female	18	39.1
Treatment		
Atezolizumab	7	15.2
Pembrolizumab	39	84.8
Line of treatment		
First	20	43.5
Second	20	43.5
Third	6	13
Histology		
Adenocarcinoma	34	73.9
Squamous	8	17.4
Other NSCLC	4	8.7
First response to treatment		
Progressive disease	18	39.1
Stable disease	3	6.5
Partial response	10	21.7
Complete response	1	2.2
Mixed response	10	21.7
Not assessed	4	8.7
Best response to treatment		
Progressive disease	17	37
Stable disease	3	6.5
Partial response	11	23.9
Complete response	2	4.3
Mixed response	9	19.6
Not assessed	4	8.7
irAE and grade (54 events)		
Anorexia, G1-2	2	3.7
Arthritis, G1-2	1	1.9
Arthritis, G3	1	1.9
Diarrhoea, G1-2	4	7.4
Diarrhoea, G3	4	7.4
Diarrhoea, G5	1	1.9
Endocrinopathies, G1-2	6	11.1
Fatigue, G1-2	12	23
Fatigue, G3	3	5.6
Liver dysfunction, G1-2	1	1.9
Nausea/Vomiting, G1-2	6	11.1
Pneumonitis, G3	1	1.9
Pruritus/Rash, G1-2	10	18.5
irAE hospitalisation events	9	19.6
Median length of hospitalisation	8.5 days (range 1 to 19)	
Mean NLR	5.90 (range 0.98 to 28.04)	
Mean PLR	272.02 (range 83.5 to 893.3)	

First recorded radiological response was a predictor of best radiological response and OS, p=0.003. NLR and PLR above mean were predictive factors for decreased OS (HR 3.99, 95% CI 2.01 to 14.35, p=0.0009; HR 2.09, 95% CI 0.84 to 4.87, p=0.119). **Conclusion:** Most patients experienced at least 1 irAE. 1 in 5 had irAE grade 3 or above requiring hospitalisation. The burden of irAE and increased hospitalisation time and costs are likely to increase secondary to the increased use of ICPi in combination with platinum-doublet chemotherapy in the first-line setting for advanced NSCLC. Response at first radiological assessment was a predictor of outcome. NLR and PLR are potential readily measurable predictive biomarkers.

Keywords: irAE, immuno-oncology, NSCLC

P2.04-69 IMPACT OF ANTIBIOTIC USAGE ON SURVIVAL DURING CHECKPOINT INHIBITOR TREATMENT OF NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Growing evidence suggests that the gut microbiome influences response to second line checkpoint inhibitor (ICI) therapy. Little has been reported about the influence of antibiotics (ABX) while on ICI. **Method:** This is an IRB approved retrospective study. Patients with advanced (stage IV or relapsed disease) NSCLC that had progressed after platinum based chemotherapy and were subsequently treated with ICIs were identified from an institutional database. Demographics, ABX usage, and survival outcomes were recorded and analyzed. Cox proportional hazard models adjusted for age at diagnosis and sex were performed. **Result:** 161 NSCLC patients met inclusion criteria for this analysis and were treated with ICIs from 2015 to 2019. Median age was 66 years old (range 46-88) and 60% were female. Most patients had prior separate lines of systemic therapy (median 2 lines, range 1-4). Histological subtypes included adenocarcinoma (70%), squamous cell carcinoma (24%) and other histologies (6%). Median ICI treatment length was 2 months. ICIs included Nivolumab and Pembrolizumab. 58 patients (36%) had ABX usage in the 90 days prior to ICI initiation. 33 patients (20%) used ABX during ICI treatment. 71 patients (44%) had no ABX usage prior or during ICI treatment. There were no progression-free survival (PFS) differences for patients receiving antibiotics in the 90 days prior to treatment start (HR 1.024, p=0.92). The use of ABX during ICI therapy was associated with increased PFS (HR 0.597, p=0.02). There were no overall survival (OS) differences for patients receiving ABX in the 90 days prior to the start of ICI therapy (HR 1.122, p=0.64).

The effect of ABX utilization on OS was not significant (HR 0.660, p=0.07). **Conclusion:** Improved PFS and a trend toward improved OS was noted in patients receiving ABX during ICI therapy. This suggests that ABX during ICI therapy may not have a detrimental effect on outcomes. Further studies are needed to determine the regimen, length of ABX treatment and its relation to survival benefits or detriment prior to and during ICI therapy.

Keyword: immunotherapy, antibiotics, ICI

P2.04-70 PD-L1 EXPRESSION IN A POPULATION WITH NON-SMALL CELL LUNG CANCER IN A REFERENCE HEALTHCARE CENTER IN LATIN-AMERICA

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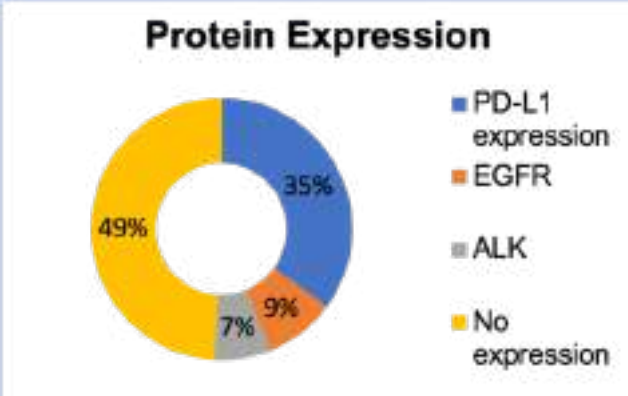
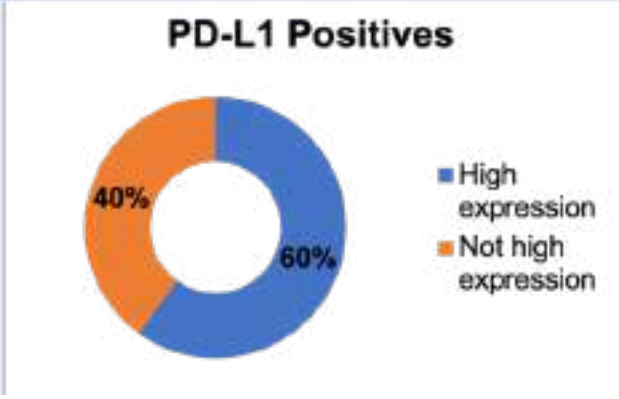
Background: Non-small cell lung cancer (NSCLC) is the most common type among malignancies of the lung, and among its histological subtypes, different mutations and protein expressions have been object of study for the past years. Epidermal growth factor receptor (EGFR) mutations and EML4-ALK fusion as driver mutations have been reported to upregulate programmed death-ligand 1 (PD-L1) expression. Despite therapeutic significance of these associations has not been yet completely elucidated, studying the prevalence and correlation of these features becomes more important with time. **Method:** Clinical and mutational features were described in 114 patients diagnosed with NSCLC between 2013 and 2016 at a reference health care center in Colombia. Among the patients in whom PD-L1 expression was tested, we reported its prevalence and distribution in patients positive for EGFR and ALK. **Result:** The mean age was 65±12 years. 72.8%(n=83) were classified as stage IV. Adenocarcinoma was the most frequent (80.7%; n=92). The prevalence for EGFR mutations was 27% (n=30) and for EML4-ALK fusion gene was 15.8% (n=9). PD-L1 expression was tested in 57 patients from which 35% (n=20) came positive, 5 were also positive for EGFR and 4 for ALK. From all PD-L1 positives, 60% (n=12) with high expression. No association was found between gender and PD-L1 expression, and being a non-smoker was associated with a lower expression of the protein. **Conclusion:** The prevalence of EGFR mutations was similar to that reported worldwide, and fusions in the EML4-ALK gene were higher than expected, as well as PD-L1 expression. Smoking has already been reported to be associated with a higher expression of PD-L1, as found in this study. More studies must be done regarding expression of the protein in patients with driver mutations to stablish reliable associations and elucidate the clinical significance of blocking PD-1/PD-L1 in EGFR and ALK-mutant NSCLC treated with TKIs.





Keywords: Non-Small Cell Lung Cancer, PD-L1 protein

P2.04-71 BULLOUS PEMPHIGOID: A RARE IMMUNOMEDIATED EVENT SECONDARY TO IMMUNOTHERAPY IN A PATIENT WITH METASTATIC LUNG CANCER

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Background: Checkpoint Inhibitors (CIs) are already part of the armamentarium in lung cancer treatment, either alone or in combination with chemotherapy. By stimulating the immune system, activation of autoreactive T lymphocytes can lead to development of immune-mediated adverse events. Dermatological toxicities are the most common of these events and may affect up to 50% of patients. The most common are pruritus, rash, dermatitis and bullous dermatitis. We present the case of a patient with metastatic lung adenosquamous carcinoma, using pembrolizumab as a second line treatment who developed pemphigus. **Method:** Case Report **Result:** A 64-year- old female was diagnosed with oligometastatic lung adenosquamous carcinoma (bones). There were no EGFR, BRAF mutations or ALK, ROS translocations. PDL1 expression was 20% (22c3 antibody). Patient received first line treatment with six cycles of carboplatin and paclitaxel, with partial response, but limiting toxicity. Radiotherapy was performed as consolidation in lung and active bone lesion in thoracic spine. There was an early progression in primary lesion, and pembrolizumab was initiated as second line. After five cycles, there was disease progression, and treatment was withheld. Six weeks later, the patient presented with bullous, hyperemic and painful lesions on both feet sole, buttocks, upper limbs, and oral mucosa. Biopsy was performed and revealed superficial and deep perivascular dermatitis with subepidermal blister and numerous eosinophils. The direct immunofluorescence test revealed presence of IgG and C3 deposits, in a linear pattern, in the membrane region. These findings lead to the diagnose of bullous pemphigoid. The lesions regressed completely after topical corticosteroid therapy used for one month. Next Generation Sequence (Foundation One) was performed, a mutation was identified in MET (exon 14) and she is currently receiving crizotinib with partial response and good tolerance. There are no new immunomediated late events. **Conclusion:** Pembrolizumab is a monoclonal antibody (IgG4) which selectively inhibits PD-1 activity in the T cell, activating the immune system but also triggering immune mediated events (IrAE). Cutaneous toxicity are the most common IrAE. The occurrence of bullous pemphigus is extremely rare with only one report in the literature. It may have an early or late onset after treatment iniciation. It is usually preceded by pruritus and nonspecific macular lesions that appear in the trunk and limbs. Histology demonstrates a subepidermal blister with mixed inflammatory infiltrate with eosinophils and immunofluorescence reveals linear deposition of IgG and C3 in the membrane. Management should ideally involve a dermatologist and require the use of systemic or topical corticosteroids, depending on the disease burden. In severe cases, immunotherapy should be discontinued. In our case, dermatologic toxicity had a late but symptomatic onset and a good response was obtained with the use of topical corticosteroids.

Keywords: Immunotherapy, Bullous Pemphigoid, Skin immunomediated toxicity

P2.04-72 CLINICAL FEATURE AND MANAGEMENT OF ACQUIRED RESISTANCE TO PD-1 INHIBITOR IN ADVANCED NSCLC

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Background: Programmed cell death-1(PD-1) inhibitors have emerged as a standard treatment for patients with advanced non-small cell lung cancer (NSCLC). However, the patterns of disease progression (PD) after an initial response (acquired resistance) to a PD-1 inhibitor and the efficacy of continuous PD-1 inhibitor therapy beyond PD remain unclear. **Method:** We retrospectively reviewed medical charts of advanced NSCLC patients treated with nivolumab or pembrolizumab as any line treatment at National Cancer Center Hospital East between January 2016 and October 2017. Acquired resistance was defined as disease progression after 6 months or more of treatment with a PD-1 inhibitor. Isolated disease progression was defined as progression in 1 site or organ, whereas systemic progression involved >1 site or organ. The clinical feature, PD pattern of acquired resistance, subsequent treatment and survival after acquired resistance were investigated. **Result:** Fifty-nine patients were treated with a PD-1 inhibitor for 6 months or more, of whom 27 patients (46%) had acquired resistance. Only 1 patient received a PD-1 inhibitor as fist-line treatment. Twelve patients were diagnosed as adenocarcinoma, 4 as squamous-cell carcinoma and 11 as NSCLC-NOS. The response at 6 months of treatment was partial response in 17 patients (63%) and stable disease in 10 patients (37%). The median time to acquired resistance was 12.2 (95%CI 9.3-17.8) months. Progression in the lesion identified at baseline was observed in 16 patients (59%), new lesions appeared in 4 patients (15%) and both of them occurred in 7 patients (26%). Overall, the most frequent progression site was lung (n=14, 52%), followed by thoracic lymph node (n=7, 26%), pleura (n=6, 22%) and brain (n=4, 15%). The median number of progressed lesions was 2 and 67% of patients had progression limited to one (30%) or two (37%) lesions. Ten patients (37%) had isolated disease progression in lung (n=3), brain (n=3), thoracic lymph node (n=2), neck lymph node (n=1) and adrenal (n=1). In 11 patients, PD-1 inhibitor therapy was continued beyond PD with (n=4) or without local radiotherapy (n=7). The median OS after acquired resistance in patients with or without continuous PD-1 inhibitor therapy beyond PD was 9.9 months and 10.7 months, respectively. **Conclusion:** Our results suggest that the most common pattern of acquired resistance to a PD-1 inhibitor was progression of thoracic lesion identified at baseline. One-third of the patients had isolated disease progression. The efficacy of continuous PD-1 inhibitor therapy beyond PD might be limited.

Keywords: PD-1 inhibitor, Acquired resistance, non-small-cell lung cancer

P2.04-73 MAINTENANCE TREATMENT USING CIMAVAX EGF VACCINE. EXPERIENCE OF SINGLE INSTITUTION

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Background: In Cuba the lung cancer represented the first cause of mortality for both sex. Approximately 75-85% of non small cell lung cancer (NSCLC) overexpresses the Epidermal grow factor receptor (EGFR) and its ligands. Overexpression of EGFR has been implicated in the process of malignant transformation by promoting cell proliferation, cell survival and motility. EGFR is a well-validated target for patients with NSCLC. CIMAvax-EGF is a therapeutic cancer vaccine composes of human recombinant EGF conjugated to a carrier protein and Montanide ISA51 as adjuvant. The vaccine is intended to induce antibodies against self EGFs that block EGF–EGFR interaction. **Method:** To characterize patients with non-small cell lung cancer treated with CIMAvax-EGF vaccine in maintenance regimen in the real world. Patients Selection: Patients diagnosed from stage IIIB and IV NSCLC at the National Institute of Oncology and Radiobiology in the period from January 2015 to June 2017 and who achieved objective response or stable disease at the end of first line therapy (chemotherapy alone or concomitant chemoradiotherapy). Treatment schedule: After finished first-line treatment, patients who achieved objective response or stabilization start vaccine maintenance regimen as previous described [Rodríguez PC, 2016]. **Result:** A total of 106 patients were treated, 52.8% of the patients were 65 or more years old, 58.5% were male and 48.5% female. The performance status was 1 in 77.4%. 62.3% of the patients were diagnosed from Adenocarcinoma. After started vaccination the 36.8% and 19.8% of patients, kept the objective response or stable disease, at 6 and 12 months respectively. The treatment was well tolerated, more frequents adverse events were pain (27,3 %) and indurations (7.3%) in the site of injection as well as local erithema (10,9%). The median overall survival was 14.6 months IC95% (10.6 -18.6). The overall survival rates were 82.1%, 57.2% and 37.6% at 6, 12 y 24 months, respectively. The median OS for patients less than 65 years old was 16,7 months IC 95% (2.2- 31.1) and for patients with ECOG 0 was 29 months IC 95% (10.4-47.5). The median progression free survival was 8.16 months IC 95%(4.9- 11.3). Progression free survival rates were 55,4%, 36,4% and 19,1% at 6, 12 and 24 months. **Conclusion:** Maintenance treatment using CIMAvax-EGF vaccine shown excellent safety profile. Median PFS and OS were higher than previously reported in phase III clinical trial. Patients less than 65 years old and with ECOG=0 achieved the better overall survival.

Keyword: CIMAvax-EGF, cancer vaccine, NSCLC

P2.04-74 RADIOTHERAPY PRIOR TO IMMUNOTHERAPY IS ASSOCIATED WITH DURABLE DISEASE CONTROL IN ADVANCED NSCLC

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Background: In an unselected patient cohort response rates for immune checkpoint inhibitors in advanced NSCLC are around 20 %[1-3]. To enhance this proportion several treatment combinations are under investigation. Radiotherapy combined with immunotherapy has shown promising results in preclinical trials and clinical trials using this combination are in progress, assessing safety and optimal dosage/timing of radiotherapy[4]. **Method:** Between May and September 2015 fifty-seven patients with advanced NSCLC were treated with nivolumab (3 mg/kg every 2nd week) at The Norwegian Radium Hospital in a named-patient-use-program. Clinical information, including dosage and timing of radiotherapy given prior to immunotherapy, has been collected and correlated to clinical outcome.

Result:

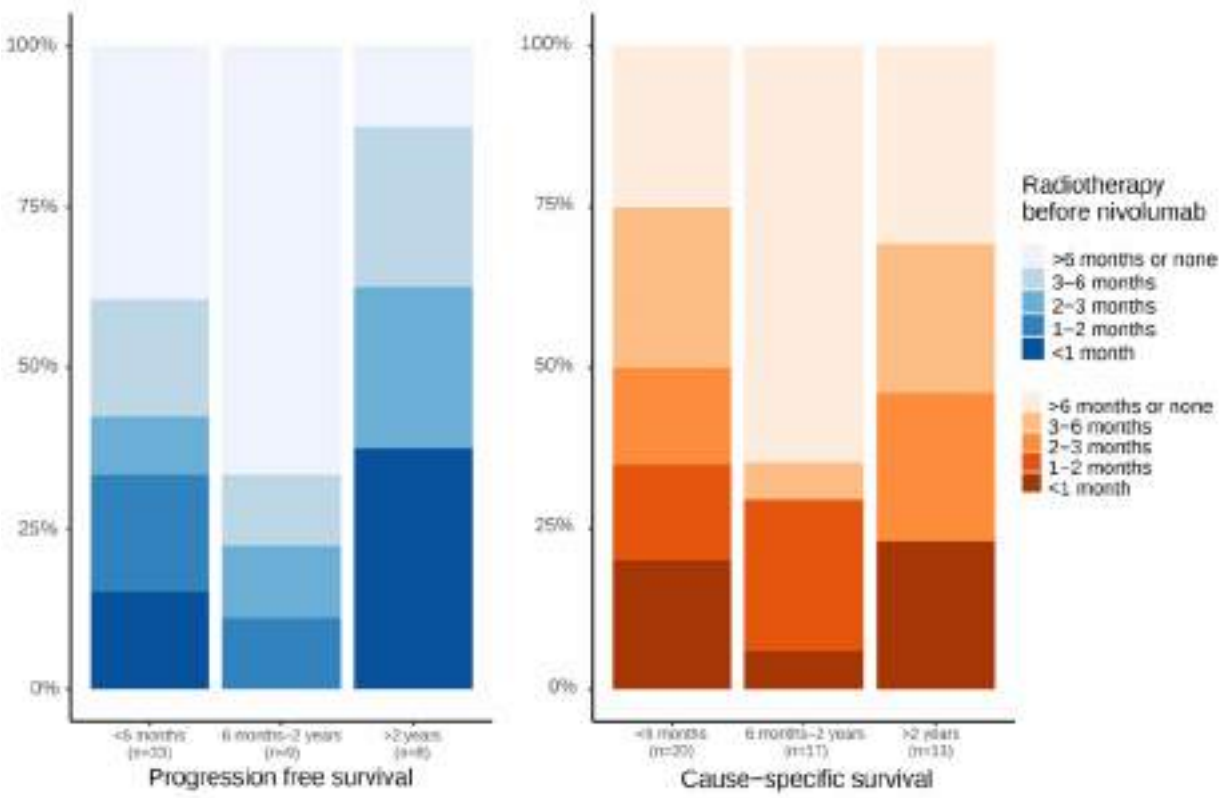

Figure 1. The patients are divided into groups based on time from starting nivolumab to progression and to death from lung cancer, respectively. Patients dead from other causes than lung cancer the first 2 years (n=7) are excluded. The color scales indicate time from last dose of radiotherapy to first dose of nivolumab.

Median follow-up time for those with no event when data was collected was 43.4 months (range 42.4-44.1 months) and overall survival 14%. Eight patients died of other causes than lung cancer. Radiotherapy administered at different time intervals before the first dose of nivolumab was correlated to progression free survival (PFS) and overall survival (OS) using cox regression analysis. We found poor PFS (HR 3.1 p=0.034) and OS (HR 3.7 p=0.015) for those who received radiotherapy between 1-2 months prior to nivolumab. The indication for radiotherapy in late stage lung cancer is most often symptomatic metastases. Hence, recent radiotherapy is usually associated with more advanced disease and poor prognosis. When patients were divided into groups according to prognosis we found that many in the group with short PFS had received radiotherapy shortly before immunotherapy but the proportion was even higher in the group with durable response (figure 1). **Conclusion:** Our findings support the hypothesis that radiotherapy can trigger a tumor-directed immune response which can be enhanced by immunotherapy and result in long-lasting disease control. We will validate our results in an additional cohort and will assess and include PD-L1 expression in our analysis. 1. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373(2):123-35. 2. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373(17):1627-39. 3. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372(21):2018-28. 4. Ngwa W, Irabor OC, Schoenfeld JD, et al. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 2018;18(5):313-22.

Keywords: Immunotherapy, Abscopal effect, radiotherapy

P2.04-75 OVERALL SURVIVAL BY IDO1 AND PD-L1 EXPRESSION IN NSCLC PATIENTS RECEIVING AN IMMUNE CHECKPOINT INHIBITOR (ICI)

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Background: Although preliminary data suggest that differential expression of the immunoregulatory enzyme indoleamine-2,3-dioxygenase 1 (IDO1) may modulate clinical response to agents that target the PD-1/PD-L1 axis, little is known about the predictive value of measuring concomitant expression of both markers for patients receiving immune checkpoint inhibitor (ICI) therapy for non-small cell lung cancer (NSCLC). **Method:** We identified patients with stage IV NSCLC who received at least one dose of an ICI alone or in combination with chemotherapy (CTX) at our institution between 2014 and 2018. Immunohistochemistry (IHC) for IDO1 (HPA023072, Sigma Prestige) and PD-L1 (SP142, Abcam) was performed on FFPE tissue. PD-L1 was scored as <1 %, 1-50%, or >50%, and IDO1 was scored as <1% or >1%. Median overall survival (OS) was calculated using proportional hazards model and groups were compared using log-rank test. **Result:** 65 eligible patients were identified. PD-L1 IHC failed in 1 patient. Patient characteristics and IHC results are detailed in Table 1. Patients with IDO1 expression had a numerically longer median OS (37.8 vs. 17.7 months, p=0.16), which was maintained regardless of PDL1 positivity. This effect was more pronounced in the ICI alone cohort (median OS of 34.4 mo vs. 17.7 mo, p=0.0995) than in the CTX+ICI cohort (p=0.92). There was no difference in OS when evaluating IDO and PDL1 expression in 4 subgroups (IDO1+/PD-L1+, +/-, -/+, -/-) using PD-L1 cutoffs of ≥1% (p=0.50) or ≥50% (p=0.49). Table 1:

Characteristic - n, (%)	ICI Alone Cohort n = 48 (73.8%)	ICI + CTX Cohort n = 17 (26.2%)
Patient Demographics		
Age (median in years)	63.5	59
Female Gender	22 (45.8)	9 (52.9)
Former/Current Smoking	44 (91.7)	14 (82.4)
EGFR Mutation	3 (6.3)	0 (0)
Line of Treatment		
1st line	6 (12.5)	15 (88.2)
≥2nd line	42 (87.5)	2 (11.8)
IHC Results		
PD-L1 IHC		
0%	9 (19.1)	9 (53.0)
1-49%	25 (53.2)	5 (29.4)
≥50%	13 (27.7)	3 (17.6)
IDO1 IHC		
0%	23 (47.9)	11 (64.7)
≥1%	25 (52.1)	6 (35.3)
PD-L1/IDO1		
<50% / 0%	20 (41.7)	10 (58.8)
<50% / ≥1%	15 (31.2)	4 (23.5)
≥50% / 0%	3 (6.3)	1 (5.9)
≥50% / ≥1%	10 (20.8)	2 (11.8)

Conclusion: In this retrospective study of NSCLC patients receiving an ICI, our results suggest IDO positivity may be predictive of improved OS. Our ability to detect a statistically significant difference may have been limited by small sample size, particularly in the ICI+CTX cohort. Further studies examining the predictive role of IDO1 IHC would be useful to identify patients most likely to benefit from PD-1 or IDO1 inhibition.

Keywords: PD-L1, IDO1, NSCLC

P2.04-76 TUMOR MUTATIONAL BURDEN BY TSO500 NEXT GENERATION SEQUENCING PANEL AND CLINICAL OUTCOME IN NON-SMALL CELL LUNG CANCER

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Background: High tumor mutational burden (TMB) can predict durable clinical response to treatment with immunotherapy across cancer types. Gold standard to determine TMB, was whole genome sequencing. TMB by targeted next generation sequencing (NGS) has shown to adequately correlate. We describe, as first to our knowledge, correlation between TMB by TSO500 and outcome in NSCLC patients treated with immunotherapy. **Method:** NSCLC patients treated from 2016 to 2018 with immunotherapy (pembrolizumab or nivolumab in first and further lines) and from whom DNA was readily available after previous routine therapeutic testing, were selected. Finally, 62 patient samples were analyzed with the Illumina TruSight Oncology 500 (TSO500) panel. TMB high was defined as more than 10 mutations/Mb. 22C3 Dako antibody was used for PD-L1 immunohistochemistry. PD-L1 high was defined as 50% or more. Demographic and clinical outcome parameters were collected. A durable response was considered partial or complete response or stable disease for at least 6 months. **Result:** Of 62 analyzed NSCLC patients treated with immunotherapy, 20 were TMB high (32%) and 42 low (68%). 57 patients were evaluated for PD-L1, and 34 (60%) were PD-L1 high and 8 patients were PD-L1 negative (14%). TMB high patients showed more durable responses than TMB low patients although the difference was non-significant [12 of 20 (60%) versus 15 of 42 (36%); p = 0.1012]. Significantly more durable responses were seen in PD-L1 high compared to PD-L1 low NSCLC patients [19 of 34 (56%) versus 5 of 23 (22%); p=0.0143]. Combined TMB and PD-L1 high patients showed significantly more durable responses compared to both TMB and PD-L1 low patients [7 of 10 (70%) versus 1 of 15 (7%) ; p = 0.0017] . A significant longer median duration of response was observed in the combined high group (6 versus 2 months; p = 0.0024) . When PD-L1 cut-off is lowered (1% or more), still a clinical meaningful higher number of responses were seen in TMB high, than TMB low patients [11 of 16 (69%) versus 12 of 33 (36%); p= 0.0654]. **Conclusion:** Patients with high TMB, as determined by TSO500, tend to show more durable responses to immunotherapy, but the difference is not statistically significant. This is probably due to limited sample size. PD-L1 appears a stronger predictor than TMB by TSO500. TMB and PD-L1 combined, is able to identify NSCLC patients likely to respond and also to select patients that will probably lack benefit from immunotherapy. Hence TMB, as assessed by TSO500 in this study, should be considered a valuable part of comprehensive genomic profiling of NSCLC.

Keywords: tumor mutational burden (TMB), Immunotherapy, Next generation sequencing

P2.04-77 HYPERPROGRESSION WITH IMMUNOTHERAPY IN METASTATIC NON-SMALL CELL LUNG CANCER: HÔPITAL CHARLES-LEMOYNE EXPERIENCE

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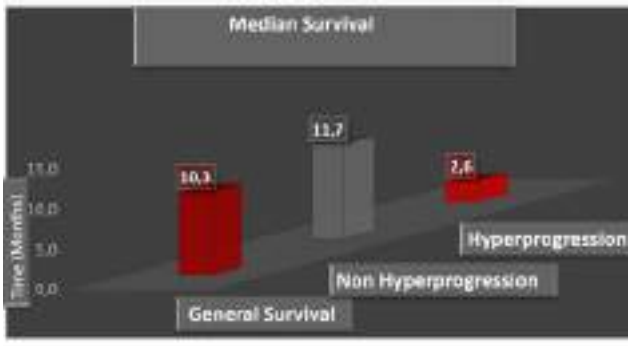
Background: Immunotherapy has revolutionized cancer treatment and particularly the perspectives of metastatic lung cancer, with durable response rates and overall survival at 5 years of up to 16%. Nevertheless, in addition to the already known immune events related to these new treatments, retrospective studies and case reports describing a rapid progression of the disease related to the beginning of immunotherapy have been published recently, reporting a rate of hyperprogression of 9 to 16%, comparable to the response rate. This phenomenon recently described deserves directed investigations to better characterize, confirm or deny its existence. **Method:** The present study is a retrospective analysis of medical records and medical imaging documents of patients with metastatic lung cancer receiving immunotherapy (nivolumab or pembrolizumab) between July 2015 and July 2017 at Charles-Lemoyne Hospital. Imaging was retrospectively reviewed to categorize patients into 3 groups: hyperprogressors, usual progressors, and non-progressers. Clinical, pathological and molecular characteristics as well as overall survival

data were analyzed according to the 3 groups. The definition by Bouzid, et al[1]. was used to define Hyperprogressive disease as a Tumor Growth Kinetics (TGK) Ratio of 2 or more, with the addition of post progressionTGK and the inclusion of patients with non messurable disease if the time to treatment failure was less than 2 months with an increase of the tumoral burden of 50% or more. [1]Bouzid, et al. Annals of Oncology 28: 1605–1611, 2017 **Result:** A total of 42 files were included with 137 images evaluated. Hyperprogression rates were similar to those reported in the recent literature (14%), and patients with demonstrated hyperprogression had decreased survival. The clinical features analyzed as the presence of recent irradiation, advanced age, and high metastatic burden were not predictive of hyperprogression.



Conclusion: In the era of immunotherapy, the identification of different patterns of progression and the sharing of institutional experiences with unexpected results following a therapy still under development becomes of major importance. This is the experience in our center with hyperprogressive disease to generate hypotheses on the evaluation of the phenomenon, the causes and risk factors. We believe, after constant reports of this finding in retrospective studies, efforts should be done in the prospective trials to actively look for and better characterize this pattern of abnormal progression as it could give us some clues in the resistance to immunotherapy.

P2.04-78 PD-L1 EXPRESSION AS A PROGNOSTIC MARKER FOR NON-SMALL CELL LUNG CANCER IN DISTINCT MUTATIONAL STATUS

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Background: Programmed death-ligand 1 (PD-L1) expression is widely used as the predictive biomarker for immunotherapy treatment in NSCLC whereas their role as a prognostic marker is limited. **Method:** Seventy-nine FFPE tissues (stage I-IV) during 2012-2017 were retrieved for Next Generation Sequencing (NGS) and immunohistochemistry (IHC) staining. PD-L1 expression was performed using 22C3 Ab. Positive-PD-L1 was defined by tumor proportion score (TPS) ≥1%. Targeted mutations and fusion genes were analyzed by Lung Cancer Panel 45 Genes and Targeted RNAscan Panel on NGS, respectively. Variants from NGS with coverage of higher than 1000X, cutoff ≥3% alternate variant frequency were considered positive. The cutoff was validated by Real-time PCR. Clinical data correlation was analyzed. **Result:** Thirty-one patients (39%) had stage I-II and 48 patients (61%) had stage III-IV disease. Mean age was 62.5 years old. Fifty-one patients (65%) were female and 55 patients (70%) were never-smoker. A majority of the patients (83.6%) were negative-PD-L1. All of the 13 PD-L1 positive patients were in stage III-IV, suggesting the increased likelihood of PD-L1 expression in advanced disease (p = 0.014). No difference in age, sex, smoking status, histological subtypes, and mutational status were seen between PD-L1 positive and negative group.However, PD-L1 negative was associated with a trend toward better survival (Table1). Subgroup analysis in stage IV patients with common EGFR mutations revealed PD-L1 positive status as a significant negative prognostic factor with HR of 3.00 (95% CI: 1.17, 7.73; *P*-value=0.023), whereas positive-PD-L1 patients with the other mutations showed a trend of worse survival outcome. Table 1: Cox regression analysis of prognostic factors associated with overall survival of NSCLC patients

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Prognostic factors	Follow up time (100 person-month)	Death		Median survival (mo)	Univariate analysis		Multivariate analysis	
		No.	Rate (95% CI)		HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age					1.00 (0.98, 1.03)	0.893	-	
Sex						0.250		
Male	8.71	18	2.07 (1.30, 3.28)	22.8	1.43 (0.79, 2.59)	0.243	-	
Female	21.14	28	1.32 (0.91, 1.92)	53.9	1		-	
PDL1						0.002		
Negative (<1%)	28.05	35	1.25 (0.90, 1.74)	53.9	1		1	
Positive (≥1%)	1.80	11	6.09 (3.38, 11.00)	7.1	3.52 (1.73, 7.16)	0.001	1.88 (0.83, 4.22)	0.128
Stage						<0.001		
I-II	19.20	6	0.31 (0.14, 0.70)	NR	1		1	
III-IV	10.65	40	3.76 (2.75, 5.12)	20.1	11.09 (4.26, 28.87)	<0.001	10.03 (3.67, 27.41)	<0.001
Smoking status						0.011		
Never smoker	24.04	28	1.16 (0.80, 1.69)	76.2	1		1	
Ex-smoker	4.55	10	2.20 (1.18, 4.09)	20.1	1.70 (0.82, 3.52)	0.154	1.02 (0.47, 2.23)	0.962
Current smoker	1.26	8	6.33 (3.17, 12.66)	8.7	3.76 (1.68, 8.41)	0.001	1.70 (0.74, 3.88)	0.208
EGFR						0.825		
Mutation	22.99	35	1.52 (1.09, 2.12)	31.9	0.93 (0.47, 1.83)	0.824	-	
No mutation	6.87	11	1.60 (0.89, 2.89)	33.5	1		-	
ALK						0.869		
Positive	2.28	3	1.32 (0.43, 4.09)	NR	1.11 (0.33, 3.78)	0.867	-	
Negative	16.50	19	1.15 (0.73, 1.81)	76.2	1		-	
KRAS						0.051		
Mutation	13.12	12	0.91 (0.52, 1.61)	NR	0.53 (0.27, 1.03)	0.062	-	
No mutation	16.73	34	2.03 (1.45, 2.84)	31.1	1		-	
Number of co-MT						0.045		
< 1000	11.84	27	2.28 (1.56, 3.33)	22.8	1		1	
≥ 1000	18.02	19	1.05 (0.67, 1.65)	57.6	0.55 (0.30, 0.99)	0.047	1.22 (0.61, 2.41)	0.574

Conclusion: Positive-PD-L1 is significantly associated with advanced disease and a trend toward unfavorable prognosis. The detrimental effect of PD-L1 is significant in stage IV patients with common EGFR mutations. A confirmatory study with a larger sample size would better identify the prognostic benefit of PD-L1 status in vast subsets.

Keyword: PDL1, Mutations, NSCLC

P2.04-79 HIGH RATE OF IMMUNE RELATED PNEUMONITIS IN LUNG CANCER PATIENTS TREATED WITH ANTI PD-1 ANTIBODIES

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Background: Treatment with anti PD-1/PD-L1 antibodies has demonstrated survival improvement in several malignancies, including non small cell lung cancer (NSCLC), but these therapies are not exempt from risks. Meta-analysis and clinical trials have reported immune related (ir) pneumonitis of any grade in 3-5% of patients treated with anti PD-1/PD-L1 antibodies, including grade 3 or higher in 0.8% to 1.8% of patients. **Method:** We have retrospectively reviewed clinical reports from 125 cancer patients treated at our center with anti PD-1/PD-L1 antibodies (55 were treated with nivolumab, 27 with pembrolizumab, 33 with atezolizumab, 6 with avelumab, and 4 with durvalumab) from January 2016 to January 2019. **Result:** Nineteen patients (15.2%) developed ir pneumonitis. Four (21%) patients had recurrent pneumonitis during tapering corticoesteroid dose after an initial improvement and finally died. Patient characteristics are summarized in Table 1. Median time to pneumonitis was 4 months (m) (range 1m to 9m). Twelve patients (9.6% %) had grade 3-5 and 7 patients (5.6 %) grade 1-2 pneumonitis. Nine (7.2 %) patients died from ir pneumonitis, including 4 patients with no tumor progression (1 had received only one cycle, and 3 patients had ongoing tumor response at 10m+, 12m+ and 30m+). Ir pneumonitis was more frequent with nivolumab (any grade 21.8 %, grade 3 or higher 18.2 %, including 7 fatal cases-12.7%-), while no patient treated with atezolizumab developed pneumonitis (Table 2).

Table 1	
Total	19
Gender Women, n (%)	7 (36,8%)
Age Median (range)	63,4 (51-82)
Cancer type, n (rate) NSCLC Adenoca NS-CLC Squamous SCLC Mesothelioma	13 (68,4 %) 4 (21%) 1 (5,3%) 1 (5,3%)
Line of therapy, n (rate) Adjuvant First line Second or further line	1 (5,2 %) 8 (42,1%) 10 (52,6%)
Tumor Response, n (rate) CR PR SD PD NE	2 (10,5%) 8 (42,1%) 5 (26,3%) 3 (15,8%) 1 (5,2%)

Table 2			
Drug,n patients treated	Any Grade, n (%)	Grade 3-5, n (%)	Grade 5, n (%)
Nivolumab, 55	12 (21,8%)	10 (18,2%)	7 (12,7%)
Pembrolizumab, 27	3 (11,1%)	1 (3,7%)	1 (3,7%)
Atezolizumab, 33	0	0	0
Durvalumab, 4	2 (50%)	0	0
Avelumab, 6	2 (33,3%)	1 (16,7%)	1 (16,7%)
Total, 125	19 (15,2%)	12 (9,6%)	9 (7,2%)

Conclusion: In our experience, ir pneumonitis rate with anti PD-1/PD-L1 antibodies in lung cancer patients was 15.2%, including 7.2% of fatal complications. It suggests that previous clinical trials could have under diagnosed this serious complication. Further studies must be performed in order to specifically assess the rate of pneumonitis in patients treated with anti PD-1 and anti PD-L1 antibodies in lung cancer patients.

Keyword: Anti PD-1, Pneumonitis, Immunotherapy

P2.04-80 PRETREATMENT NUTRITIONAL STATUS AND RESPONSE TO CHECKPOINT INHIBITORS IN LUNG CANCER

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Background: Immunotherapy has developed as an integral part of the treatment for lung cancer. Obesity has become a pandemic accounting for >20% of the total United States healthcare expenditure. Obesity has been shown to be associated with an increased efficacy of PD-1/PD-L1 blockade. On the other hand, cachectic patients have been shown to not respond as well to immunotherapy. In this study, we aim to assess the pretreatment nutritional status with outcomes of lung cancer patients being treated with immunotherapy. **Method:** An IRB approved retrospective review of lung cancer patients receiving immunotherapy between 2014 and 2017 at the Monter Cancer Center, Northwell Health was conducted. Low nutritional status as defined by either a Body Mass Index (BMI) < 18.5 and/or albumin <3.5 mg/dL prior to immunotherapy treatment. Patients were stratified by BMI: underweight (BMI<18.5), normal weight (BMI of 18.5 to <25), overweight (BMI 25 to 30) and obese (BMI >30). The groups were compared using the log-rank test. Kaplan-Meier was used for overall survival (OS) and progression free survival (PFS) and Cox regression models were used to adjust for potential confounders. **Result:** A total of 116 were included in the analysis, with a median age of 70 (95% CI, 62.5 to 75.5). Patients with a low nutritional status had a median PFS of 2.2 months compared to those who did not of 5.2 months (p<0.00032). Ten (8.6%) were underweight, 44 (37.9%) were normal weight, 32 (27.6%) were overweight, and 30 (25.9%) were obese. PFS was 6.6, 6.0, and 6.9 months for patients in the underweight, normal weight, and overweight/obese groups, respectively. A total of 46 (40%) deceased within the follow up period: 3 (30%), 17 (39%), 11 (34%), and 15 (50%) respectively. BMI classification were not found to be a significant predictor of survival, after adjusting for therapy duration (p=0.44). **Conclusion:** In this single institution retrospective review, lung cancer patients receiving immunotherapy with our defined low nutritional status had a lower PFS. BMI or albumin as individual factors did not have a significant effect on PFS or OS. Additional studies are needed to validate these findings and assess the effects of nutritional status on immunotherapy.

Keywords: Immunotherapy, nutrition status, cachexia

P2.04-81 NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNOTHERAPY: MULTI-INSTITUTIONAL EXPERIENCE FROM ARGENTINA

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Background: Immunotherapy (IO) has been established as the standard treatment for metastatic non-small cell lung cancer (NSCLC) patients improving survival. It has been approved both in first line and after platinum-treated patients. We aimed to study the efficacy and tolerability of anti PD-(L)1 inhibitors in pts with NSCLC in Argentina providing more evidence about efficacy and toxicity **Method:** Metastatic NSCLC patients (pts) treated with immunotherapy in six hospitals between 11/2013 - 2/2019 were included. Data was collected retrospectively by the investigators. Progression-free survival (PFS) and overall survival (OS) were assessed. Cox-regression model was performed for uni- and multivariate analysis. All pts who received at least one dose of immunotherapy were evaluated for efficacy and toxicity. **Result:** A total of 269 patients were included. Median age (range) was 66 ys (28-88), 164 (61%) were men, 226 (84%) were current/former smokers and 223 (82.9%) had performance status (PS) 0-1. The predominantly histology was non-squamous (N=239; 88.8%), 158 (58.7%) tumors were evaluable for PD-L1 expression and 9 (3.3%) had EGFR mutations. 86 (32%) pts received IO as first-line and 155(57.6%) as second-line therapy. Anti-PD1 antibodies were most commonly administered (83.3%). Baseline brain and liver metastases were present in 50 (18.6%) and 29 (10. 8%) pts, respectively. The

overall response rate was 30.4% (76/256). The most common sites of progression were (N=261) bones 142 (54.4%), lung/lymph nodes 74 (28.4%) and brain 26 (10%), visceral 19 (7.3%). Grade ≥ 3 adverse events occurred in 48 pts (17.8%) and 28 (10.4%) pts discontinued treatment due to toxicity. With a median follow up of 15.88 months (95% CI 12.08-19.68), median PFS was 7.26 (95%CI 5.15-9.38) and OS was 15.18 (95%CI 9.47-20-90). In univariate analysis smoking status (p 0.049), PDL1 (p 0.002), PS (p 0.000), corticoid therapy at beginning of IO (p 0.001), grade≥3 toxicity (p 0.027), first line therapy (p=0.003) and driver mutation (p 0.028) were all associated with PFS. Age (p=0.030), PDL1% (p=0.007), corticoid therapy at beginning of IO (p<0.001), grade≥3 toxicity (p=0.012) and first line therapy (p=0.038) were all associated with OS. In multivariate analysis, PDL1 and PS were independently associated with both, PFS (p=0.011 and p=0.000, respectively) and OS (p=0.036 and p<0.001, respectively). **Conclusion:** Treatment with anti PD-(L)1 inhibitors in the real-world is effective and tolerable, supporting the use of immunotherapy in pts with NSCLC. As previously reported, low PDL1 expression and poor PS confer worst clinical outcomes. Other factors such as age, line of treatment, corticoid use, toxicity and driver mutations may impact treatment response.

Keywords: Immunotherapy, Non-Small Cell Lung Cancer, Real-world setting

P2.04-82 DISCONTINUATION OF ANTI-PD-1/PD-L1 ANTIBODY THERAPY IN THE ABSENCE OF DISEASE PROGRESSION: CLINICAL OUTCOMES IN ADVANCED NSCLC

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Background: Treatment with anti PD-1/PD-L1 immune checkpoint inhibitors (ICIs) prolongs survival in patients (pts) with advanced non-small cell lung cancer (NSCLC). Treatment discontinuation in the absence of disease progression rises concern on treatment efficacy in patients and providers. We aim to study the outcomes of patients with NSCLC who discontinued treatment with ICIs. **Method:** Retrospective, multicenter descriptive study. Patients diagnosed with advanced NSCLC who discontinued therapy with pembrolizumab, nivolumab or atezolizumab in the absence of disease progression (PD) between 11/2013 - 2/2019 were included. All pts who received at least one dose of immunotherapy were evaluated for efficacy and toxicity. **Result:** A total of 269 patients diagnosed with metastatic NSCLC and treated with anti-PD-1 or anti-PD-L1 antibodies were retrospectively studied. Median follow-up for the entire cohort was 15.8 months (95% CI: 12.08-19.68). Median age 66 ys (r 28-88), 61% men, 83,4% were former or current smokers. Non-squamous NSCLC was the most common histologic subtype (N=239; 89%). Performance status (PS) was 0-1 in 223 pts (83%), 86 pts (32%) received ICIs in first line, 154 pts (57.4%) in second line and 28 pts (10.6%) in third line or beyond. Pembrolizumab was the most common treatment for pts (N= 129; 48%), followed by nivolumab (N= 113; 42%) and atezolizumab (N=27; 10%).Within the entire cohort, 39 pts (14.5%) discontinued treatment with ICIs for reasons other than PD, 35 pts due to toxicity and 4 pts for other reasons. At the time of treatment discontinuation, 3 pts (7.7%) had achieved a complete response (CR), 10 (25.6%) a partial response (PR), 17 pts (43,5%) a stable disease and 9 (23%) had PD. Median duration of response after discontinuation of ICIs was 6 months (range 0.1-27). Of the CR + PR + SD subgroup at the time of analysis 76, 9% remain without PD. If we consider only patients who maintained at least 3 months' therapeutic benefit when discontinuing treatment in the absence of PD, only 3 patients had PD (at 6, 7 and 17 months of discontinuation) and the median duration of response for this group was 8 months (3.74-27). **Conclusion:** Patients who discontinue treatment with ICI in the absence of disease progression can achieve sustainable benefit. Further studies are needed to assess the safety and efficacy of reintroducing ICIs in the event of disease progression in this population.

Keywords: NSCLC, Immunotherapy, Discontinuation

P2.04-83 LONG-TERM FOLLOW-UP COMPASIONATE USE PROGRAM NIVOLUMAB IN NSCLC

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Background: From August 2015 until March 2016, patients with NSCLC were treated in the Early Access Program (EAP) or commercially available nivolumab. Here, we report the long term survival figures for this Real Life treatment (early data were presented at WCLC in 2016). Currently, the median follow-up is 3 years for the patients treated in the EAP, and 2.5 years for the patients that have been treated with commercially available nivolumab. We address open questions of the efficacy of nivolumab in real life on special subgroups (brain mets, elderly, ECOG, smoking, platinum sensitivity) with regards to OS. **Method:** A prospective follow up of 248 pts was performed with respect to the above mentioned subgroups using Kaplan Meier curves and Cox proportional hazards regression. **Result:** Median age 63 (29-84); 55% male; 81% (ex)-smoker; 67% adeno, 22% squamous and 11% mixed type carcinoma; PS 0-1: 84%; PS 2-3: 16%; brain mets 23%. Overall survival in the whole group was 17% at 3 years. For the subgroups, the PS 2-3 vs 0-1 showed a HR of 1.77 (p=0.0023); Platinum sensitive vs resistant showed a HR of 0.55 (p=0.00032): (Ex) Smoker vs never smoker showed a HR of 0.62 (p=0.007) and no difference was observed between Squamous vs Non-squamous or for patients who initially presented with or without brain mets. **Conclusion:** These data confirm the activity of nivolumab in second line treatment outside of a reported study. The 17% 3 yrs survival is exactly in line with the pooled data from the Checkmate 017/057 study (Vokes et al. Ann Oncol 32018, 29;9590-65). Long term efficacy of this checkpoint inhibitor is confirmed. Good performance status, smoking, non-squamous carcinoma and platinum sensitive tumors are positive predictive factors.

Keywords: Real life, nivolumab, second line

P2.04-84 NSCLC SURVIVAL EXPECTANCY FOR PATIENTS TREATED WITH DOCETAXEL/NINTEDANIB IN THE SENECA TRIAL AND PREVIOUS IMMUNOTHERAPY

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Background: The phase IIb SENECA trial was an Italian real-world experience recently ended, which demonstrated similar progression free survival (PFS) and overall survival (OS) in non-squamous non-small cell lung cancer (nsNSCLC) patients treated with second-line docetaxel/nintedanib, regardless the relapsing-time from end of first-line chemotherapy and the docetaxel schedule employed (weekly or q3wks), with a slightly higher toxicity-trend in the q3wks arm. During accrual period (January 2016-April 2018), no therapeutic alternative to the use of docetaxel was available for patients with recurrent nsNSCLC until April 2017, when the first immune-checkpoint inhibitor was approved and reimbursed in Italy in this setting. At that point, the study was amended allowing enrolment of patients previously treated with immunotherapy (IT). Because of the lack of data about the optimal therapeutic algorithm in this context, aim of the present evaluation is to investigate if survival expectancy of patients treated with docetaxel/nintedanib could positively influenced when previously treated with IT. **Method:** In the SENECA trial, 212 nsNSCLC patients, progressing after first-line chemotherapy, were treated with docetaxel plus continuous oral nintedanib, with the possibility of maintenance in case of stabilization or response. This evaluation

focus on 16 patients previously treated with IT and compares them to the rest of patient population. Survival analysis is performed using Kaplan Meier curves; Hazard Ratios (HR) with 95% Confidence Interval (95%CI) are reported to compare the two groups. **Result:** Patients treated with IT (2 combined with first-line chemotherapy, 14 alone) correspond to 7.5% of the entire study population; they were 9 males and 7 females, with a median age of 62.5 years, mainly current or former-smokers, with an ECOG-performance status 0 in 93.7% of cases. At the cut-off date (December 25th, 2018), after a median follow-up of 35.5 months, no significant differences appear between patients previously treated with IT and the other ones in terms of PFS (5.84 vs 4.31 months, respectively; HR 0.564 [95% CI 0.283-1.122], p-value=0.1029), and OS (9.37 vs 9.02 months, respectively; HR 1.108 [95% CI 0.393-3.123], p-value=0.8456). No significant differences have been observed also in disease-control rates (80.0% vs 66.7%, p-value=0.5436). **Conclusion:** Despite this report does not show a greater survival expectancy for patients treated with docetaxel/nintedanib and previous IT, it's likely that the small sample size may affect this result. The longer PFS and greater disease-control rate are attractive hints for future evaluations with larger sample sizes, supposing a new therapeutic algorithm for recurrent nsNSCLC patients.

Keywords: Docetaxel, Nintedanib, Immunotherapy

P2.04-85 CLINICAL SIGNIFICANCE OF THE PD-L2 EXPRESSION IN PATIENTS WITH NSCLC RECEIVING ANTI-PD-1 INHIBITORS

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Background: The programmed cell death 1 (PD-1) receptor–ligand interaction is a major pathway often hijacked by tumors to suppress immune control. Programmed cell death-ligand 1 (PD-L1), a ligand of PD-1, can potentially predict the response to anti-PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer (NSCLC); however, the role of PD-L2, another ligand of PD-1, remains unclear in patients receiving anti-PD-1 inhibitors. This retrospective study aims to determine the significance of the PD-L2 expression in anti-PD-1 inhibitors–treated patients with NSCLC. **Method:** We enrolled 82 patients with advanced or recurrent NSCLC who received anti-PD-1 inhibitors. The PD-L2 expression was assessed by immunohistochemical analysis staining with an antibody of PD-L2 (1:200, clone 176611), and cases with >1% tumor staining of PD-L2 were considered positive. Furthermore, we analyzed correlations between PD-L2 expression and patients' characteristics, efficacy, and immune-related adverse events (irAEs) of anti-PD-1 inhibitors. **Result:** In this study, 59 (72.0%) and 56 (68.3) patients with NSCLC exhibited positive tumor PD-L2 and PD-L1 staining, respectively. Overall, 39 irAEs developed in 36 patients. The PD-L2 expression markedly correlated with the development of irAEs; however, we observed no correlation between PD-L2 expression and the efficacy of anti-PD-1 inhibitors. Other factors, including the PD-L1 expression, age, sex, smoking status, histology, did not correlate with the development of irAEs. **Conclusion:** This study suggests that the PD-L2 expression could be accountable for the development of irAEs in anti-PD-1 inhibitors–treated patients with NSCLC.

Keywords: PD-L2, immune-checkpoint inhibitor, irAE

P2.04-86 EFFICACY OF IPILIMUMAB IN COMBINATION WITH CHEMOTHERAPY FOR FIRST-LINE TREATMENT OF ADVANCED LUNG CANCER

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Background: Lung cancer is the second most common cancer in both sexes and is the leading cause of cancer mortality in the United States. Combination of checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab, or atezolizumab) and chemotherapy has shown synergistic anti-tumor activities and has created a fundamental paradigm shift in the management of first-line treatment of advanced lung cancer. We performed a systematic review and meta-analysis of currently available randomized controlled trials (RCTs) to evaluate the efficacy of ipilimumab in combination with chemotherapy for the first-line treatment of advanced lung cancer. **Method:** We systematically conducted a comprehensive literature search using PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019. RCTs utilizing first-line ipilimumab chemoimmunotherapy in patients with advanced lung cancer were incorporated in the analysis. A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q -statistic. Random effects model was applied. **Result:** A total of 3178 patients with advanced lung cancer from 5 RCTs were included in the analysis. The study arm used standard chemotherapy regimens in combination with ipilimumab while control arm used only standard chemotherapy regimens. The randomization ratio was 1:1 in all studies. Ipilimumab was employed either in phased or concurrent with chemotherapy. The I^2statistic for heterogeneity was 63%, suggesting some heterogeneity among RCTs. The pooled HR for PFS was significant at 0.85 (95% CI: 0.78-0.93; P = 0.0004) when ipilimumab was utilized in phased with chemotherapy. In non-small cell lung cancer population, the pooled HR for PFS was noted at 0.82 (95% CI: 0.68-1.00; P = 0.05), and the pooled HR for OS was 0.92 (95% CI: 0.83- 1.02; P = 0.10). In patients with extensive-stage small cell lung cancer, the pooled HR for PFS was statistically significant at 0.86 (95% CI: 0.77-0.97; P = 0.01), and the pooled HR for OS was 0.92 (95% CI: 0.81-1.06; P = 0.26). **Conclusion:** Our meta-analysis depicted that upfront ipilimumab chemoimmunotherapy significantly improved PFS compared to standard chemotherapy, when ipilimumab was either employed in phased with chemotherapy or in patients with extensive-stage small cell lung cancer.

Keywords: ipilimumab, first-line treatment, Advanced lung cancer

P2.04-87 EFFICACY OF IMMUNE CHECKPOINT INHIBITORS FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS BEFORE DURVALUMAB APPROVAL

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Background: Standard treatment for patients with locally advanced (LA) non-small cell lung cancer (NSCLC) was concurrent chemoradiotherapy (CRT) with 40-70% of 2-year overall survival (OS). Immune checkpoint inhibitors (ICIs) have been shown efficacy in advanced or recurrent NSCLC and approved on December 2015 in Japan. After that, the ICI durvalumab was approved as maintenance therapy after concurrent CRT even in unresectable LA-NSCLC on July 2018 in Japan. **Method:** To investigate the feasibility of concurrent CRT for LA-NSCLC patients and efficacy of ICI treatment for the relapsed patients after CRT, we assessed consecutive LA-NSCLC patients treated with concurrent CRT between July 2013 and June 2018 (before durvalumab approval), retrospectively. **Result:** 108 eligible patients (81 males and 27 females with median age of 65 years old, including 7 patients with targeted mutations; 2 EGFR, 4 ALK and 1 ROS1) were analyzed. All patients received radical thoracic radiotherapy using 3D planning system and concurrent with platinum-based chemotherapy. 79 (73%) received one or two cycles of consolidation chemotherapy of same regimen. 105 (97%) patients completed planned radiotherapy, and radiation pneumonitis was observed in 93 (85%) patients with median 130 (range, 41-317) days from initiation of radiation to onset. 74 (69%) patients met the PACIFIC criteria and were considered to be eligible for durvalumab. The overall response rate was 64% and the progression free survival was 10.3 (95% CI, 8.4–12.2) months. The OS was 41.8 (95%CI, 20.1-63.5) months and 2-year OS were 63%. Of the 82 patients who relapsed after CRT, 18 patients received ICI treatment (14 nivolumab, 3 pembrolizumab, 1 atezolizumab) in the course of treatment. Patients who received ICI after relapse had significantly better survival than those who did not receive ICI (2-year OS, 87% vs. 41%; p=0.001). **Conclusion:** Concurrent CRT using platinum-based regimen was considered effective treatment with acceptable toxicity for LA-NSCLC patients. The efficacy of ICI treatment has been

shown in patients with relapse after concurrent CRT in LA-NSCLC, and indication with durvalumab maintenance therapy is expected to further improve the prognosis in patients with LA-NSCLC. The optimal use timing of ICI treatment for patients with LA-NSCLC should be considered.

Keywords: immune checkpoint inhibitor, locally advanced, chemoradiotherapy

P2.04-88 SURGICAL OUTCOMES OF A MULTICENTER PHASE II TRIAL OF NEOADJUVANT ATEZOLIZUMAB IN RESECTABLE STAGES IB-IIIB NSCLC: UPDATE ON LCMC3 CLINICAL TRIAL

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Background: The role of immune checkpoint inhibitors in resectable NSCLC remains undefined. We report the updated safety results of the first multicenter trial assessing neoadjuvant atezolizumab (a PD-L1 inhibitor) for resectable NSCLC. **Method:** Eligible patients with clinical stage IB-IIIB resectable NSCLC received 2 cycles of neoadjuvant atezolizumab (1200 mg, days 1, 22) followed by surgical resection (day 40±10). Pre- and post-treatment PET/CT, pulmonary function tests (PFT), and bio-specimens were obtained. Adverse events (AE) were recorded according to CTCAEv.4.0. Preoperative treatment-related TRAE (preop-TRAE) and postoperative TRAE (postop-TRAE) defined as AE onset on, or after date of surgery, were analyzed. **Result:** Follow-up data to post-surgery visit were analyzed for 101 patients out of planned 180: mean age: 64.6 years; male: 47/101(46.5%); current smokers: 23/101(22.8%); non-squamous histology: 66/101(65.3%); and clinical stages IB(10.9%), IIA(15.8%), IIB(27.7%), IIIA(38.6%), and IIIB(6.9%). Two cycles of atezolizumab were not completed in 5/101(5.0%) patients due to grade 1 or 2 AEs. Surgery was not performed in 11/101(10.9%) patients: 5 demonstrated disease progression, and 6 for 'other' reasons. 6/101(5.9%) patients were deemed unresectable. Surgery was delayed (outside of 10-day window) in 10/90(11.1%) patients by an average of 11(1-39) days. Two of these delays were due to TRAEs (hypothyroidism and pneumonitis), 3 were patient-elected delays, 2 were surgeon-related, and 3 for 'other' reasons. Intraoperative vascular complications occurred in 2/90(2.2%) and extensive hilar fibrosis was noted in 20/90(22.2%) patients. Overall, there was insignificant mean change in the PFTs pre- vs. post-atezolizumab therapy. Only 3/101(3.0%) patients had treatment-related dyspnea, dyspnea on exertion, or pneumonitis. Table 1

Treatment Related Adverse Events (TRAE)	Preoperative TRAE (N = 101)	Postoperative TRAE (N = 90)
All AEs		
Any grade	55 (54.5%)	20 (22.2%)
Grade 1	29 (28.7%)	7 (7.8%)
Grade 2	24 (23.8%)	9 (10.0%)
Grade 3	2 (2.0%)	4 (4.4%)
Grade 4	0	0
Grade 5	0	0
Specific AEs		
Dyspnea	1 (1.0%; grade 2)	3 (3.3%; grade 1)
Dyspnea on exertion	1 (1.0%; grade 1)	0
Myalgia	4 (4.0%; grade 1 or 2)	0
Hyperthyroidism	3 (3.0%; grade 1 or 2)	1 (1.1%; grade 1)
Hypothyroidism	0	1 (1.1%; grade 2)
Pneumonitis	1 (1.0%; grade 3)	3 (3.3%; grade 2 or 3)
Transaminitis (AST or ALT)	8 (7.9%; grade 1 or 2)	3 (3.3%; grade 1 or 2)
Post-atezolizumab Change in Pulmonary Function Tests		
PFT factor	Mean change (95% Confidence Interval)	
FEV1 (N = 72)	-0.6% (-2.6% to 1.3%)	
FVC (N = 72)	0.0% (-1.8% to 1.8%)	
DCLO (N = 64)	-1.2% (-4.1% to 1.7%)	

Conclusion: Treatment with neoadjuvant atezolizumab in resectable stage IB-IIIB NSCLC was well tolerated, with minimal delay to surgery, and few treatment associated AEs. This trial continues to accrue and assess MPR, survival, and other long-term endpoints.

Keyword: neoadjuvant, immuno-oncology, early stage lung cancer

P2.04-89 NEOADJUVANT PEMBROLIZUMAB IN EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC): TOXICITY, EFFICACY, AND SURGICAL OUTCOMES

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Background: Pembrolizumab is a programmed death receptor-1 masking antibody approved for advanced NSCLC in program death receptor ligand-1 high tumors, and in chemotherapy combinations. This trial studies the effect of neoadjuvant pembrolizumab on surgical tolerability (primary endpoint), tumor response, side effects, and immune biomarkers in blood and tumor. **Method:** Baseline PET/CT, brain imaging, histologic diagnosis NSCLC, and surgical consultation were required for eligibility. Patients with stage T > 3 cm and N0, N1, or resectable N2 NSCLC received neoadjuvant pembrolizumab 200 mg every 21 days 2 cycles prior to pre-operative chest CT scan followed by standard surgery. Adjuvant chemotherapy was strongly encouraged but not required. After completion of standard chemotherapy, 4 cycles of adjuvant pembrolizumab 200 mg every 21 days was offered. Blood for immune profiling of circulating immune cells was collected at baseline, after cycle 2 pembrolizumab, after surgery, and after adjuvant pembrolizumab. Excess tumor was disaggregated for tumor infiltrating lymphocytes, regulatory immune cells, and tumor cells, and viably stored for later analysis. We report

clinical outcomes of tumor response and surgical outcomes. **Result:** Study activated 31/1/2017, last enrollment 6/2/2019, and last surgery 19/3/2019. 35 patients signed consent and 30 received at least 1 dose pembrolizumab: 2 withdrew consent, 3 screen failed. Characteristics of 30 treated patients (%): male 16 (53), adenocarcinoma 10 (33), squamous 17 (57), other histology 3 (10), and stages 1B 8 (27), IIA 8 (27), IIB 6 (20), IIIA 8 (27). Planned surgery completed for 25/30 (83%). Reasons for not undergoing surgery: distant metastatic disease (1 brain metastases, 2 pleural metastases), 1 would not tolerate required pneumonectomy, 1 N3 nodal disease. Surgeries performed: video-assisted thoracic surgery (VATS) lobectomy 12, thoracotomy lobectomy 9, VATS pneumonectomy 2, thoracotomy pneumonectomy 1, and VATS bilobectomy and chest wall resection 1. All surgery was performed within range 38-77 days (median 48 days) after cycle 1 day 1 pembrolizumab. Data will be presented for toxicities neoadjuvant pembrolizumab, surgical outcomes, and neoadjuvant pembrolizumab RECIST responses, and pathologic responses. Some major pathologic responses (< 10% viable tumor) and at least 2 pathologic CRs were observed. **Conclusion:** Two doses of neoadjuvant pembrolizumab was tolerable and produced major or complete pathologic responses in some tumors. Neoadjuvant pembrolizumab is tolerable and is an ideal platform to investigate mechanisms of immune resistance and sensitivity in early stage NSCLC.

Keywords: neoadjuvant, Pembrolizumab, Early Stage Lung Cancer

P2.04-90 NODAL IMMUNE FLARE (NIF) FOLLOWING NEOADJUVANT ANTI-PD-1 AND ANTI-CTLA-4 THERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (ICIs) have induced durable responses in selected non-small cell lung cancer (NSCLC) patients. However, ICIs have also shown to induce tumor pseudo-progression in some cases. We report the incidence and consequences of a distinct phenomenon – the apparent radiographic progression of lymph nodes without pathological evidence of tumor – that we define "nodal immune flare" (NIF), following neoadjuvant ICIs in the NEOSTAR phase 2 trial of nivolumab or nivolumab plus ipilimumab for operable NSCLCs. **Method:** NEOSTAR randomized 44 patients with stage I-IIIA (AJCC 7th edition) to nivolumab (3 mg/kg IV, days 1, 15, 29) or nivolumab/ipilimumab (1 mg/kg IV, day 1) with planned surgery between 3-6 weeks after last dose. Computed tomography (CT) and positron emission tomography (PET-CT) were obtained prior to ICIs and prior to resection. Response Evaluation Criteria in Solid Tumors v1.1 were used to evaluate responses. **Result:** 44 patients, median age 66 years (range 43-83), 28 (64%) males, 37 (84%) white were randomized to nivolumab (n=23) or nivolumab/ipilimumab (n=21). 26 (59%) had adenocarcinoma, 17 (39%) squamous cell, 1 (2%) adenosquamous carcinoma. 23 (52%) stage I, 12 (27%) stage II, 9 (20%) stage IIIA. 39 (89%) underwent complete resection, 2 off trial, and 5 (11%) were not resected. NIF occurred in 5/44 (11%) patients, 3 post nivolumab (3/23, 13%) and 2 (2/21, 10%) post nivolumab/ipilimumab. All patients had no evidence of malignancy in nodes of interest prior to ICIs. 2 (2/26, 8%) occurred in adenocarcinoma and 3 (3/17, 18%) in squamous cell. 2 (5%) required additional invasive restaging, 3 (7%) change in surgical plan, 1 (2%) declined surgery, 1 (2%) was thought to have disease progression and was treated with chemotherapy plus ICI prior to resection off study, and 1 (2%) underwent planned resection. Pathologic evaluation of the flared nodes revealed no evidence of cancer in all 5 patients, rather demonstrated noncaseating granulomata. In a previous neoadjuvant trial utilizing platinum-based chemotherapy with nintedanib, we did not observe NIF in 21 patients in absence of pathologic evidence of tumor progression (primary or nodal metastases). **Conclusion:** NIF occurred in 11% of patients following neoadjuvant ICIs and changed treatment plan in 9% of patients. This is the first preliminary report of NIF in operable NSCLCs treated with neoadjuvant single and combined ICIs. Considering the number of ongoing neoadjuvant immunotherapy trials, we highlight the importance of judicious and invasive restaging of sites of suspected progression after neoadjuvant ICIs prior to definitive treatment decisions.

Keywords: Lung cancer, neoadjuvant immunotherapy, nodal immune flare

P2.04-91 TARGET ANTIGEN LEVELS IN NSCLC DEFINE A CLINICALLY RELEVANT ACTIVATION THRESHOLD FOR NY-ESO-1^{c259} TCR T-CELL THERAPY

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Background: Chimeric antigen receptor (CAR) and T cell receptor (TCR) T cell therapies are innovative 'living drugs' with the potential for transformational benefit to patients. T cell therapies, have so far, shown impressive efficacy in haematological malignancies. However, treatment of solid tumours remains challenging. Unlike CARs, that recognize cell surface proteins, TCRs recognize intracellular targets presented in the context of human leukocyte antigen (HLA). NY-ESO-1 and LAGE-1a are tumour-associated intracellular antigens that generate a shared SLLMWITQC peptide bound to HLA-A*02 and expressed on multiple malignancies, including non-small cell lung cancer (NSCLC). Our TCR T cell product (GSK3377794) consists of autologous, lentivirally (LV) transduced T cells engineered to express an affinity enhanced NY-ESO-1^{c259} TCR recognizing the SLLMWITQC/HLA-A*02 peptide. Cell therapy trials with NY-ESO-1^{c259} TCR T cells have shown the highest objective responses to date to solid cancer in patients with synovial sarcoma, metastatic melanoma and multiple myeloma. Recently a partial response in a patient with advanced lung adenocarcinoma was reported with a another TCR-engineered T cell product targeting NY-ESO-1. The aims of our study were (1) to systematically assess the prevalence of target antigen expression for NY-ESO-1 and LAGE-1a in NSCLC (2) to determine the product-specific threshold of target antigen expression in NSCLC required to induce a specific T cell response, and (3) to explore means to selectively modulate NY-ESO-1/LAGE-1a expression in lung cancer with the aim of increasing patient benefit from TCR T cell treatment. **Method:** We established and characterized a NSCLC tumour biobank consisting of: primary patient tumour tissues, patient derived xenograft (PDX) samples and tumour cell lines. Expression of HLA-A*02 was confirmed by flow cytometry and levels of NY-ESO-1/LAGE-1a were measured via RT-qPCR. GSK3377794 response against these samples was determined by IFN-γ secretion and correlated with NY-ESO-1/LAGE-1a expression levels. **Result:** Expression of NY-ESO-1 and LAGE-1a antigen varied across the NSCLC tumour biobank samples. GSK3377794 activation correlated with NY-ESO-1/LAGE-1a expression levels in NSCLC. The functional readouts identify a product-specific antigen expression threshold for GSK3377794 in NSCLC, which could translate to a potential patient population that may benefit from GSK3377794 treatment. Our experiments further indicate that it is possible to increase NY-ESO-1/LAGE-1a expression in NSCLC cells by use of epigenetic modifiers enhancing specific targeting by GSK3377794. **Conclusion:** To date this is the most comprehensive and systematic analysis that correlates target antigen expression in NSCLC with functional responses of GSK3377794 using a set of clinically relevant sample specimens.

Keywords: Pre-clinical evidence, NYESO-1 TCR T Cell therapy, Cell Therapy for Lung Cancer

P2.04-92 NEOADJUVANT DURVALUMAB WITH OR WITHOUT SUB-ABLATIVE STEREOTACTIC RADIOTHERAPY (SBRT) IN PATIENTS WITH RESECTABLE NSCLC (NCT02904954)

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Background: Preclinical evidence suggests that sub-ablative doses of radiation may have immunomodulating properties and may result in potent local and systemic anti-tumor immune-responses when combined with immune checkpoint-inhibitors (ICIs). Here we report the preliminary results of an ongoing phase-II trial of neoadjuvant therapy (NT) with Durvalumab alone or SBRT+Durvalumab followed by adjuvant Durvalumab for 12-months. **Method:** Eligible patients were randomized to 2-cycles of Durvalumab (Arm-1) or 3 consecutive doses of SBRT(8GX3) plus 2-cycles of Durvalumab (Arm-2). Surgery was

planned 1-2 weeks after last cycle of Durvalumab. Primary endpoint was DFS for both arms versus historical controls. Secondary endpoints were safety and efficacy determined by clinical/pathological response rates. We compared tumor immunephenotype (IP) in pre- and post-treatment samples by XCell deconvolution of RNAseq transcriptomic data. **Result:** 34 patients were randomized (1/1/17-1/11/19,). Patients in Arm-2 were more frequently ever-smokers and had more PD-L1+ve tumors (Table). All patients completed NT. Grade 3/4 adverse events (AEs) occurred in 4 patients after NT (3 in Arm-1, 1 in Arm-2). One patient (Arm-1) died preoperatively from an unrelated stroke. 32 patients were surgically explored and 30 resected (28R-0:87%). There were no perioperative deaths. Grade 3/4 perioperative AEs occurred in 10/32 patients (31%). In Arm-2, 8/17 (47%) patients had a major pathologic response (MPR: £10% residual tumor) compared to none in Arm-1. Excluding 4 patients with EGFR mutations, MPR occurred in 8/13(61.5%) patients in Arm-2. Relative to Durvalumab alone, SBRT+Durvalumab was associated higher abundance of dendritic cells, myeloid cells and fibroblasts. In Arm-2, tumors with MPR had a higher immunoscore and greater abundance of dendritic cells and higher HLA gene expression. **Conclusion:** In this randomized-trial, neoadjuvant Durvalumab with or without SBRT was well tolerated. The rates of MPR after SBRT+Durvalumab are promising and suggest that sub-ablative doses of radiation may significantly enhance local immune response.

Patients characteristics	Arm 1 (n=17)	Arm 2 (n=17)
edian age	72	73
oking (ever/never)	12/5	14/3
tage (% I/II/IIIA)	41/24/35	24/41/35
Adeno/Squamous/Other	53/41/6	53/41/6
FR mutation (%)	23	25
-L1 status (0,<25%/≥25%/unknown)	7/7/1/2	4/4/9

P2.04-93 PERFORMANCE STATUS AND AGE AS PREDICTORS OF IMMUNOTHERAPY OUTCOMES IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy has become a standard of care treatment for patients with advanced non-small cell lung cancer (NSCLC). While a survival advantage has been proven for patients who are medically fit, it is unknown whether a benefit exists for patients with poor performance status (PS). PS has been established as one of the most powerful independent prognostic factors in advanced NSCLC since it is a strong predictor of survival and adverse events. When treated with conventional chemotherapy, patients with poor PS have worse outcomes and higher rates of toxicity which is why they have been excluded from many clinical trials. Standard treatment is generally recommended in patients with PS 0-1, while best supportive care is offered to patients with PS 4. Clinical trials are needed to define the best practices for patients with PS 2 and PS 3. **Method:** We performed a retrospective analysis of NSCLC patients who received immunotherapy in our health system. Patients were identified using drug administration and diagnosis codes. Age and PS at the time of initial immunotherapy administration were assigned based on physician documentation. Radiographic response and date of progression were initially assigned according to the treating physician's assessment and confirmed by the study team. Immune related adverse events (irAE) were extracted from records. All steroid prescriptions and hospitalizations were independently reviewed and attributions assigned. **Result:** We identified 285 NSCLC patients who received immunotherapy between January 2014 and April 2018. In this group, 153 patients (53.7%) had PS 0-1, 114 (40.0%) had PS 2, and 18 (6.3%) had PS 3. Response rates were similar across PS groups with responses in 26.6% for PS 1, 25.2% for PS 2, and 23.1% for PS 3 (p=.95). Survival outcomes varied with pre-treatment PS. For PS 0-1, PS 2, and PS 3, median overall survivals (OS) were 14.7 months, 8.3 months, and 1.5 months (p<0.001), and progression-free survivals (PFS) were 7.4 months, 5.1 months, and 1.3 months (p<0.001). OS and PFS outcomes were not significantly different for older and younger patients. Patients less than 70 years had a lower rate (7.6%) of irAE requiring steroids compared to patients over 70 (15%) (p=0.04). Patients less than 70 had a higher mean number of ICU admissions (p=0.04) and total days in the ICU (p=0.007) compared to patients over 70. **Conclusion:** Patients with poor baseline PS demonstrate similar response rates but inferior PFS and OS compared to medically fit patients. Prospective trials are needed to optimize treatment for this large population. Differences in irAE management and irAE severity according to age warrant further investigation.

Keywords: performance status, elderly, Immunotherapy

P2.04-94 PD-L1 EXPRESSION IN UNCOMMON EGFR-MUTANT NON-SMALL CELL LUNG CANCER AND ITS RESPONSE TO IMMUNOTHERAPY

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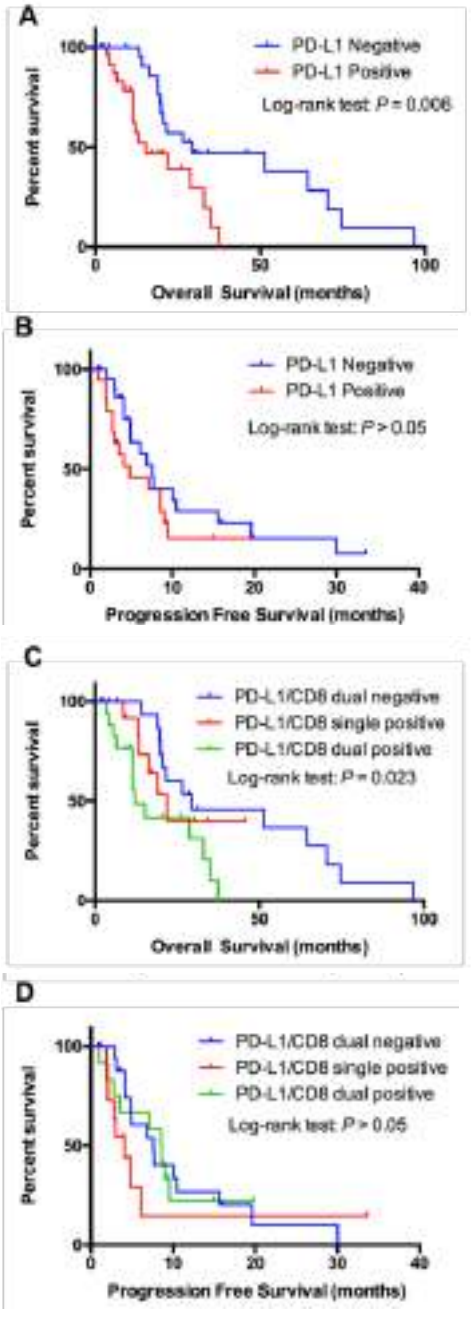
Background: The efficacy of immunotherapy treating EGFR-positive non-small cell lung cancer (NSCLC) patients has been proved to be limited. However, a series of mutant-patients could be benefit from PD-1 blockade. Therefore, this study evaluated the immune microenvironment in NSCLC with uncommon EGFR mutation, and explored the prospect of immunotherapy in this cohort. **Method:** We retrospectively evaluated the expression of PD-L1, CD4 and CD8 in NSCLC patients who harbored uncommon EGFR mutation at Zhejiang Cancer Hospital between April 2016 and September 2017. The association with clinical factors and outcomes were also explored, as well as the effectiveness of immunotherapy in uncommon mutation-positive cases. **Result:**



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Among the 600 NSCLC patients with EGFR mutation, we retrospectively collected 49 (8.2%) cases bearing uncommon mutation. In total, 49.0% (24/49) of NSCLC patients showed a strong PD-L1 expression in tumor cells, which was significantly higher than common sensitive (19del and L858R) or negative EGFR mutation (49.0% vs 12.1% vs 26.3%, respectively, $P<0.05$). Furthermore, positive PD-L1 expression was associated with a significantly shortened OS when compared with the negative PD-L1 expression (20.0 vs 44.3 months, $P=0.006$). And PD-L1 positivity was predominantly observed among patients with high CD8 expression rather than low cases (72.0% vs 25.0%, $P=0.001$). Notably, we found PD-L1 and CD8 dual-positive cases demonstrated the worst prognosis (OS: 19.3[dual-positive] vs 31.1[single-positive] vs 44.3[dual-negative] months, $P=0.023$). Additionally, this approach revealed PD-L1 and CD8 positivity were not associated with the response to *EGFR-TKIs*, playing no role in the *de novo* resistance of *EGFR-TKIs* among the uncommon mutated patients. Finally, one patient harboring EGFR G719A mutation with PD-L1 and CD8 dual positivity experienced a favorable response to anti-PD-1 therapy. **Conclusion:** This study revealed the expression of PD-L1, CD4 and CD8 in uncommon EGFR-mutated NSCLC patients. The findings indicated the reshaping of an inflamed immune phenotype characterized by PD-L1 and CD8 dual positivity and suggest potential therapeutic sensitivity to PD-1 blockade.

Keywords: PD-L1, EGFR, Immunotherapy

P2.05 INTERVENTIONAL DIAGNOSTIC/PULMONOLOGY
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.05-01 BROAD GENOMIC PROFILING OF BRONCHOALVEOLAR LAVAGE FLUID IN LUNG CANCER

V. Nair[1], A. Bik-Yu Hui[2], J. Chabon[2], M. Esfahani[2], H. Stehr[2], B. Nabet[2], J. Benson[2], A. Chaudhuri[3], L. Zhou[4], K. Ayers[2], H. Bedi[2], M. Ramsey[2], R. Van Wert[2], A. Sung[2], N. Lui[2], L. Backhus[2], M. Berry[2], P. Massion[5], J. Shrager[2], A. Alizadeh[2], M. Diehn[2]

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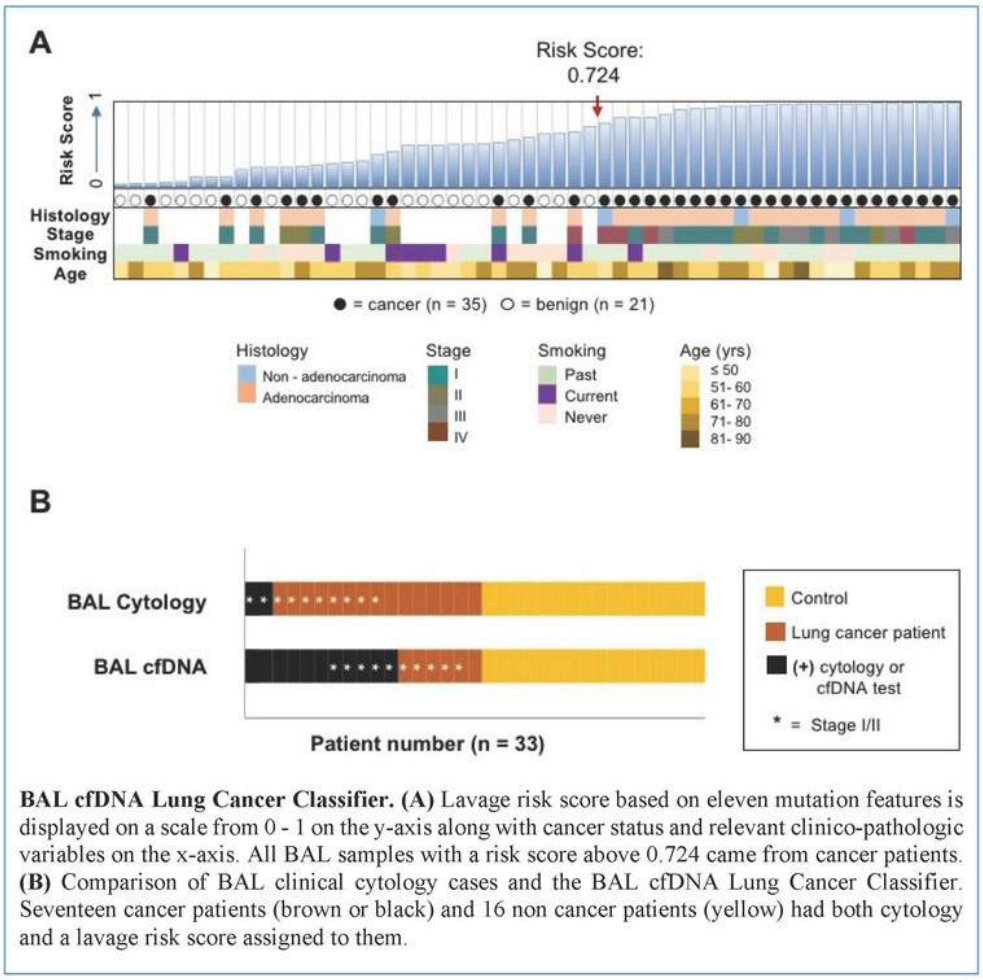
Background: We hypothesized that tumor-derived mutations from non-small cell lung cancer (NSCLC) are readily detectable in bronchoalveolar lavage (BAL). To explore our hypothesis, we employed the CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) method to identify somatic mutations in BAL compared to blood. **Method:** We profiled 200 matching lavage, plasma, and PBMC samples from a total of 38 NSCLC patients and 21 controls. We first applied a tumor-informed calling approach to most sensitively detect mutations in BAL and plasma. We then applied a tumor-naïve mutation calling strategy to explore the effect of field cancerization in at risk patients with lung nodules or who smoked. Last, we developed a BAL mutation classifier to differentiate patients with cancer from those without and compared the performance of this classifier to BAL cytology. **Result:** Tumors were primarily lung adenocarcinomas (84%) and mostly early stage disease (I-II 71%; III-IV 29%). We called a median of 4 mutations per tumor. TP53 and KRAS were the most frequently detected variants in tumor (47% and 35% respectively) and lavage cell free (cf) DNA (38% and 26% respectively). Using a tumor-informed approach, we detected significantly more variants in lavage cfDNA than in plasma from cancer patients ($p<0.001$) and variants were more frequently called in lavage cfDNA than in plasma from cancer patients (77% vs. 41%, $p=0.004$). As expected, tumor-naïve calling resulted in fewer variants detected in both sample types when compared to tumor-informed calling but we identified more tumor mutations ($p<0.001$) and more putative cancer driver mutations ($p< 0.003$) in lavage cfDNA than in plasma. Mutations of cancer driver genes at the patient level and average %VAF at the gene level were significantly lower in lavage cfDNA controls compared to cancer patients ($p=0.017$ and $p=0.016$ respectively). Since we also detected mutations in controls, presumably secondary to field cancerization and somatic mosaicism, we developed a risk score of mutation features to classify whether a BAL specimen was likely to come from a cancer patient or control. At a risk score level that identified all non-cancers as benign (A), this BAL classifier of 11 mutation features identified more cancers than cytology for all stages of lung cancer (65% vs 12%, $p=0.001$) and in stage I/II disease (50% vs. 20%, $p=0.25$; B).



BAL cfDNA Lung Cancer Classifier. (A) Lavage risk score based on eleven mutation features is displayed on a scale from 0 - 1 on the y-axis along with cancer status and relevant clinico-pathologic variables on the x-axis. All BAL samples with a risk score above 0.724 came from cancer patients. **(B)** Comparison of BAL clinical cytology cases and the BAL cfDNA Lung Cancer Classifier. Seventeen cancer patients (brown or black) and 16 non cancer patients (yellow) had both cytology and a lavage risk score assigned to them.

Conclusion: We show here that BAL genomic profiling may augment plasma profiling and BAL cytology for diagnosing and profiling NSCLC. Validation studies will be required to confirm our findings.

Keyword: genomics bronchoalveolar lavage

P2.05-02 ADDED VALUE OF TRANSBRONCHIAL CRYOBIOPSY SAMPLING IN NAVIGATION BRONCHOSCOPY FOR SMALL PULMONARY NODULES

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Background: There is an increased demand for diagnostic procedures for incidental nodules and suspected early stage lung cancer detected on CT. Endobronchial diagnosis using advanced techniques have been able to increase diagnostic yield when compared to previous (semi-) blind transbronchial biopsy. Yet even when state of the art techniques such as intra-operative cone beam CT imaging (cbCT), radial ultrasound miniprobes and / or electromagnetic navigation technology (EMN) are used, in up to 30% of procedures no final histological diagnosis is made even when these small (<2cm) lesions are reached. In this study we aim to investigate the added value of transbronchial cbCT controlled cryobiopsy for peripheral pulmonary nodule evaluation. **Method:** From a case series of 97 patients who underwent navigation bronchoscopy with histological sampling using either forceps biopsy, cryobiopsy or both were included for analysis. In our routine 6-10 forceps biopsy samples are obtained and when possible followed by a single or repeated cryobiopsy using 3-dimensional cbCT imaging guidance for confirmation for target lesion access during sampling. Retrospective evaluation of specimen quality was performed by a blinded expert pathologist [KG] using a visual analog score for specimen quality classification (range 1-5: very poor to very good). Student T and Pearson chi-square testing were used. **Result:** The mean nodule size was 14 mm (range 4-43mm). In total 37 cryobiopsy specimens were obtained (from n=33 patients). In 31 samples direct comparison of cryobiopsy and forceps biopsy specimens was available from the same target lesions. The cryobiopsy specimens were larger and showed a better quality than the forceps biopsies, with a mean specimen quality score of 4.2 ± 0,2 compared with 2.9 ± 0,2 ($p<0.001$). However, the overall sensitivity to prove malignant or benign origin of nodules using cryobiopsy was 43% (16 out of 37) compared to 78% (76 out of 97) for forceps biopsies ($p<0.001$). **Conclusion:** Navigation bronchoscopy guided cryobiopsy sampling for small peripheral pulmonary nodules is feasible and renders specimens of significantly better quality with less artefacts and larger size. However, the diagnostic yield is still inferior to forceps biopsy. This can likely be attributed to probe stiffness resulting in mis-alignment in these small nodules and to the fact that the complex navigation procedure allows for obtaining only one single cryobiopsy sample in the vast majority of cases.

Keywords: cryobiopsy, pulmonary nodules, navigation bronchoscopy

P2.05-03 TUMOR ATELECTASIS GIVES RISE TO SOLID APPEARANCE IN PULMONARY ADENOCARCINOMAS

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Background: Ground glass opacities (GGO) on CT scan, if malignant, correlate with adenocarcinoma in situ in histology. Solid appearance on HRCT, either ground glass nodule (GGN) or a solid nodule (SN), is considered to be invasive carcinoma. Histological recognition of invasion in pulmonary adenocarcinoma revealed low kappa scores among expert pathologists. A likely explanation is that morphological collapse is not taken into account in the WHO lung cancer classification. This study aims to compare radiological features in HRCT and histological features of primary adenocarcinomas in resection specimen for the presence of collapse. **Method:** Patients with primary adenocarcinoma in the lung, resected between November 2016 and November 2018, were selected. HRCT scans and CT-PET imaging were evaluated for GGO, GGN, and SN. For pathology diagnosis the 2015 WHO classification was used. Both evaluations were blinded for other information. Lepidic growth pattern with collapse was considered if reduction of air in the histological section was present, while underlying pulmonary architecture was maintained (organoid pattern without invasion). **Result:** In total 47 lesions of 41 patients were evaluated. The number of GGO, GGN and solid nodules was 2, 8 and 37, respectively. Lepidic growth pattern with collapse was present in both GGO lesions, 7 out of 8 (88%) GGN lesions and 24 out of 37 (65%) solid lesions. Remarkably, pre-existing pulmonary architecture with air spaces between alveoli covered with epithelial tumor cells (lepidic pattern) can be detected in over 50% of the adenocarcinomas with solid appearance on HRCT. This can only be explained by tumor related atelectasis (collapse) in vivo. **Conclusion:** Tumor related atelectasis is a frequent finding in pulmonary adenocarcinomas and may be a feature in a solid appearance on HRCT. Therefore, a solid appearance on HRCT cannot be solely attributed to invasion, as has been the assumption until now.

P2.05-04 DEVELOPMENT OF A NEW ENDOBRONCHIAL TREATMENT FOR PERIPHERAL-TYPE LUNG CANCER

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Background: Photodynanic therapy (PDT), is a treatment modality for many cancers, and uses a tumor-specific photosensitizer and laser irradiation. PDT is recommended as a treatment option for centrally located early lung cancer, not for peripheral-type lung cancer. With conventional laser probes, peripheral lung cancer was not an indication for laser therapy, as it was impossible to irradiate the peripheral lung field. Therefore, we have developed a laser probe in this study, we aimed to develop a new endobronchial treatment for peripheral lung cancer using PDT, and we evaluated the feasibility of PDT for peripheral lung cancer. **Method:** This phase I study enrolled 7 patients with peripheral lung cancers (primary tumor< 20 mm, stage IA), which were definitively diagnosed by bronchoscopic modalities such as endobronchial ultrasound-guide sheath (EBUS-GS) and brocnhoscopic navigation system such as electromagnetic navigation bronchoscopy (ENB). We administered NPe6 (40mg/m2) as a photosensitizer intravenously, and 4 hours later we accurately introduced the guide sheath (GS) to the peripheral lung cancer lesions using ENB, and we confirmed the tumor lesions by EBUS. After the confirmation of the tumor location, we inserted the new laser probe by ENB. **Result:** We performed PDT for 3 patients with c-stage IA peripheral lung cancer, using a laser dose (120mW, 50J/cm2), and confirmed the feasibility of the dose. We escalated the laser dose and performed 4 patients using a laser dose (120mW, 100J/cm2). Seven patients met our criteria, and 5 cases were adenocarcinoma and 2 case squamous cell carcinoma. Two weeks and 3 months after NPe6-PDT, complications such as pneumonia and pneumothorax were not found, but one mildly found light skin-photosensitivity. Six months later, we found CR in 3 cases and SD in 4 cases. **Conclusion:** PDT was a feasible and non-invasive treatment for a peripheral type early lung cancer. In the future, for non-invasive adenocarcinoma such as AIS, NPe6-PDT will become a treatment modality. Now, we are planning a physician -initiated clinical trial that conducts PDT for "peripheral small-sized lung cancer patients in whom surgery and radiation therapy are inadequate". For lung cancer cases with interstitial pneumonia combined with low lung function, there are no standard treatments. By expanding the application of PDT to these cases, it is expected to establish a new treatment method that can establish low-cost lung cancer treatment and contribute to improvement of QOL suitable for aging society.

Keywords: photodynamic therapy (PDT), peripheral-type lung cancer, electromagnetic navigation bronchoscopy (ENB)

P2.05-05 AVAILABILITY OF FOUR DIMENSIONAL COMPUTED TOMOGRAPHY (4DCT) FOR LUNG CANCER

H. Arai[1], M. Tajiri[1], Y. Mishina[1], S. Nakamura[1], H. Masuda[1], K. Shiino[1], K. Okudela[2], T. Iwasawa[1], M. Masuda[2]

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Background: Four-dimensional computed tomography (4DCT) imaging is a new form of chest CT that can detect continuous movement of the airways and lungs under free breathing conditions. This method is likely to be used increasingly to evaluate pulmonary function or predict intraoperative adhesion or tumor invasion. **Method:** A total of 31 cases that underwent 4DCT at the Kanagawa Cardiovascular Respiratory Center from October 2017 to February 2019 were reviewed. Dynamic ventilatory scans were performed using a 320-row multi detector CT (Aquilion ONE GENESIS, Canon Medical Systems, Otawara, Tochigi, Japan). The frame rate was 0.25sec/volume and the total estimated radiation exposure was 3.9 mSV. In surgical cases of lung cancer, the 4DCT findings were compared with the intraoperative assessment. We obtained 2 sets (upper lung region and lower region) of 4DCT covering the whole lung. These volume sets were connected and evaluated using imaging processing software. Intrathoracic adhesion and tumor invasion were defined by the differential movement between the tumor and adjacent structures, and laterality of the respiratory motion. **Result:** There were 16 cases of non-neoplastic diseases, such as non-tuberculous mycobacteriosis, giant bulla and lung sequestration. The 15 neoplastic diseases included 2 solitary fibrous tumors and 13 lung cancers. Among them, 12 cases in the lung cancer group underwent surgical procedures and were able to be evaluated. The purposes of the preoperative 4DCT were as follows: evaluation of tumor invasion (n=8), reoperation cases (n=2), medical history of tuberculous mycobacteriosis (n=2) and suspicion of intrathoracic adhesion on chest X-ray (n=1). Adjacent structures were the descending aorta (n=2), pulmonary artery (n=1), subclavian artery (n=1) and chest wall (n=5). The surgical procedures included 10 lobectomies, 1 wedge resection and 1 open lung biopsy. The 4DCT findings were comparable with the intraoperative findings in eleven cases; intraoperative adhesions were noted at the same locations and there were no signs of direct tumor invasion to vital structures, as indicated by 4DCT. In only one case of suspected invasion of the subclavian artery, was unexpected adhesion to the upper mediastinum observed during surgery. As the motion of the apical region was restricted in all cases, we were not able to evaluate apical adhesion. **Conclusion:** The intraoperative findings supported those of 4DCT in 11/12cases. 4DCT of the whole lung was an useful and reliable tool for the preoperative assessment and determination of the surgical indication for lung cancers.

Keywords: 4DCT, Lung cancer, operation

P2.05-06 NEW DOSIMETRIC PARAMETERS ENCOMPASSING HIGH ATTENUATION ENABLES MORE ACCURATE PREDICTION OF RADIATION PNEUMONITIS IN VARIOUS TYPES OF CANCERS

Y. Uchida[1], D. Kinose[1], K. Noma[2], T. Tsugawa[1], K. Aoki[1], H. Nakagawa[1], K. Fukunaga[1], M. Yamaguchi[1], M. Osawa[1], S. Tanaka-Mizuno[1], E. Ogawa[1], Y. Nakano[1]

[1]*Shiga University of Medical Science, Otsu/Japan,* [2]*Shiga University of Medical Science Hospital, Otsu/Japan*

Background: Radiation pneumonits (RP) is an important side effect of radiotherapy, especially symptomatic pneumonitis interferes chemotherapy after radiotherapy. Therefore, prediction and prevention symptomatic radiation pneumonitis is very important. Even if only lung cancer patients, the reported threshold values of dosimetric volume

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histogram to predict radiation pneumonitis were ranging among studies . This caused the guidelines of thoracic radiation therapy set ambiguous cut-off values of conventional dosimetric parameters like Mean lung dose (MLD) (20–23Gy) and the percentage of lung volume receiving 20 Gy or more (V20%) (30%–40%) to reduce the risk of RP. We had previously shown that dosimetric parameters calculated using only high attenuation area by excluding emphysematous lesion were better predictors of RP than conventional parameters. Little is known about the threshould value of dosimetric parameters to predict RP among different types of cancers, and if the threshould were closer or same, it will be able to provide a more reliable and versatile . To evaluate if our new dosimetric parameters can predict RP more accurately without changing threshold values among different types of cancers, we compared the performance of our new dosimetric parameters with conventional parameters to predict RT in esophageal cancer patients and lung cancer patients. **Method:** We retrospectively evaluated 77 patients who received radiotherapy for lung cancer and 71 patients for esophageal cancer. RP was graded according to the Common Terminology Criteria for Adverse Events (version 5.0). We quantified high attenuation volume (HAV) using quantitative computed tomography analysis. We compared traditional dosimetric parameters and dosimetric parameters with HAV in both lung cancer and esophageal cancer patients. Finally, the threshold of dosimetric parameters predicted of symptomatic RP and the difference of the threshold of dosimetric parameters between lung cancer patients and esophageal cancer patients were compared. **Result:** The predictive performance of dosimetric parameters for symptomatic RP was compared using AUC. MLD, HAV30% (The percentage of lung with high attenuation volume receiving ≥ 30 Gy), and HAV20% were top three parameters in lung cancer and, HAV10%, HAV5%, and V10% were in esophageal cancer. Comparing difference of the threshold of parameters predicting RP between two cancers, HAV30% revealed same value in both two cancers. In any dosimetric parameters, dosimetric parameters with HAV have smaller difference of the threshold between both cancer patients than in cases of traditional dosimetric parameters. **Conclusion:** Dosimetric parameters with high attenuation area may have higher commonality than traditional dosimetric parameters in any populations.

Keywords: radiation, Radiation pneumonitis, dosimetric parameters

P2.05-07 THE LIVERPOOL "STRAIGHT TO CT" AND "VIRTUAL WORKING" LUNG CANCER PATHWAY – 5 YEARS ON

M. Ledson[1], A. Mciver[2], N. Maddock[2], J. Dunbar[2], S. Sanders[2], C. Smyth[2], M. Walshaw[2]

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Background: Streamlining the diagnosis of lung cancer is pivotal to improving outcomes and thereby the quality of the patient journey. As part of this, in 2014 Liverpool introduced the concepts of "straight to CT" (where patients with suspicious imaging or symptoms have a directly arranged rapid [< 72 hours] CT scan), and also the "virtual assessment" service (where those with scans suggestive of lung cancer are contacted by a lung CNS and the initial clerking and investigation planning is made by telephone) into its lung cancer diagnostic pathway This pathway is now in its 5th year and we report our experience. **Method:** As regards "straight to CT", there has been no increase in the demand for outpatient scan capacity for suspected lung cancer (about 400 scans per year). Patients with scans arranged in primary care without suspicious changes remain in the community, but those with other changes can be referred to a general chest clinic (21%). Of those who enter the virtual assessment pathway, 81% are diagnosed with lung cancer. **Result:** To date, approximately 1200 patients have been through the "virtual assessment" service. Audit has shown that 98% prefer telephone assessment rather than physical clinic attendance, and most wish to be called on the same day as the scan. Patients feel that they had been given correct and timely information and feedback from primary care colleagues is uniformly positive. Lung CNS job satisfaction has improved since skills are now focussed more appropriately. Although the cancer unit diagnoses about 400 cases per year, using the virtual working model means that on average only 7 physical patient clinic attendances per week are necessary to provide the service, thereby greatly reducing resource use, saving 40% of costs overall. Furthermore, the more efficient service easily exceeds the 14 and 62 day cancer targets (99% and 97% respectively). **Conclusion:** Many lung cancer services are now moving towards "straight to CT" and virtual working models. Our experience is positive, and we would recommend its adoption.

Keywords: virtual, straight to CT

P2.05-08 DIAGNOSTIC YIELD OF EBUS-TBNA IN EVALUATION OF PD-L1 EXPRESSION FOR ADVANCED NON-SMALL CELL LUNG CANCER

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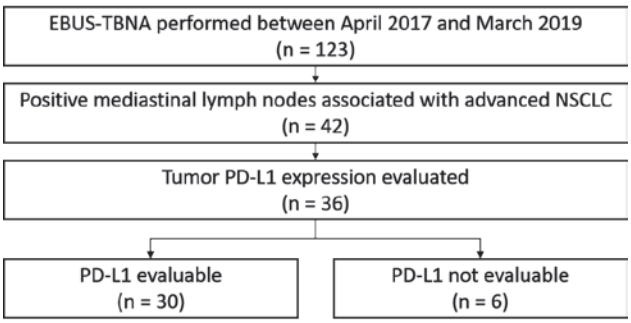
Kyoto University Hospital, Kyoto/Japan

Background: Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) plays a major role in mediastinal staging for advanced non-small cell lung cancer, but the amount of obtained tissue is limited compared to surgical biopsy. The purpose of this study was to assess the diagnostic yield of EBUS-TBNA in evaluating PD-L1 expression in positive mediastinal lymph nodes. **Method:** A retrospective chart review was performed on our prospectively maintained database to identify patients who underwent EBUS-TBNA to evaluate PD-L1 expression in mediastinal lymph nodes associated with advanced non-small cell lung cancer between April 2017 and March 2019. Relevant factors were extracted and compared between those whose PD-L1 expression was able to be evaluated and those whose PD-L1 expression was not. **Result:** Thirty-six patients were identified. The PD-L1 expression was able to be evaluated in 30 (83%) of 36 patients. There were tendencies for a greater diameter (p=0.19) and higher standard uptake value (SUV) in positron emission tomography (p=0.22) of biopsied lymph nodes, and a greater number of biopsies (p=0.28) in those whose PD-L1 expression was be able to be evaluated. Among 30 patients with evaluable PD-1 expression, the degree was high expression (tumor proportion score (TPS) ≧ 50%) in 7 patients (23%), low expression (TPS 1-49%) in 10 patients (33%), and no expression (TPS < 1%) in 13 patients (44%).



Conclusion: Evaluation of PD-L1 expression was feasible in more than 80% patients undergoing EBUS-TBNA for positive mediastinal lymph nodes associated with advanced non-small cell lung cancer. EBUS-TBNA appeared to play an important role in evaluating PD-L1 expression. A larger lymph node, and a lymph node with higher SUV, and a greater number of punctures appeared favorable in evaluation of PD-L1 expression.

Keywords: Non-Small Cell Lung Cancer, EBUS-TBNA, PD-L1

P2.05-09 FDG-PET FOR PREDICTING ACUTE EXACERBATION OF INTERSTITIAL PNEUMONIA AFTER LUNG CANCER SURGERY

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Background: Acute exacerbation of interstitial pneumonia (IP) is a critical complication after lung cancer resection. Although FDG-PET is commonly used for preoperative assessment of lung cancer, its role for predicting acute exacerbation of IP after lung cancer resection is unclear. **Method:** We retrospectively analyzed data of lung cancer patients that underwent surgical resection at Gunma University Hospital between 2008 and 2016. We analyzed data from

patients with IP based on computed tomography findings (IP group). As control, we also analyzed data in patients with no underlying lung disease (normal group) and with emphysema (emphysema group). Patients with sufficient FDG-PET data were selected and a final of 92 patients in the IP group, 21 patients in the normal group, and 20 patients in the emphysema group were enrolled in analysis. The FDG-PET values were measured at the aorta and the basal lung. Aorta values were used for reference and we calculated the basal/aorta ratio and analyzed correlation with preoperative factors, including acute exacerbation of IP and mortality. **Result:** The basal/aorta ratio was significantly higher in the IP group when compared to normal and emphysema group (both p<0.01). The incidence of acute exacerbation of IP was 10.9%, and the sensitivity and specificity of basal/aorta value for predicting acute exacerbation of IP were 70.0% and 77.2%, respectively (cutoff of basal/aorta ratio at 0.833). Patients were further classified into high basal/aorta ratio group (n=35) and low basal/aorta ratio group (n=57). The incidence of acute exacerbation of IP was significantly higher in the high basal/aorta ratio group (p=0.035). We also compared the value of basal/aorta ratio in comparison to the existing IP acute exacerbation score. Patients were divided into low score (less than 10, n=64) and high score (higher or equal to 11, n=28). The sensitivity and specificity for predicting acute exacerbation of IP was 60.0% and 82.3%, respectively, and there was no significant difference between the high and low score groups (p=0.062). **Conclusion:** The basal/aorta ratio of FDG-PET values showed a significant correlation with the incidence of postoperative acute exacerbation of IP. Since FDG-PET is commonly used for preoperative assessment of lung cancer in Japan, it may be used not only for lung cancer staging but also for surgical indication in IP patients with lung cancer by preoperatively detecting patients at high risk for acute exacerbation.

Keywords: Acute exacerbation of interstitial pneumonia, Lung cancer, FDG-PET

P2.05-10 LIQUID BIOPSY: ASSOCIATION BETWEEN THE BURDEN OF DISEASE IN PATIENTS WITH EGFR-MUTATED NSCLC AND THE FREQUENCY OF ITS DETECTION IN BLOOD

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Background: In the management of patient's whit non small cell lung cancer (NSCLC) with EGFR mutations after progression to first and second generation tyrosine kinasa inhibitors (TKI), the mechanism of resistance is very important. Our objective is to analyse the appearance kinetics of the T790M by means of digital PCR techniques in liquid biopsy. **Method:** We conducted a multicenter study with 100 patients with EGFR-mutated NSCLC, treated with first-line TKI therapy. We analyze the ctDNA by dPCR before the start of treatment, at first follow up evaluation, at 6 months and at disease progression. **Result:** We included a total of 100 patients from July 2016 to December of 2017. Seven patients with Exon 20 insertion in EGFR were excluded (final sample 93). The median of follow-up was 12 months. There were not significant differences in progression free survival (PFS) or overall survival (OS) according to treatment (erlotinib, gefitinib or afatinib). dPCR detected EGFR sensitizing mutation in 77% of the pre-treatment samples. Of these cases, EGFR sensitizing mutation was detected in 75% of the patients with stage IVA and 85% in stage IVB respectively, p=0,075. The resistance mutation p.T790M was detected in 52% of the samples collected at disease progression. The probability to detect the resistance mutation p.T790M by liquid biopsy, is greater if the pre-treatment sample was positive for EGFR sensitizing mutation (11% vs 62%) p 0,009. In cases with progression of the disease the percent of detection of p.T790M was 52% and 54% in patients with Exon 19 deletion and L858R mutation respectively. The OS in patients with progression of the disease and p.T790M negative was 85% at 12 months (95%CI: 60%-94%) and 75% with p.T790M positive (95%CI: 49%-88%), p=0,01. **Conclusion:** The burden of disease in patients with NSCLC mutated with EGFR is related to the appearance of sensitivity and resistance mutations in liquid biopsy. The probability to detect the resistance mutation p.T790M in blood, is greater if the pre-treatment sample was positive for EGFR sensitizing mutation.

Keywords: liquid biopsy, EGFR mutation, first-line TKI

P2.05-11 3D CT IS USEFUL FOR SEGMENTECTOMY BUT IS NOT ALWAYS TRUE

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Background: Pulmonary vessels and bronchus have a lot of variations. 3D CT is a good guide for segmentectomy, but sometimes shows images different from real anatomy of the lung structures. The aim of this study is to evaluate effectiveness and problems to apply 3D CT for segmentectomy. **Method:** From July 2018 to December 2018, 78 cases underwent chest surgery in our hospital. Using contrast enhanced volume dataset of 64-row CT, pulmonary artery (PA) was separated form pulmonary vein (PV) based on the difference of CT number between them. Image interpretations for surgery were performed by one experienced thoracic surgeon (TM) using axial, sagittal, coronal images, and 3D image containing PA, PV, bronchus, and lobar fissure in this study. **Result:** Of 29 case underwent lobectomy or segmentectomy, 23 cases were performed 3D CT. Failure to discriminate among PA, PV, and other structures were observed in 9 cases: Ascending A2 → branch of V2 in 2 cases; V2t → Ascending A2 in 4 cases; A3a → branch of V3 in 1 case; V3b → branch of A3 in 1 case; V1a → A1 in 1 case; V1 runs dorsal side of A1,3 → part of A1,3 in 1 case; #12l →lower lobe PA in 1 case. Case 7 underwent right S1 segmentectomy. 3D CT showed recurrent A2 runs ventral side of B1, but did not show V1 runs dorsal side of A1,3 which was found during surgery.

Case	true structure	misdrawing to
1	V2t	part of Ascending A2
2	A3a	V3
3	Ascending A2	branch of V2
4	Ascending A2	branch of V2
5	#12l	lower lobe PA
6	V2t	part of Ascending A2
7	V3b	A3
	V1 runs dorsal side of A1,3	part of A1,3
8	V2t	part of Ascending A2
9	V2t	part of Ascending A2
	V1a	part of A1

Conclusion: 3D CT is useful for segmentectomy to understand the lung anatomy, but does not always give us true anatomy. Surgery should be performed keeping the fact in mind.

Keywords: 3D-CT, surgery, segmentectomy

POSTERS

P2.05-12 ANALYSIS OF BIOMARKERS IN LUNG CANCER IN SPAIN

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Background: The analysis of biomarkers in lung cancer (LC) is currently one of the most important care needs, given the importance of their presence in the selection of specific treatments. Our objective was to know the implementation degree of these tests in a large cohort of patients in Spain using the Thoracic Tumor Registry (TTR) of the *Grupo Español de Cáncer de Pulmón* (Spanish Lung Cancer Group). **Method:** The TTR is an observational cohort multicenter study of the LC in Spain. Information on patients (p) enrolled from August 2016 to December 2018. The study is conducted according to the Declaration of Helsinki and approved by the institutional review board of each participating institute. The registry was approved by the Spanish Drug Agency as a non-post-authorization, non-interventional study. **Result:** A total of 7,872 patients from 58 Spanish sites were enrolled. Analysis of molecular markers considering all the LC stages: A molecular test, the most frequent being the EGFR test, was performed in 4,456 patients (67.5%). The proportion of biomarker evaluation has varied over time, ranging from 57.9% prior to 2012 up to 73.7% in 2017. Molecular markers in patients with stage IV. Three thousand four hundred forty-six (3,446) patients (52.2%) had a stage IV on diagnosis. The molecular assessment of some biomarkers reached 81.4% of all the patients, there being differences between Regional Communities in regard to the molecular tests made. There was performed some biomarker test in 92% of the 2570 patients with stage IV and adenocarcinoma histology. The analysis of ALK was tested in 79% of the patients, this being in 40% only 2 years ago. ROS was studied in 20% of the cases and EGFR in 92%. **Conclusion:** Although no national plan exists for molecular biomarker analysis in LC in Spain, the implementation of the biomarkers analysis in all the hospitals that contribute to the TTR is high, as close to the maximum as possible. The increase in the ALK analysis in the last period is relevant. As regional differences exist, it would be of interest to go in depth to study its cause

Keywords: biomarkers analysis, EGFR, ROS, ALK

P2.05-13 IMPACT OF DIFFUSING CAPACITY FOR POSTOPERATIVE PULMONARY COMPLICATIONS IN PATIENTS WITHOUT OBSTRUCTIVE PULMONARY DISEASE

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Background: This study evaluated the impact of diffusing capacity of the lungs for carbon monoxide (DLco) on postoperative pulmonary complications (PPCs) after lung resection in patients without obstructive pulmonary disease **Method:** We retrospectively reviewed non-small cell lung cancer patients undergoing anatomical lung resection without induction treatment between 2015 and 2016. Of these, 1233 patients without obstructive pulmonary disease were included in the study. We considered the following PPCs as study outcomes: pneumonia, acute respiratory distress syndrome (ARDS), significant atelectasis, empyema, bronchopleural fistula, prolonged air leakage and pneumothorax. The independent effects of DLco on PPCs were evaluated using multivariate logistic regression. Models were adjusted for age, sex, smoking status, comorbidity, histology and type of surgery. **Result:** Twenty three percentage of patients showed the decrement of pred % of DLco less than 80. A total of 104 patients (8.4%) developed at least one PPC. More PPCs were occurred in the patients with impaired DLco (6.2% vs 15.7%, p<0.001). In multivariable-adjusted analyses, risk of PPC in patients with impaired DLco was more than 2 times [the adjusted odds ratio (aOR)=2.44 (1.58,3.77)] compared to those in patients with preserved DLco. Also, with every 10% decreasing in % pred DLco, the risk of developing PPC was gradually increased. [DLco ≥ 80 vs. 70≤DLco<80, aOR=2.07 (1.22, 3.49); 60≤DLco<70, aOR=2.79 (1.45, 5.36); DLco<60, aOR=4.69 (1.72, 12.75), p<0.001] **Conclusion:** Patients with impaired DLco had more risk of PPCs after lung resection even without airflow obstruction. Assessment of DLco is necessary for the prediction of PPCs in lung resection surgery for NSCLC.

Keyword: non-small cell lung cancer, diffusing lung capacity, surgical outcomes

P2.05-14 SAFETY AND RISK FACTORS OF CT-GUIDED PERCUTANEOUS TRANSTHORACIC NEEDLE RE-BIOPSY FOR NSCLC

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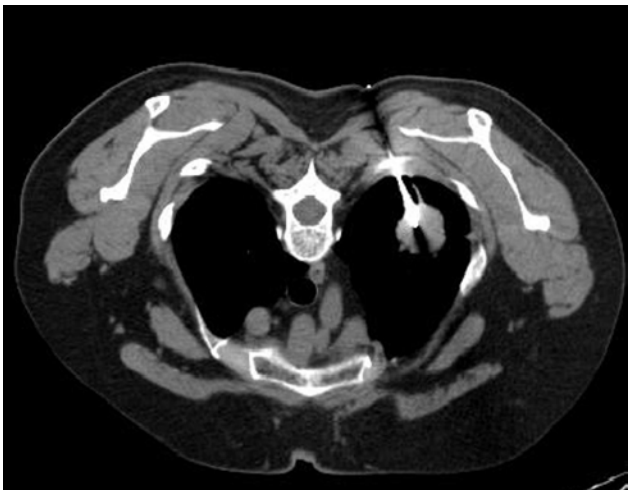
Background: Re-biopsy of NSCLC after systemic therapy to identify molecular resistance mechanism is very important. CT-guided needle lung re-biopsy has proven feasible. This study aimed to discover the safety of computed tomography (CT)-guided percutaneous transthoracic needle re-biopsy for patients with NSCLC, and its risk factors. **Method:** This was a retrospective, single-institution study. 113 patients who diagnosed as IIIB/IV NSCLC and treated with EGFR-TKIs/chemotherapy from January 2016 to February 2018 in our hospital. Compare the differences incidence of complications between first biopsy and re-biopsy by computed tomography (CT)-guided percutaneous transthoracic needle, and analysis the clinical factors affecting main complications in re-biopsy. **Result:** Success rate of re-biopsy was 88.5% (100/113). The number of patients with complications in first biopsy was 25 (23.9%), and it's 37 (34.5%) in re-biopsy (Table). The main complications were hemorrhage and pneumothorax. Hemorrhage rate in re-biopsy, male was 18.5% (10/54), and female was 3.4% (2/59). Re-biopsy needle size 17G (Angiotech 17G coaxial trocar together with Biopince 18G automatic biopsy needle) was 5.7% (5/87), and needle size 18G (18G Angiotech soft biopsy needle) was 26.9% (7/26). The mean frequency of intraoperative needle adjustment with and without hemorrhage was 3.3±1.8 vs 2.2±1.6. The mean distance (cm) of pleura-to-target in with and without hemorrhage was 3.7±1.5 vs 2.3±1.9. High rate of

pneumothorax for needle through interlobular septal puncture in re-biopsy, 62.5% (5/8). CT-guided percutaneous transthoracic needle re-biopsy of NSCLC was showed in Figure.

First biopsy	Re-biopsy	
Variable	Non-complication	Complication
All complications		
No	60 (53.1%)	28 (24.8%)
Yes	16 (14.2%)	9 (8.0%)
Hemorrhage		
No	94 (83.2%)	11 (9.7%)
Yes	7 (6.2%)	1 (0.9%)
Pneumothorax		
No	78 (69.0%)	19 (16.8%)
Yes	12 (10.6%)	4 (3.5%)
pleural reaction		
No	106 (93.8%)	4 (3.5%)
Yes	3 (2.7%)	0 (0%)



Conclusion: First biopsy and re-biopsy complications were similar. Both of hemorrhage and pneumothorax were acceptable. CT-guided percutaneous transthoracic needle re-biopsy of NSCLC showed safe and feasible.

Keywords: non-small-cell lung cancer, Re-biopsy, Safety

P2.05-15 RADIAL ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL BIOPSY IN PERIPHERAL LUNG LESIONS. WHAT CAN CRYOBIOPSY CONTRIBUTE?

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Background: Radial probe endobronchial ultrasound (RP-EBUS) is a modern technique for diagnosis of peripheral lung lesions. The addition of transbronchial cryobiopsy (TBCB) could increase the diagnostic value for RP-EBUS. AIM: To evaluate the efficacy of RP-EBUS guided TBCB for diagnosis of peripheral lung lesions. **Method:** We collected 60 patients with peripheral lung diseases. Were excluded 15 patients for not be fit for general anesthesia (necessary for TBCB) or high risk of bleeding. 45 patients were subjected to forceps transbronchial biopsy (forceps TBB) and TBCB guided by RP-EBUS. The diagnostic outcomes including digital assessment for qualitative and quantitative measures of collected samples were detected. Also, the associated complications were recorded. **Result:** The diagnostic yields for forceps TBB versus TBCB is detailed in Table 1. TBCB has achieved higher accuracy than forceps TBB (ROC area of 0.88 versus 0.84 respectively), with no statistical difference between their values (p=0.32). The combination between both techniques has achieved excellent accuracy (ROC area 0.91). In 36 cases were possible the anatomopathological diagnosis with both type of samples, there were significant statistical differences ($p \leq 0.05$) in favour of TBCB when compared to forcep TBB regarding; mean biopsy diameter, mean biopsy surface area, mean biopsy necrosis, percentage and mean biopsy viable tissue area. Only two patients had significant complications (pneumothorax; hypoxemia), and 8 moderate bleeding.

Table 1.

Variable	Forceps TBB	TBCB	Combined
Sensitivity	67.5%	75%	82.5%
Specificity	100%	100%	100%
PPV	100%	100%	100%
NPV	18.8%	23.1%	30%
Accuracy	69.8%	76.7%	83.7%

Conclusion: RP-EBUS guided TBCB is a safe and effective technique for diagnosis of peripheral lung lesions. TBCB could achieve higher diagnostic value than forceps TBB due to better quantity and quality of the samples. *The project was partially funded by SEPAR, grant AEER 2016, grant FUCAP 2017 and Egyptian Ministry of Higher Education.*

Keyword: cryobiopsy; radial EBUS; Lung cancer

P2.05-16 DIAGNOSTIC VALUE OF CONCOMITANT USE OF RADIAL PROBE ENDOBRONCHIAL ULTRASOUND WITH GUIDE SHEATH AND TRANSBRONCHIAL BIOPSY IN LUNG CANCER

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Background: Although using radial endobronchial ultrasound with guide sheath (r-EBUS-GS) has shown its diagnostic power in peripheral pulmonary lesion, its actual utility is still low due to variable diagnostic performance. To overcome its limitation, we evaluated the feasibility and efficacy of r-EBUS-GS when combined with transbronchial biopsy (TBB). **Method:** We retrospectively reviewed the medical records of 74 patients with NSCLC who underwent r-EBUS-GS plus TBB or TBB alone as diagnostic methods between 2017 Aug. and 2018 Nov. at the Severance hospital. Subjects were grouped by diagnostic modalities used (r-EBUS-GS plus TBB vs. TBB alone). Each group was matched by age, sex, biopsy location. Chi-square analysis and paired-t test were used to compare the characteristics, and to find the factors which affect to the diagnostic yield. **Result:** In each group, the number of male subjects was 21 and their mean age was 67.5 and 67.3, respectively. Lesion size was statistically smaller in r-EBUS-GS group. Although r-EBUS-GS alone (15/37, 40.5%) showed poor diagnostic yield, combination of r-EBUS-GS and TBB (27/37, 72.9%) showed higher than TBB alone group (23/37, 62.1%). Lung lesion with bronchus sign was revealed significant relationship with higher diagnostic yield (p<0.005).

Table 1. Lesion characteristics of each group			
Lesion characteristics	**r-EBUS-GS+TBB (n=37)**	**TBB only (n=37)**	**P-value**
Location			1.000
- RUL	8 (21.6%)	8 (21.6%)	
- RML	3 (8.1%)	3 (8.1%)	
- RLL	10 (27.0%)	10 (27.0%)	
- LUL	11 (29.7%)	11 (29.7%)	
- LLL	5 (13.5%)	5 (13.5%)	
CT finding			0.193
- Nodule/mass	27 (73.0%)	26 (70.3%)	
- Subsolid GGO	9 (24.3%)	6 (16.2%)	
- GGO or consolidation	1 (2.7%)	5 (13.5%)	
Size	23.6 ± 7.6	34.5 ± 15.5	< 0.001
- < 20	13 (35.1%)	7 (18.9%)	
- 20-30	17 (45.9%)	11 (29.7%)	
- > 30	7 (18.9%)	19 (51.4%)	
Pleural distance	14.8 ± 14.4	10.3 ± 10.5	0.102

Table 2. Comparison of diagnostic yield according to biopsy methods			
Diagnostic yield	r-EBUS-GS+TBB (n=37)		TBB only (n=37)
	r-EBUS-GS only	combined	
- Accuracy	15/37 (40.5%)	27/37 (72.9%)	23/37 (62.1%)

Conclusion: Combination of r-EBUS-GS and TBB has higher diagnostic power than using r-EBUS-GS or TBB alone.

Keywords: Biopsy, Bronchoscopy, Non-Small Cell Lung Cancer

P2.05-17 PREOPERATIVE IDENTIFICATION OF THE LEFT COMMON PULMONARY VEIN FOR SAFE VIDEO-ASSISTED LOBECTOMY

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Background: The pulmonary veins (PVs) display many anatomical variations. Some anomalies, especially the common trunk of the left PV, are associated with serious surgical morbidity for patients undergoing lung surgery. Compared with thoracotomy, video-assisted thoracic surgery (VATS) has a limited view of the surgical field, thus thoracic surgeons must be familiar with anatomical variations in the PVs. We aimed to investigate the anatomical variants of the left PVs using three dimensional (3D)- computed tomography (CT) images. **Method:** We reviewed anatomical variations of the left PVs of 156 consecutive patients who had undergone surgical pulmonary resection at our institution, using the multidetector contrast-enhanced CT. The common trunk was defined anatomically as the presence of a single ostium at the point of reflection of the parietal pericardium along the left atrium. **Result:** We identified the common trunk of the left PV in 11 of the 156 patients (7.1%), and the discrete left lingular vein (V4+5) draining near the inferior PV in 2 patients (1.2%). Of which, 5 had the long common trunk; the length of the common trunk outside the pericardium was equal to or longer than 10mm. Of these 11 patients, 5 were men, 4 had hypertension, 3 had valvular disease, 1 had coronary artery disease, 1 had paroxysmal atrial fibrillation (Paf), and the remaining 7 had no hypertension or structural heart disease. Although the anatomical variants of PV have been related to a higher arrhythmogenic potential, only 1 (9%) patient had postoperative complication of Paf. In 11 cases, 3 had incomplete lobulation and 3 had left lingular pulmonary artery arising from pars mediastinalis. The common trunk of the left PV was accompanied by other variant anatomies, that included; 1) right V6 draining into the superior PV in 3 cases; 2) right superior vein passing dorsal to right main pulmonary artery in 1 case; 3) supernumerary bronchus corresponding to left B7 in 2 cases. We encountered three cases demonstrating a common trunk of the left PV during VATS lobectomy. 3D-CT reconstruction was useful for recognizing such anomalies before surgery and allows safe VATS lobectomy. In surgical findings, the common trunk was located in the normal superior pulmonary vein drained into the left atrium. We should expose this vein adequately and dissect peripherally for confirmation of the common trunk. **Conclusion:** We conclude that the common trunk of the left PV is not a very rare anomaly and might be accompanied by other variant anatomies. Careful preoperative radiological evaluation of the pulmonary veins is essential to perform safe VATS lobectomy. 3D-CT can provide detailed information for assessing abnormalities of venous return.

Keywords: a common trunk of the left pulmonary vein, anatomical variations, VATS

P2.05-18 TISSUE SAMPLING AND PROGNOSTIC BIOMARKERS ANALYSIS OF PERIPHERAL LUNG TUMORS USING R-EBUS. SINGLE CENTRE RETROSPECTIVE STUDY

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Background: Tissue sampling of peripheral pulmonary neoplasms for patohistology and analysis of prognostic biomarkers can be challenging. Radial endobronchial ultrasound (R-EBUS) is one of sophisticated guiding bronchoscopic modalities used for more precise localisation of the peripheral lesions. Novel therapeutic strategies rely on different prognostic biomarkers status. In this retrospective study we explored sufficiency of specimens for patohistology and prognostic biomarkers analysis obtained by ultra-thin bronchoscope combined with R-EBUS. **Method:** Retrospective analysis of bronchoscopy cases positive on malignancies when R-EBUS was used for visualisation of peripheral tumors and tissue was obtained with commercial sampling kit. **Result:** 80 consecutive cases with pathologic ultrasound pattern found with R-EBUS were analysed. Malignant disease was diagnosed in 49 cases (61%). Mean lesion diameter was 24mm (range 15 to 40mm). The most common histology types were adenocarcinoma, squamous cell carcinoma and small cell carcinoma – 78%, 12% and 4% respectively. Extrathoracic malignancies were diagnosed in 6% of cases. The tissue was sufficient for prognostic biomarker analysis in 91% of the cases – whereas EGFR, ALK, ROS1 and PDL-1 testing was performed for adenocarcinomas and PDL-1 for squamous cell lung carcinomas. In 9% of cases samples were sufficient for histologic typing only. **Conclusion:** Bronchoscopy with R-EBUS is useful diagnostic method for peripheral lung tumours. Obtained samples can be used for histology subtyping and prognostic biomarkers analysis in most cases as well.

Keyword: peripheral tumors, R-EBUS, predictive biomarkers

P2.05-19 THE PATENCY OF RIGHT UPPER LOBE BRONCHUS AFTER Y-STENT PLACEMENT AFFECT OUTCOME ON MALIGNANT TRACHEOBRONCHIAL STENOSIS

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Background: Dumon silicone Y-stent is useful for releasing the tracheobronchial stenosis. We often encounter patients with tumors involving the carina between the bronchus to the right upper lobe

and bronchus intermedius. However, there has not been ideal stenting for such cases, especially to maintain the patency of the right upper lobe bronchus. We investigated the clinical outcome in patients with malignant tracheobronchial stenosis, especially focused on the patency of right upper lobe bronchus after Y-stent placement. **Method:** From January 2012 until December 2018, 102 patients who had placed Y-stent on malignant tracheobronchial stenosis in our department were examined retrospectively. This study involved 73 male and 29 female. The mean age was 64 years (range, 30-91 years). Fifty-nine patients had lung cancer, 29 had esophageal cancer, and 14 had other carcinomas. All procedures were carried out in the operating room under general anesthesia, and the stents were implanted via rigid bronchoscopy. The patients were divided into two groups based on the patency of right upper bronchus: patency group (P group, n=73) and stenosis /occlusion group (S group, n=29).The clinicopathological features, clinical course, and the survival after stenting of the groups were compared. **Result:** Stents were implanted and symptoms were resolved in all cases. No operative death occurred. Stent indwelling types were only Y-stent in 69 patients and Y-stent with additional self-expanding metallic stent (SEMS) in 33. Although there was no difference between the two groups in age, gender, preoperative Hugh-Jones classification, hospitalization days, and size of Y-stent, esophageal cancer was significantly more frequent in P group. The total length of placed stent was significantly longer in S group (median 10.5cm) compared to P group (8cm) ($p<0.01$) and the postoperative Hugh-Jones classification (I or II) in S group (47%) was inferior compared to the P group (72%). After stent placement, 67% of the P group could be treated chemotherapy/radiotherapy to primary disease, while only 43% of the S group was received these because of their poor general condition ($p = 0.03$).The median survival time (MST) and 1-year survival rate of the two groups was 7 months and 32% (P group), and 2 months and 17% (S group), respectively ($p<0.01$). **Conclusion:** The patency of right upper lobe bronchus after Y-stent placement affects not only the improvement of postoperative Hugh-Jones classification but also the administration of subsequent treatment to primary disease and associated to their clinical outcome.

Keywords: silicone Y-stent, tracheobronchial stenosis, malignant

P2.06 MESOTHELIOMA
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.06-01 STELLAR TRIAL: RADIOLOGICAL RESPONSE PATTERNS OF TTFIELDS PLUS CHEMOTHERAPY IN FIRST-LINE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, utilizing low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. TTFields have significantly extended survival of glioblastoma patients. In-vitro, human malignant pleural mesothelioma (MPM) cells were highly susceptible to TTFields. In the STELLAR trial [NCT02397928], patients with unresectable MPM treated with first-line chemotherapy in combination with TTFields had a significantly higher median overall survival compared to historical controls (18.2 Vs. 12.1 months). We analyzed radiological data from STELLAR patients whose tumors responded while receiving the combined therapy. **Method:** The trial accrued 80 patients with unresectable, previously untreated mesothelioma who were treated with continuous 150 kHz TTFields (>18h/day) in combination with pemetrexed and cisplatin or carboplatin (at standard dosing). Inclusion criteria: ECOG PS of 0-1, pathologically proven mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients were followed q3w (CT scan q6w) until disease progression. Radiological assessments were done at each study site. EOCG status and cancer-related pain were assessed until disease progression using a visual analog scale. **Result:** Partial responses (PRs) were seen in 40.3% of evaluable patients and clinical benefit (PR+SD) was seen in 97.2% of patients. The median time between treatment start and PR was 1.8 (1.4-4.4) months). All patients presenting with PR during the STELLAR study had continuous reduction in the total sum of lesion diameters, suggesting no initial/pseudo-progression. 83% of the patients who responded to the combined therapy finally had disease progression within median response duration of 5.7 (1.4-13) months, per Kaplan-Meier Estimator. One patient did not progress for more than 27 months. Median time to deterioration in performance status was 13.1 months. Average pain score was lower compared to baseline during the first 7 months of treatment and higher later with a median time to a clinical significant 33% increase in pain of 8.4 months. Compliance with TTFields was 68% (16.3 hours/day) during the first 3 months of therapy. No TTFields-related other than expected dermatitis below the arrays were reported. **Conclusion:** The STELLAR study showed significant survival extension in previously untreated MPM patients. Response rates were similar to that of current SOC treatment, but lasted longer with the addition of TTFields. TTFields was not associated with a decrease in performance status or an increase in pain. TTFields in combination with chemotherapy are efficacious in MPM vs chemotherapy alone reported in historical data.

Keywords: TTFields Radiological response patterns in MPM, Phase 2 STELLAR study, Tumor Treating fields (TTFields) in mesothelioma

MESOTHELIOMA STRATIFIED THERAPY (MIST): A PHASE IIA UMBRELLA TRIAL FOR ACCELERATING THE DEVELOPMENT OF PRECISION MEDICINES

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Background: There are currently no approved therapies for the treatment of relapsed mesothelioma. Recent advances in our understanding of inter-patient genomic heterogeneity, identification of potential drivers, and application of high throughput -omic technologies to clinical trial samples, has created opportunities to explore novel treatments in prospectively biomarker-enriched cohorts. **Method:** MiST is a British Lung Foundation funded, University of Leicester sponsored multicentre national clinical trial. Patients (Pts) harbouring either pleural (any histological subtype) or peritoneal mesothelioma are eligible. Pts must have ECOG performance status 1 or 0, received prior standard chemotherapy and progressed from their last treatment (in any line). The study is designed in three stages. Stage 1 comprises prospective molecular profiling of the tumour suppressors BAP1, BRCA1, p16ink4A and the immune checkpoint inhibitor PDL1 (22C3), using automated immunohistochemistry. Stage 2: Patients meeting eligibility criteria are presently stratified into Arm 1: Rucaparib (PARP inhibitor) for BAP1 inactivated (cytoplasmic or loss of expression) /BRCA1 negative mesothelioma. Arm 2: Abemaciclib (CDK4/6 inhibitor) for p16ink4a negative tumour, Arm 3, Pembrolizumab (anti-PD1) and Bemcentinib (AXL) to patients without biomarker specification. Arm 4, Atezolizumab (anti-PDL1) and Avastin (anti-VEGF) for PDL1 positive MM. Further arms are in development. The primary endpoint is 12 week disease control (12wDCR), with the secondary endpoints, 24wDCR, response rate (modified RECIST1.1) and safety/tolerability. 12wDCR>50% will be considered worthy of further investigation. Stage 3: Genome wide somatic copy number analysis and transcriptomic analysis with in-silico deconvolution of immune cell infiltrates will be used to refine molecular correlates of response. Gut microbiome 16RNA sequencing will be conducted in arms 3 and 4. Patients exhibiting a response to treatment who then progress,

will be re-biopsied to facilitate molecular interrogation of acquired resistance mechanisms. MiST is coupled to our laboratory functional genomics programme, aimed at exploring co-clinical trial models, to robustly define or validate mechanisms that underpin drug responses. **Result:** Section not applicable **Conclusion:** In summary, MiST is a new clinical research platform that will support proof-of-concept studies capable of testing biomarker enrichment/efficacy hypotheses, with the aim of advancing personalised therapy for mesothelioma.

Keyword: mesothelioma, biomarker, stratified therapy

P2.06-03 TIMING OF SURGERY AFTER INDUCTION THERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA: A NATIONAL ANALYSIS

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Background: The safe window to offer surgery following induction chemotherapy for malignant pleural mesothelioma (MPM) is unknown. **Method:** The National Cancer Database (NCDB) was queried for patients with cT1-3N0-1M0 MPM undergoing induction chemotherapy followed by definitive surgery. Patients with induction radiation, missing survival data, and time to surgery <1 or >180 days were excluded. Patients were stratified into quartiles based on time from chemotherapy to surgery: Q1 (<85 days), Q2 (85-100 days), Q3 (101-120 days), and Q4 (>120 days). The primary outcome was overall survival, and secondary outcomes were pN2 disease and margin-positive (>R0) resection. Survival was modeled with Kaplan-Meier and Cox Proportional Hazards, and upstaging and >R0 resection with multivariable logistic regression. **Result:** A total of 205 patients were included, with a median time from induction therapy to surgery of 104 days. There was no difference in unadjusted median survival between the groups: 23 (Q1), 25 (Q2), 25 (Q3), and 20 (Q4) months (log-rank p=0.92). In multivariable regression, increasing time to surgery was not associated with survival examined by quartile (Table) or as a continuous variable (adjusted hazard ratio [AHR] 1.00; 95% confidence interval [CI] 0.99-1.01). Increasing time to surgery was also not associated with increased pathologic upstaging to N2 (adjusted odds ratio [AOR] for Q4 vs. Q1: 1.22; 95%CI 0.33-4.65). In a multivariable regression, increased time from chemotherapy to surgery was not associated with >R0 resection (AOR 0.81; 95%CI 0.23-2.87 for Q4 vs. Q1). **Conclusion:** Increased time from induction therapy to surgery for MPM was not associated with worse survival, nodal upstaging, or margin-positive resection in this study. Patients with MPM can be safely offered surgery even three months after induction chemotherapy.

Variable	Adjusted HR	95% CI	P value
Interval (ref:Q1) Q2 Q3 Q4	0.83 0.92 1.08	0.49-1.40 0.55-1.53 0.61-1.92	0.49 0.74 0.79

Keywords: Mesothelioma, induction therapy, surgery

P2.06-04 TREATMENT PATTERNS AND OUTCOMES OF ADVANCED MALIGNANT PLEURAL MESOTHELIOMA (MPM) PATIENTS IN A COMMUNITY PRACTICE SETTING

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Background: MPM is an aggressive neoplasm with a poor prognosis and limited therapeutic options. Pemetrexed+platinum is standard of care (SOC) for advanced MPM in the United States with cisplatin doublet as the only approved first-line (1L) treatment by the Food and Drug Administration (FDA). There are no FDA approved treatments in second-line (2L) or later. Understanding how patients are currently treated and the associated outcomes is important to assess the unmet needs in MPM. **Method:** Retrospective data were abstracted from the US Oncology Network's iKnowMed electronic health record (EHR) for patients with advanced MPM receiving systemic therapy between 01-Jan-2008 and 31-Dec-2016, followed through 31-Dec-2017. Eligibility criteria: ≥18 years of age, ≥2 visits, no clinical trial enrollment or other malignancy during study period. Baseline demographic/clinical characteristics, treatment patterns, duration of chemotherapy (DOT) and overall survival (OS) were assessed, using Kaplan-Meier methods for 1L, 2L+ survival. **Result:** 474 advanced MPM patients receiving treatment were identified; median age was 72 years, majority were male (82%) with an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1 (71%). Cisplatin+pemetrexed (n=194; 41%) and carboplatin+pemetrexed (n=175; 37%) were the most frequent 1L regimens, followed by pemetrexed monotherapy (n=51; 11%). Only 108 (23%) patients received 2L and 33 (7%) received 3L. The most common 2L regimens included monotherapies gemcitabine (n=40; 37%), pemetrexed (n=27; 25%), vinorelbine (n=9; 8%), and IO therapy (avelumab, nivolumab or pembrolizumab n=9; 8%). Median DOT was 2.7 months in 1L SOC and 1.7 months in all 2L regimens. Unadjusted median OS in patients 1L SOC was 14.0 months (95%CI, 11.6-17.0) with similar survival observed among cisplatin+pemetrexed (13.7 months; 95%CI, 10.8-18.5) and carboplatin+pemetrexed (14.2 months; 95%CI, 11.1-19.8); OS for 1L pemetrexed monotherapy (10.7 months; 95%CI,6.2-14.3). Unadjusted OS in 2L was 6.4 months (95%CI, 5.1-7.6) ranging from 3.4 months (95%CI, 2.7-6.5) with gemcitabine to 11.8 months (95%CI, 0.3-NR) with immunotherapies. **Conclusion:** This real-world analysis of advanced MPM showed a majority of 1L patients received SOC pemetrexed+platinum based therapy, with carboplatin almost as common as cisplatin. The platinum agent paired with pemetrexed in 1L SOC did not affect unadjusted survival in the community setting. Less than a quarter of 1L patients received a 2L therapy, with gemcitabine as the most common treatment. Overall survival in MPM remains poor and treatment rates in 2L are low, highlighting the need for more effective therapies.

Keywords: malignant pleural mesothelioma, real-world study, systemic therapy

P2.06-05 MULTIMODALITY THERAPY USING TOTAL PLEURECTOMY IN MALIGNANT PLEURAL MESOTHELIOMA: LONG-TERM OUTCOMES IN 150 CONSECUTIVE CASES

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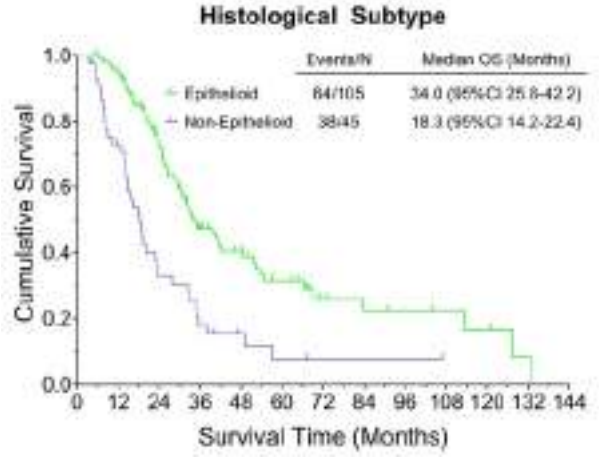
Background: We wished to evaluate the long-term outcomes of patients receiving multimodality therapy including total pleurectomy/decortication, radiotherapy and systemic chemotherapy for malignant pleural mesothelioma. **Method:** Retrospective analysis of patients treated between September 2004 and April 2019 by a specialised thoracic multidisciplinary team. Treatment involved total pleurectomy and decortication of lung, prophylactic radiotherapy (21 Gy in 3 fractions) and systemic chemotherapy based on pemetrexed and platinum. PET-CT was used routinely to diagnose disease recurrence or progression. Second or third-line therapies were administered when appropriate. Survival and prognostic factors were analysed by the Kaplan-Meier method and Cox regression analysis. **Result:** 150 patients had multimodality therapy over a 15-year period. Median age at operation was 62 years (range 32-82) and the male/female ratio was 122/28. Thirty-one patients (20.6%) had received chemotherapy before surgery. Thirty-three patients (22%) had extended resections. Sixty-two patients suffered a postoperative complication and 90-day mortality was nil. Eleven patients (7.3%) had reoperation within 30 days. Histological types were epithelioid in 105 patients and non-epithelioid in 45. Pathological stages were: I:86, II: 9, III: 54, and IV:1 (8th TNM classification). All patients but one received prophylactic radiotherapy. Six patients (4%) did not received systemic chemotherapy. Sixty-five patients (43.3%) received second-line or further systemic therapies. Five patients received stereotactic radiotherapy and three patients had late reoperation for focal tumour recurrence. Median survival was 30.5 months overall (95% CI 25.4-35.6), 34 months for epithelioid type

(95% CI 25.8-42.2) and 18.3 months for non-epithelioid type (95% CI 14.2-22.4). Histological type and macroscopic complete resection were predictive of extended survival in our analysis. **Conclusion:** Total Pleurectomy /Decortication is a safe and well-tolerated procedure associated with no mortality and acceptable morbidity. Most patients can receive prophylactic radiotherapy and systemic chemotherapy in due time. Many can receive second-line or further therapy on progression, resulting in prolonged survival.



Keywords: Mesothelioma, multimodality therapy, surgery

P2.06-06 Y-BOX BINDING PROTEIN-1, A POTENTIAL TARGET IN MALIGNANT PLEURAL MESOTHELIOMA, DRIVES GROWTH THROUGH DISTINCT MECHANISMS

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Background: Malignant pleural mesothelioma (MPM) is an asbestos-related disease with a fiveyear survival of five percent. Current therapy provides limited success and finding other targetable molecules remains a top priority. We recently identified Y-box binding protein-1 (YB1) as a significantly overexpressed oncogene with prognostic relevance in MPM. YB-1 is a multifunctional transcription and translation factor of the cold-shock protein family. Using siRNAmediated knockdown of YB-1 we showed that silencing YB-1 inhibited the proliferation, migration and invasion of four MPM cells by an unknown mechanism. Here we extend this work to examine how YB-1 regulates MPM growth. **Method:** Functional activity of YB-1 was investigated by siRNA-mediated knockdown in MPM cells followed by TALI apoptosis assays, multi-dimension flow cytometry or live-cell imaging. Transcript expression was determined using reverse transcription qPCR (RT-qPCR) and RNA sequencing (RNAseq) with poly(A) selection. **Result:** Following our previous data demonstrating growth inhibition after YB-1 knockdown, we transfected three MPM cell lines with YB-1 siRNA and conducted multidimension flow cytometry and TALI apoptosis assays to begin understanding how this growth inhibition was occurring. We found that cells underwent either apoptosis or a G0/G1 cell cycle arrest. Using live-cell imaging and single cell fate mapping we found that each cell line undertook a distinct mechanism of growth inhibition. MSTO cells displayed apoptosis during interphase, VMC23 cells showed no death but underwent a G0/G1 cell cycle arrest, while REN cells did not delay during interphase but entered prolonged aberrant mitosis resulting in mitotic catastrophe and cell death. To examine the interphase arrest in MSTO and VMC23 further we analysed the expression of cyclin D1 and Myc, known cell cycle targets of YB-1, in knockdown samples using RT-qPCR. Transcripts of cyclin D1 and Myc were downregulated in both cell lines in response to reducing YB1, partially explaining the growth inhibition observed. To further understand the effects of YB-1 inhibition we have undertaken a global analysis of downstream targets and pathways after YB1 siRNA transfection in all three cell lines using RNAseq analysis. **Conclusion:** This project delves into the complex mechanism underlying YB-1-driven MPM proliferation and found it plays a broader role than expected due to its influence over multiple cancer-promoting genes and pathways. Our study significantly extends our understanding of this important protein in MPM, a disease in dire need of actionable targets.

Keywords: Mesothelioma, therapeutic target, cell cycle and apoptosis

P2.06-07 PHASE 1 STUDY OF CA-170: FIRST-IN-CLASS SMALL MOLECULE TARGETING VISTA/PD-L1 IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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Background: In contrast to PD-L1, VISTA is expressed in up to 90% of malignant pleural mesothelioma (MPM) patients with strong expression on infiltrating lymphocytes and on mesothelioma cells. Recent work also found that expression of VISTA in epithelioid MPM is strikingly higher than in other solid tumors. PD-1 and PD-L1 immune checkpoint inhibitors (ICI) have shown modest activity in ≥2nd line MPM which has fueled interest in novel targets, such as VISTA. Many genes associated with VISTA signaling are proliferative and may help drive cancer, providing strong rationale for inhibitors blocking VISTA. VISTA and PD-1 are independent immune checkpoints negatively regulating T-cell function. VISTA is expressed on immune and tumor cells and implicated in resistance to ICI. Preclinical studies show that dual blockade of VISTA and PD-L1 can be synergistic. CA-170, a small molecule inhibitor of VISTA and PD-L1, has demonstrated anti-tumor activity in multiple *in vivo* models including syngeneic models that do not respond to anti-PD-1 treatment. Phase 1/2 trialsof CA-170 monotherapy showed that CA-170 has a favorable safety profile with preliminary signs of anti-tumor activity in PD-1 malignancies. Pharmacological activity, as measured by immune-modulating effects, was observed across a wide dose range. Development of CA-170 is on-going with evaluation of BID doses in VISTA expressing tumors, such as MPM. **Method:** CA-170-101 is a Phase 1 dose finding study in advanced solid tumors and lymphomas. Selected dose levels can be expanded with additional patients in tumor types of interest. Two pharmacologically active doses, 200 and 1200 mg BID, were selected to further expand with MPM patients to better understand CA-170 activity in this high VISTA-expressing tumor type. As of April 2019, 12 patients with MPM have been enrolled; 8 have completed the 21-day safety evaluation period without DLT. Objectives: tolerability and RP2D (primary), anti-tumor activity (PFS and ORR, secondary) and exploratory biomarkers and PD effects. Key eligibility: histologically confirmed epithelioid, ≥1 prior therapy including pemetrexed-platinum doublet, no prior ICI, measurable disease, paired tumor biopsies if medically feasible, ECOG 0-1, life expectancy >3 months, and adequate organ function. Clinical trial: NCT02812875. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Mesothelioma, VISTA, PD-L1

P2.06-08 NIVOLUMAB FOR MALIGNANT MESOTHELIOMA: A REAL-WORLD EXPERIENCE

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Background: Nivolumab, an anti-PD-1 monoclonal antibody, has beneficial effects against pretreated malignant pleural mesothelioma (MPM). Although this drug is approved in Japan, data on the efficacy and safety of nivolumab in MPM are limited to those from a small number of patients of the MERIT study. Therefore, it is important to accumulate real-world data of nivolumab. **Method:** We retrospectively analyzed all patients with MPM who received

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nivolumab at Hyogo College of Medicine Hospital from August 2018 to December 2018. The tumor response was assessed according to RECIST guidelines (version 1.1), and adverse events were evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. **Result:** A total of 39 patients (31 males and 8 females)were included. There were 29, 6, and 4 patients with a performance status of 0-1, 2, and 3, respectively. There were 34, 4, and 1 patientswith epithelioid, sarcomatoid, and bi-phasic histology, respectively. Nivolumab was given as second-, third-, and ≥fourth-line treatment to 18, 10, and 11 patients, respectively. The response rate (RR)was 20.5% (8/39), and disease control rate (DCR)was 56.4% (22/39). Twelve patients were evaluated asprogressive disease and 5 patientswere not evaluable. The RR and DCR were 11.8% (4/34) and 50.0% (17/34) in the epithelioid-type, and 50.0% (2/4) and 100.0% (4/4)in the sarcomatoid-type.The median progression-free survival was 4.1 months and median overall survival was not reached. Regarding adverse events, fatigue (grade 1–2) was observed in 8, hypothyroidism (grade 1-2) in 4, renal dysfunction (grade 1-2) in 3, loss of appetite (grade 1-2) in 2, pneumonitis (grade 3) in 1, rash (grade 1) in 1and hypopituitarism (grade 2) in 1 patients, respectively. **Conclusion:** The findings of this retrospective study revealed the effectiveness and safety of nivolumab for MPM in the real-world setting. Nivolumab can be used as a standard second-line treatment for MPM.

Keywords: MPM, nivolumab

P2.06-09 DROP THE SCALPEL: LONG-TERM SURVIVAL IN MESOTHELIOMA WITHOUT EXTRAPLEURAL PNEUMONECTOMY OR PLEURECTOMY DECORTICATION

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Background: Survival times following multimodality treatment with extrapleural pneumonectomy (EPP) and pleurectomy decortication (P/D) for malignant pleural mesothelioma (MPM) are poor with a need to identify factors that predict long-term survival. **Method:** A retrospective single-institution review was performed on all patients who underwent EEP or P/D for histologically confirmed MPM between 1996 and 2015. Patients who underwent a diagnostic biopsy or limited tumor excision were included for survival comparison in a non-operative group (NO). Clinical characteristics, perioperative outcomes, stage, nodal disease, R1 versus R2 resection, treatment modalities, and survival data were collected. The top decile of patients with longest overall survival were studied in subgroup analysis as "long-term survivors." **Result:** A total of 206 patients with MPM underwent any type of operations with a median survival time of 13 months (range, 0-134 months) and a 3-year and 5-year survival rates of 15.9% and 8.1% respectively among all patients. Median survival times following EPP (n=28), P/D (n=102) and NO (n=76) were 14 months, 13 months, and 11 months respectively. Better survival was observed in patients with epithelial histology (16 months, n=146) than biphasic histology (7 months, n=28) or sarcomatoid histology (5 months, n=27) (logrank p<.001). Patients with epithelial histology had the greatest median survival times, EPP (29 months, n=23), P/D (16 months, n=77) and NO (16 months, n=46). Three-year and 5-year overall survival rates among patients with epithelial histology were 34.7%, 14.9% after EPP, 16.7, 10.4% after PD and 25.9%, 8.1% after NO, with the patients in the NO group presenting with the most advanced disease. The top decile of long-term survivors all had epitheliod histology and were treated with a variety of chemotherapy regimens leading to a median survival of 64 months with a mean of 71 months. Patients with disease too advanced for surgical resection in the NO group were equally likely to become long-term survivors (9.2%, median survival 57 months) compared with patients who underwent major surgical resection like EPP or P/D (10.0%, median survival 72 months). **Conclusion:** In this non-randomized retrospective review, patients with MPM too advanced for EPP or PD, who instead underwent palliative limited operations as part of a multimodality treatment regimen had long-term survival rates of approximately 10% that were equivalent to rates of long-term survival following major resections like EPP or P/D. Long-term survival is mesothelioma is therefore more likely determined by outside factors such as disease biology and pace of tumor growth than it is major surgical resection.

Keywords: pleurectomy/decortication, Mesothelioma, extrapleural pneumonectomy

P2.06-10 ABT-806 DERIVED ANTIBODY DRUG CONJUGATES (ADCS) INHIBIT GROWTH OF MALIGNANT MESOTHELIOMA IN-VIVO

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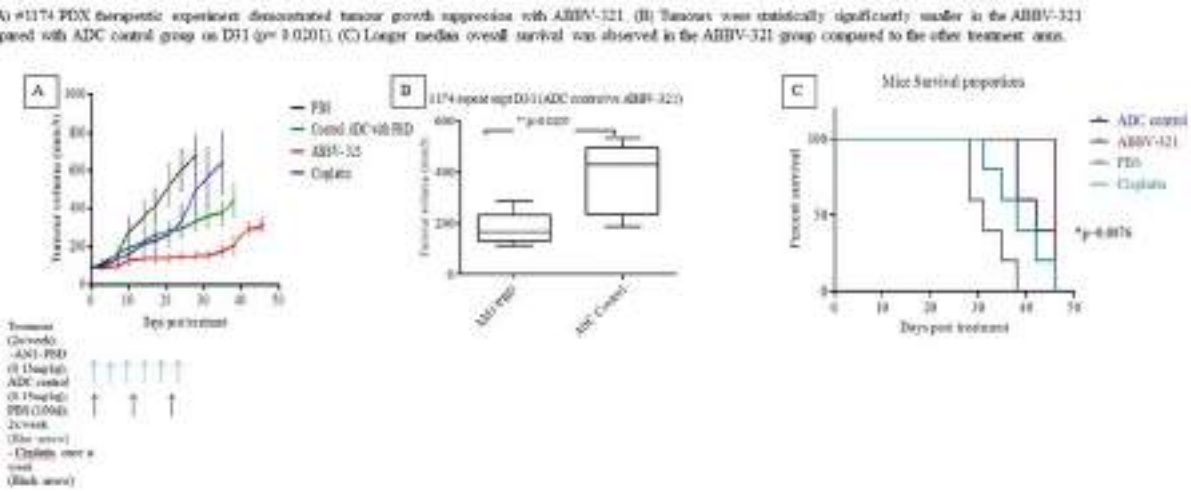
Background: Malignant mesothelioma (MM) is an aggressive malignancy of the pleura with limited therapeutic options, and is associated with a poor prognosis. EGFR is known to be highly over-expressed in mesothelioma with reported EGFR overexpression between 44 to 97%. We have investigated an anti-EGFR antibody (ABT-806), which is tumour specific and robustly inhibits EGFR-expressing tumors. We have previously shown that ABT-806 ADCs demonstrate potent anti-tumor activity in 806 immunohistochemistry (IHC) positive MSTO-211H MM cell line xenograft model. We present data in MM using ABT-806 novel ADCs [ABT-414 (ABT-806- monomethyl auristatin F), ABBV-221 (ABT-806- monomethyl auristatin E), ABBV-322 (ABT-806- pyrrolobenzodiazepine)] and ABBV-321 (Affinity-matured ABT-806- pyrrolobenzodiazepine) in MM patient derived xenografts (PDX). **Method:** We evaluated expression of EGFR and mAb 806 IHC in MM cell lines and PDXs. PDXs were implanted into 5 to 10 NOD-Scid mice per group and treated with control ADC, saline, cisplatin or ABT-806 ADCs and followed longitudinally with caliper measurements. Comparative statistics were performed in Graphpad prism. Quantitative biodistribution and imaging of mAb806 uptake (89Zr-ch806) were performed to allow correlation of mAb806 concentration in MM tumours. **Result:** Three PDX models were selected according to their 806 IHC statuses (2 epithelioid 806 IHC positive, 1 biphasic histology 806 IHC negative). In one epithelioid PDX model, ABBV-322 resulted in significantly reduced tumor growth on day 27 post therapy with median tumour volumes of 180 mm3 (ADC control) compared with 78mm3 (ABBV-322; p=0.0159 two-sided). Moreover, the median survival was also significantly longer in ABBV-322 treated models (p=0.018). In the other epithelioid PDX model, ABBV-321 also resulted in significant responses (median 428mm3 (ADC control) vs 167mm3 (ABBV-321, p= 0.0201) [Figure 1]. In the 806 IHC negative PDX model, the differences in tumor volumes between all groups were found to be non-statistically significant (ADC control vs ABT-414, ADC control vs ABBV-221, ADC-control vs ABBV-321 groups) with p=0.0597 for one-way ANOVA. MSTO211H cell line xenograft model also demonstrated significant anti-tumour response to both ABT-414 and ABBV-221 (p<0.01). Whole-body PET/MR images also confirmed localization of 89Zr-Ch806 to the established MSTO-211H xenograft tumours.



Conclusion: In a disease with limited therapies, ABT-806 targeting ADCs in MM demonstrated significant responses in 806+ PDX and cell lines. These data support clinical expansion of these compounds in 806+ MM patients.

Keywords: Antibody drug conjugates, anti-EGFR, malignant mesothelioma

P2.06-11 MEDUSA: PHYLOGENETIC ANALYSIS OF MESOTHELIOMA TUMOURS BY MULTIREGIONAL SAMPLING, WHOLE EXOME SEQUENCING, AND COPY NUMBER ANALYSIS

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Background: The Mesothelioma evolution: Drugging somatic alterations (MEDUSA) project aims to investigate the genomic evolution and heterogeneity of malignant pleural mesothelioma and identify genomic changes early in mesothelioma evolution that can be targeted by drugs. For 20 malignant pleural mesothelioma patients, we have analysed the exomes of at least four regions of the tumour and paired whole blood. **Method:** Using paired tumour-normal analysis with the software Sequenza, we have called copy number alterations specific to the tumour, and used the software Tumult to reconstruct a phylogeny of the tumour for each of the 20 patients. **Result:** We show that mesothelioma shows extensive heterogeneity in copy number changes, and accumulates typically between 100-200 copy number gains and losses while evolving in a branching pattern. We identify and validate copy number alterations that occur truncally, early in the evolution of the tumour, and are recurrent across patients, including homozygous loss of CDKN2A and MTAP in 4/20 patients, heterozygous loss of MTOR in 6/20 patients and heterozygous loss of BAP1 in 4/20 patients. Losses of these key genes are observed in some other patients, but only in a subset of regions, suggesting that they have occurred later in the evolution of the tumour compared to truncal changes. **Conclusion:** As truncal changes are likely to be present throughout the tumour, identifying them highlights potential Achilles' heels for drug targeting and treatment.

Keywords: evolution, Mesothelioma, Genomics

P2.06-12 DYSPHAGIA IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Background: Dysphagia is common with advanced malignancies but is not well characterized in MPM and is under-recognized as a symptom attributable to this disease. The prevalence of dysphagia in MPM is unknown. Available literature is limited to a few case reports. Dysphagia can lead to nutritional compromise, pain and deterioration of quality of life. It can occur as a result of extrinsic compression of the esophagus by mediastinal lymphadenopathy, intrinsic mechanical obstruction or pseudo-achalasia secondary to infiltration of the esophagus. Palliation is an important goal of therapy and recognizing the underlying etiology will guide selection of interventions. **Method:** We performed a single center, retrospective cohort study of MPM patients who reported dysphagia treated at the University of Chicago between 6/1/2016 and 4/1/2018. 250 consecutive patient records were reviewed for the report of dysphagia and chart extraction was performed. Patient factors collected included patient age at diagnosis, gender and comorbid medical illness. Mesothelioma specific factors included tumor histology, treatment history and overall survival. Dysphagia specific factors including onset of dysphagia relative to diagnosis and patient death, characteristics of dysphagia, findings on imaging and evaluation and interventions performed. **Result:** Eleven patients (4.4%) reported dysphagia. Median age was 72 (range 55-88). 100% male. 8 had right sided, 3 had left sided disease. Tumor histology: 6 epithelioid, 1 sarcomatoid and 4 biphasic. Of these, one patient had dysphagia unrelated to mesothelioma that resolved with surgical intervention. Of the remaining 10 patients, 9 had mediastinal adenopathy and/or esophageal involvement on CT scans. 1 patient had no CT findings to explain dysphagia and EGD revealed extrinsic compression. 3 patients were stented. 2 of 3 required repeat procedures. 1 required a feeding tube. Median time from diagnosis to onset of dysphagia was 18 months (range 0.7-31.7) One patient developed dysphagia 2 months prior to diagnosis. Median time from development of dysphagia to death was 5.7 months (range 2-7.7) One patient remains alive. Median overall survival was 19.8 months (range 4.4-159.7). **Conclusion:** Dysphagia in patients with malignant pleural mesothelioma is most often attributable to the underlying malignancy due to extrinsic compression from mediastinal adenopathy or direct tumor extension. This development is a poor prognostic sign and, in this sample, signaled a median survival just under 6 months. Patients with the shortest interval from diagnosis to onset of dysphagia had the shortest overall survival. A prospective study to further characterize dysphagia in MPM and optimize interventions is ongoing.

Keyword: Mesothelioma, Dysphagia, Palliative Care

P2.06-13 TARGETING RAS SIGNALING IN MALIGNANT MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is distinguished by molecular features, such as activated and redundant multiple tyrosine kinases signaling via the Ras pathways. Several pharmacologic strategies have been attempted to disrupt this pathogenic axis, but clinically effective agents remain elusive. We propose to leverage microRNA (miRNA) as a potential therapeutic approach, since miRNA can coherently regulate multiple simultaneous gene targets that comprise critical biologic networks. **Method:** Our prior miRNA profiling results of human MPM (GSE40345) were cross-referenced with TCGA-Meso data to identify prognostic miRNAs. Both MPM cell lines and tissues (tumors and normal pleura) were assessed using quantitative and functional biologic assays that revealed specific molecular mechanisms of relevant miRNA. In silico algorithms identified downstream gene targets that were verified by 3'-UTR luciferase assay. Murine models of MPM xenografts were used to verify *in vitro* observations of miRNA effects. Kaplan-Meier assessed outcomes in vivo. **Result:** Our analyses showed underexpression of miR-206 by 12-fold in MPM tumors compared to normal pleura. TCGA data (n=74 MPM) indicated worse survival in patients with low miR-206 (25-fold decrease) compared to higher miR-206 expression. We confirmed that miR-206 was significantly underexpressed by qRT-PCR analysis of new, randomly selected MPM tumors versus normal pleurae tissues. In MPM cell lines, ectopic re-expression of miR-206 dramatically suppressed cell proliferation, invasiveness, and growth in soft-agar. Interestingly, we noted several MPM-prognostic genes ($p<0.05$) regulated by miR-206: KRAS, CDK4, CCND1, and IGF1R. This signaling axis of KRAS/CDK4/CCND1 is important in MPM as it summates well-known dysregulated tyrosine kinase receptors (EGF, IGF-1, VEGF, MET, etc) that are upstream. The KRAS/CDK4/CCND1 axis is associated with cell cycle progression and survival of cancer cells, but is not an easily druggable target. *In vitro*, miR-206 treatment significantly downregulated KRAS, CDK4 and CCND1 as well upstream target genes such as MET, EGFR, IGF1R and VEGFA. In vivo, miR-206 treatment significantly suppressed MPM tumor growth in subcutaneous and orthotopic xenograft models compared to control. Kaplan-Meier analysis showed that miR-206 treatment improved overall survival. **Conclusion:** miR-206 exerts tumor suppressive effects in MPM via inhibition of KRAS/CDK4/CCND1 signaling, which mimics simultaneous blocking of multiple tyrosine kinases. Loss of miR-206 and concomitant overexpression of KRAS, CDK4 and CCND1 formed a novel poor prognosis signature in MPM. Our results indicate that miR-206 is a rational agent to be developed further in preclinical MPM models as a promising therapeutic.

Keywords: RAS, Tyrosine kinase, Mesothelioma

P2.06-14 BAP1 MUTANT MALIGNANT PLEURAL MESOTHELIOMA (MPM): OUTCOMES WITH CHEMOTHERAPY, ICPI AND PARPI

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Background: Little is known regarding the outcomes of systemic treatments (Tx) in BAP1 altered MPM. **Method:** 45 patients (pts) with advanced MPM (Group A: 8 MPM with a BAP1 inactivating mutation/copy number loss (FoundationOne CDx/TEMPUSxT), selected from the electronic databases (eD) of 4 Israeli cancer centers (ICC); Group B: 37 consecutive (years 2016-2018) MPM without a BAP1 alteration/not tested, selected from the eD of 2 ICC) were analyzed for ORR, PFS (mRECIST 1.1) and OS with platinum/pemetrexed+/-bevacizumab/nintedanib (CT, n-28), immune check-point inhibitors (ICPi, n-16) and poly (ADP-ribose) polymerase inhibitors (PARPi, n-4). OS since diagnosis (OSDx) was assessed. **Result:** Pt and Tx characteristics are presented in the Table. There were no differences in ORR, mPFS or mOS with CT between the Groups: ORR-50% in both Groups, mPFS-9.1mo (95%CI, 1.2-16.1) vs 9.2mo (95%CI, 2.9-17.8) (log-rank-0.01, p-0.9), mOS-NR (95%CI, 6.6-NR) vs 18.5mo (95%CI, 5.4-46.3) (log-rank-1.1, p-0.3), in Groups A and B, respectively. There were no differences in ORR, mPFS or mOS with ICPi between the Groups: ORR- 33% vs 50% ($p>0.5$), mPFS-2.5mo (95%CI, 1.4-3.7) vs 3.0mo (95%CI, 0.3-10.5) (log-rank-0.5, p-0.4), mOS-NR (95%CI, 4.0-NR) vs 5.8mo (95%CI, 0.3-13.2) (log-rank-0.1, p-0.7), in Groups A and B, respectively. In Group A, no responses were seen with PARPi; PFS with PARPi was 1.8mo (95%CI, 1.8-1.9). OSDx was NR (95%CI, 9.7-NR) vs 19.5mo (95%CI, 9.7-82.2) in Groups A and B, respectively (log-rank-1.6, p-0.2). In the univariate analysis, sex (p-0.04), histology (p-0.002), ECOG PS (p-0.03), but not BAP1 mutation (p-0.3) correlated with OSDx.

	Group A, n-8	Group B, n-37	p value
Age, y (median, range)	65 (25-76)	70 (30-93)	0.2
Male, %	62	70	0.7
Asbestos exposure, %	25	40	0.4
ECOG PS 0/1, %	87	81	1
Epithelioid histology, %	87	84	0.6
PD-L1 TPS: >50%/1-50%/<1%/NA, %	25/0/12/63	0/11/5/84	0.05
TMB, mut/Mb (median, range)/% tested	3 (0.8-5)/62	1.5 (0-2)/11	0.2
MSI high, n (%)/% tested	0/100	0/16	NA
Tx: CT/ICPi/PARPi, %	100/37/50	54/35/0	NA

Conclusion: Outcomes with CT and ICPi in BAP1 mutant MPM are similar to non-selected MPM. No responses were seen so far with PARPi. According to our data, presence of BAP1 mutation does not affect OS. Additional follow-up is needed.

Keywords: BAP1, immune check-point inhibitors, poly (ADP-ribose) polymerase inhibitors

P2.06-15 CLINICAL VALUE SCORES OF TTFIELDS TREATMENT OF UNRESECTABLE MALIGNANT PLEURAL MESOTHELIOMA USING THE ASCO AND ESMO FRAMEWORK

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Background: The effectiveness and safety of TTFields in addition to pemetrexed and cisplatin or carboplatin in unresectable malignant pleural mesothelioma (MPM) was recently shown through the analysis of the phase II single arm EF-23 STELLAR trial. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have both developed frameworks accounting for the need of physicians and policymakers to objectively and comparably capture the clinical value of new cancer treatments. We quantified the clinical value of the TTFields treatment in MPM by applying ASCO and ESMO frameworks to the comparison of the STELLAR data to historical controls. **Method:** The EF-23 STELLAR trial (n=80) demonstrated that adding TTFields to pemetrexed and cisplatin or carboplatin for malignant pleural mesothelioma patients resulted in overall survival of 18.2 months (95% CI 12.1-25.8) and progression free survival of 7.6 months (95% CI 6.7-8.6). The median time to deterioration in ECOG performance status was 13.1 months. Average pain score was lower compared to baseline during the first 7 months of treatment. The ESMO Magnitude of Clinical Benefit Scale (MCBS) and the ASCO Net Health Benefit (NHB) frameworks were applied to the EF-23 trial data using a historical control as comparator. **Result:** The application of the ASCO framework to the EF-23 data resulted in a NHB score of 52, the first such score reported for MPM. This result is at the higher end of the score range of novel cancer treatments and compares well to the results for nivolumab in NSCLC as reference point. Applying the ESMO framework resulted in MCBS scores of A/5 (adjuvant/advanced) which is also the first MCBS score reported for MPM. The MCBS scores of A/5 are the highest scores achievable in the ESMO framework, and higher then most ESMO MCBS scores reported in the literature for NSCLC treatments. **Conclusion:** Despite differences in their respective concepts, both the ASCO and ESMO frameworks suggest that adding TTFields to Pemetrexed and Cisplatin or Carboplatin in malignant pleural mesothelioma patients may provide a significant clinical benefit. The high scores underline that treatment with TTFields may extended time to deterioration of performance status, progression free and overall survival without additional systemic toxicities.

Keywords: Mesothelioma, TTFields, Clinical value

P2.06-16 RACIAL DISPARITIES IN TREATMENT PATTERNS AND SURVIVAL AMONG SURGICALLY TREATED MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

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Background: Although surgical intervention improves survival for patients with malignant pleural mesothelioma (MPM), black patients are less likely to receive surgery. It is not known what the treatment patterns in MPM surgical patients are according to race. This study sought to examine treatment patterns and survival between black and white surgical patients using a large nationwide cancer database. **Method:** This study used the National Cancer Database (NCDB) to examine the subset of black and white MPM patients who received surgery, defined as pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP). Multivariable logistic regressions were used to evaluate the racial differences in the extent of surgery, receipt of additional treatment (chemotherapy and/or radiotherapy), and 30-/90- day mortality, while accounting for clinical and demographic factors. A multivariable Cox proportional hazards model was used to assess the independent associations of race with overall survival. Association between race and survival was also analyzed using a 1:1 propensity score matching with the greedy algorithm. **Result:** There were 2550 MPM patients in the NCDB who received surgery; 2462 white (96.5%) and 88 black (3.5%). Most patients received P/D (77.8%); 63.8% received additional treatment. Black patients were significantly less likely to receive EPP (ORadj: 0.36, 95% CI: 0.17-0.78). There was no significant difference with race in the receipt of additional treatment (ORadj: 0.79, 95% CI: 0.46-1.34); EPP patients were significantly more likely to receive additional treatment (ORadj: 1.34, 95% CI: 1.02-1.74). Black patients tended to have worse 30- and 90- day mortality than white patients (ORadj: 1.52, 95% CI: 0.58-4.01; ORadj: 1.50, 95% CI: 0.75-3.01, respectively). There was no significant difference in overall survival between black and white patients (HRadj: 0.96, 95% CI: 0.72-1.27); patients who had treatment in addition to surgery had significantly better survival (HRadj: 0.71, 95% CI: 0.64-0.80). Results remained similar after propensity matching. **Conclusion:** Among MPM patients receiving surgery, black patients received less extensive surgery, and are less likely to receive additional treatment, indicating less aggressive treatment overall. Although overall survival was similar, black patients tended to have worse short term outcomes after surgery. Racial disparities in treatment and short term outcomes need to be better addressed.

Keywords: racial disparity, EPP, P/D

P2.06-17 THE RESULTS OF TRI-MODALITY TREATMENT WITH EXTRAPLEURAL PNEUMONECTOMY, RADIATION, AND CHEMOTHERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA

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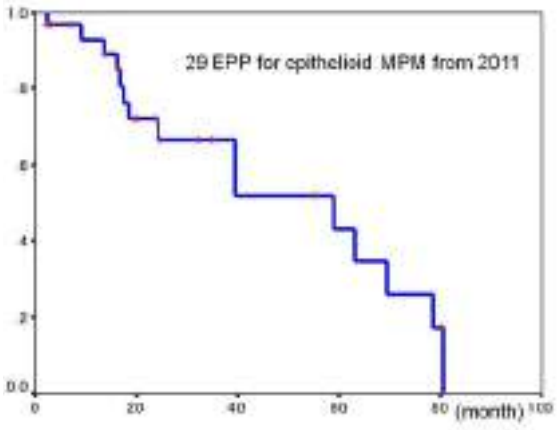
Background: Extrapleural pneumonectomy (EPP) or Pleurectomy/Decortication (P/D) is performed for operable malignant pleural mesothelioma (MPM). International Mesothelioma Interest Group (IMIG) guidelines (Rusch V, et al. JTCVS 2013) concluded that EPP or P/D should be selected on the basis of disease distribution, institutional experience, and surgeon preference and experience. Our first choice is EPP followed by radiation and chemotherapy. If EPP is inappropriate, P/D followed by chemotherapy is performed. Our improving results of tri-modality treatment strategy to treat MPM by EPP are reported. **Method:** 58 consecutive EPP for MPM from June 2006 to January 2019 in our hospital were reviewed. We have instituted a trimodality therapy protocol consisting of EPP, adjuvant 45-50.4 Gy hemithoracic radiation, and adjuvant CDDP plus PEM chemotherapy. 48 patients were treated with this protocol. However, 10 patients were given induction chemotherapy, and referred to us. They were scheduled to undergo EPP and adjuvant radiation. Overall survival from the treatment start was calculated using Kaplan-Meier method. The prognosis data were updated in February 2019. **Result:** Median age at EPP was 62 years old (39-74). Female was 11, and male was 47. Right side was 30, and left side was 28. Epithelioid was 39 (67%), biphasic was 14, sarcomatoid was 2, and special variants was 3. Median EPP time was 7 hours 33 minutes (5 h 50 m-12 h 2 m). No blood transfusion during EPP was 20 cases (34%). Mortality was one patient (1.7%) who died due to acute aggravation of interstitial pneumonia. Atrial fibrillation was the most common morbidity, and developed in 20 patients (34%). IMIG pathological stage was IV in 6, III in 31, II in 13, and Ib in 8. Adjuvant 45-50.4 Gy radiation was completed for 49 patients (84%). 11 of 54 patients (20%) could not undergo chemotherapy, and four patients are waiting for chemotherapy. 37 of 54 patients (69%) underwent trimodality therapy, and 4 patients are waiting for chemotherapy. Postoperative median follow-up period was 6 years and 7 months. 5 year survival, 2 year survival, and median survival of all 58 patients were 27%, 53%, and 30 months, and those of 39 epithelioid patients were 32%, 63%, and 37 months, and those of recent 29 epithelioid patients from 2011 were 43%, 72%, and 59 months (Figure).



Conclusion: This tri-modality treatment strategy with EPP, radiation, and chemotherapy for MPM is feasible, and the prognosis has been greatly improved.

Keywords: malignant pleural mesothelioma, extrapleural pneumonectomy, tri-modality treatment

P2.06-18 TARGETING POLYAMINES FOR TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA IN XENOGRAFT MODELS

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Background: Inhaling asbestos fibers is the commonest cause of malignant pleural mesothelioma (MPM). Although the import and use of asbestos have been restricted, the incidence of MPM is still rising due to a long lag time in malignant transformation. In 2004, the US Food and Drug Administration approved a combination of pemetrexed with cisplatin for treatment of unresectable MPM. However, overall prognosis is still extremely poor. As such, development of novel therapeutic options is urgently needed. Ornithine decarboxylase (ODC) is highly expressed in 211H and H226 MPM xenografts and clinical tumor samples. Upregulation of ODC increases polyamine production and enhances tumor growth. a-difluoromethylornithine (DFMO) is a specific ODC inhibitor which can suppress polyamines production. Recent preclinical studies have demonstrated the therapeutic effect of DFMO in colon cancers using xenograft model. However, therapeutic effect of DFMO in MPM has not yet been studied. This study aims to disclose the therapeutic effect of DFMO in MPM xenograft models. The findings from this study will provide scientific foundation for future design of clinical trials of DFMO for therapy for advanced MPM. **Method:** Nude mice were subcutaneous inoculated with tumor cells [211H (biphasic) or H226 (epithelioid)]. Mice were treated with DFMO in drinking water when tumor size reached 50-100 mm3. Mice with tumor size >600mm3 were considered reaching humane endpoint. Spermidine levels, protein expression, cytokines concentrations and apoptosis were investigated by Dot plot, Western blot, ELISA and TUNEL assay respectively. **Result:** DFMO suppressed tumor growth in both xenografts. DFMO increased median survival from 29 days in control arm to 41 days in treatment arm in mice with 211H xenografts (p = 0.0234), while from 30 days to 43.5 days in those with H226 xenografts (p = 0.0050). There was no synergism when combining DFMO (0.5% or 2%) with either cisplatin (1.25 or 2.5 mg/kg) or pemetrexed (75 or 150 mg/kg). The tumor suppressive effect of DFMO was more effective when compared with cisplatin or pemetrexed. Upon DFMO treatment, decrease in spermidine level, increase in nitrotyrosine content, and activation of apoptosis were observed in both xenografts. In addition, increase in nitrosocysteine level, increase in intratumoral IL-6, keratinocyte chemoattractant (KC) and TNF alpha as well as elevation of DNA lesion and downregulation of pAkt were induced by DFMO in H226 xenografts. **Conclusion:** DFMO may have a potential role in treating MPM. Acknowledgment: This research was supported by Hong Kong Pneumoconiosis Compensation Fund Board, HKSAR and YC Chan Scientist Award.

Keywords: Alpha-difluoromethylornithine, malignant pleural mesothelioma, xenograft models

P2.06-19 A META-ANALYSIS OF MESOTHELIN, OSTEOPONTIN, AND FIBULIN-3 AS BIOMARKERS OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant Pleural Mesothelioma (MPM) is a rare and aggressive cancer; the use of mesothelin, fibulin-3, and osteopontin as biomarkers has been proposed as a screening tool. The following meta-analysis examines average levels of these biomarkers in blood and pleura in comparison to several control groups. **Method:** A PubMed search was conducted for studies that measured the levels of mesothelin, osteopontin, and fibulin-3 in patients with MPM compared to several control groups (other malignancies, benign lung disease, or healthy participants). **Result:** Thirty two studies with 28 distinct datasets were identified as reporting mesothelin levels. Statistically significant mean differences (MD) were observed between mesothelin in the blood of MPM patients and each of the control groups. The overall MD (95% confidence interval) between MPM and non-MPM controls was 3.88 (2.73-5.05) nM/L (nMPM=455). Statistically significant MDs in pleural levels of mesothelin were also seen between MPM patients and non-MPM cancers and benign lung diseases. The overall MD (95%CI) was 31.45 (23.63-39.27) nM/L (nMPM=571). Twelve articles with 10 distinct datasets reported the mean level of osteopontin in MPM cases and controls. Statistically significant MDs in blood levels of osteopontin were seen between MPM patients and benign lung diseases or healthy controls (overall MD (95% CI) 103.75 (54.77-152.72) ng/mL (nMPM=504)), but not with other cancers. Studies on pleural levels of osteopontin were too scarce to conduct a meta-analysis. Nine articles measured fibulin-3 in blood or pleura of MPM patients compared to controls. There was a statistically significant MD in blood levels of fibulin-3 between MPM and each of the control groups. The overall MD (95%CI) was 46.52 (34.04-59.00) ng/mL (nMPM=330). There was also a statistically significant MD in the pleural levels of fibulin-3 between MPM and the cancer and benign lung disease groups. The overall MD (95% CI) was 385.35 (287.98-482.73)ng/mL (nMPM=137). **Conclusion:** This meta-analysis supports the concept that mesothelin and fibulin-3 in control groups are significantly lower than in MPM, and thus they might be useful as screening biomarkers. Further studies are necessary to better assess the value of these promising biomarkers.

Keywords: Biomarker, Meta-analysis

P2.06-20 CHARACTERIZATION OF CLAUDIN15 AS A NEW DIAGNOSTIC MARKER FOR MALIGNANT PLEURAL MESOTHELIOMAS

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Background: Malignant pleural mesotheliomas (MPMs) is a fatal disease mainly caused by past exposure to asbestos. MPMs are classified into three main histological subtypes: epithelioid, sarcomatoid, and biphasic type. There have been known several immunopathological markers for diagnosing MPMs, but there are not enough reliable markers, which often makes it difficult to diagnose MPMs correctly. In the present study, we investigated whether Claudin15 serves as a diagnostic and therapeutic target for MPMs. Claudins are four-transmembrane proteins and form a protein family consisting 27 members in humans. Specific combination of claudins are differentially expressed in different organs and form tight junctions with different permeability. Expression of Claudin15 has been known to be increased at mRNA level in MPMs. **Method:** Since 2003 to 2018, 34 patients were diagnosed with MPMs in our hospital. We made a new anti-Claudin15 rat monoclonal antibody, and established a hybridoma clone suitable for IHC. We immunostained 34 tissues with newly established anti-Claudin15 antibody, and compared the staining intensity and occupation with those of Calretinin, a known marker for MPMs. We also immunostained poorly differentiated lung adenocarcinomas, which are sometimes hardly distinguishable with MPMs, with anti-Claudin15 antibody to examine whether Claudin15 staining can distinguish MPMs from adenocarcinomas. **Result:** Of the 34 cases, the epithelial type was 27 cases, the sarcomatoid type was 1 case, and the biphasic type was 6 cases. The overall expression rate was 53% for Claudin15 and 59% for Calretinin. In terms of histology type, Claudin15 was 50% and Calretinin was 65% in the epithelial type, while Claudin15 was 80% and Calretinin was 40% in the biphasic type. There was only one sarcomatoid type, neither was expressed. Poorly differentiated adenocarcinomas showed no or very low-level expression of Claudin15. **Conclusion:** Our results suggest that Claudin15 could be a novel diagnostic marker for MPMs, especially for biphasic type. Greater number of cases and further analyses would be required to establish Claudin15 as a diagnostic impact for MPMs in clinical use.

Keywords: tight junctions, malignant pleural mesothelioma, Claudin

P2.06-21 EFFICACY AND SAFETY OF TUMOR TREATING FIELDS DELIVERY TO THE THORAX BY COMPUTATIONAL SIMULATIONS

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Background: Tumor Treating Fields (TTFields), an anti-mitotic therapy low intensity, intermediate frequency, alternating electric fields, are approved for glioblastoma. The STELLAR phase 2 registration trial recently demonstrated a significant extension in overall survival in mesothelioma patients treated with TTFields and standard of care chemotherapy vs historical control data on chemotherapy alone. The results highlight the potential benefit of TTFields to treat cancer located in the thorax. Preclinical studies show that efficacy increases with the intensity of the electric field. Optimizing treatment requires a thorough understanding of how TTFields distribute within the body. Simulations can be used to evaluate the treatment safety by assessing tissue heating associated with absorption of the electric field. We present a simulation based study on field distribution and associated heating when delivering TTFields to the thorax. **Method:** We delivered TTFields to the thorax of realistic computational phantoms of a male, female, and obese male (ZMT, Zurich, Switzerland). The field was delivered to the computational phantoms using transducer arrays similar to those used to deliver TTFields to the thorax with the NovoTTF-100L. The field intensities within the lungs of the models were evaluated. Specific Absorption Rate (SAR), a metric for assessing heating due to electromagnetic absorption, was calculated. **Result:** The highest field intensities within the lungs were obtained when the arrays were axially-aligned with the parenchyma as anatomically possible. Field intensities throughout the lungs exceeded the therapeutic threshold of 1 V/cm in all models. Within the internal organs, SAR values were below the allowed level of 10 W/kg set out in the ICNIRP guidelines for occupational exposure. Maximum SAR levels did not exceed 20 W/kg. Occupational exposure standards typically incorporate a safety factor of around 10 when setting basic restrictions, therefore this level of SAR is considered safe and unlikely to lead to heat-related tissue damage. **Conclusion:** TTFields can be delivered to the lungs at therapeutic levels that do not cause damage through tissue heating.

Keywords: Safety, Tumor Treating Fields, Efficacy

P2.06-22 IS LABORATORY PROGNOSTIC INDEX A VALUABLE PROGNOSTIC INDEX FOR MALIGNANT PLEURAL MESOTHELIOMA?

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Background: Prognostic significance of Laboratory Prognostic Index (LPI) was demonstrated in non-small cell lung cancer before. We aimed to assess the prognostic value of LPI in patients with malignant pleural mesothelioma (MPM). **Method:** Records of MPM patients were examined retrospectively for serum laboratory results at diagnosis along with demographical and clinicopathological features. LPI is consisted of white blood cell count (>10000/mm3), albumin (<3.5 g/dL), lactate dehydrogenase (>248 U/L), alkalene phosphatase (>120 U/L) and calcium (>10.5 mg/dL) levels; and it is graded according to the number of abnormal parameters: 0 (none), 1 (one) and 2 (two or more). Kaplan-Meier method and stratified log-rank test were used in univariate analysis and a Cox regression model was conducted to determine independent predictors of overall survival (OS). **Result:** Sixty-one patients were included in the study. Median age at diagnosis was 59 (51-66) years. 45 deaths (73.8%) have occurred at the time of final analysis and median OS was 19.5 months. One-year survival rates for patients with LPI 0, 1 and 2, were 82%, 61% and 59%; 2-year survival rates were 75%, 47% and 24%, respectively. Median OS of patients with LPI 0, 1 and 2 were 36.5, 21.7 and 15.6 months, respectively (p=0.007). Age, ECOG performance status, histology, hemoglobin level and LPI were found to effect OS significantly or to have a trend (p<0.1). In multivariate analysis, LPI (p=0.033) and ECOG performance status (p<0.001) were the independent prognostic factors. **Conclusion:** The LPI may be a valuable prognostic factor in mesothelioma as well. Larger studies are needed to confirm this result.

P2.06-23 THE ACCURACY OF VIDEO-ASSISTED THORACIC SURGERY PLEURAL BIOPSY IN PATIENTS WITH SUSPECTED MALIGNANT PLEURAL MESOTHELIOMA: A REAL-LIFE STUDY

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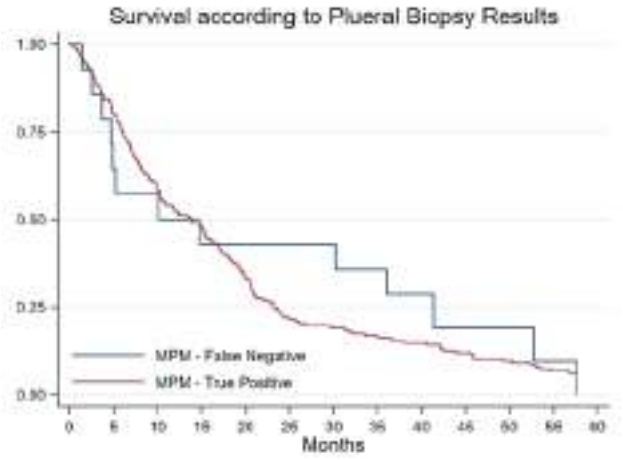
Background: The heritage of occupational and environmental asbestos exposure in Piedmont, Italy, is an enduring epidemic of malignant pleural mesothelioma (MPM). Pleural biopsy (PB) performed *via* thoracoscopy (or video-assisted thoracic surgery (VATS)) remains the diagnostic gold standard for patients with suspected mesothelioma. The aim of our study was to investigate the accuracy of PB *via* VATS and to analyze the diagnostic path of the patients who experienced an initial MPM misdiagnosis. **Method:** Patients who underwent PB by VATS for suspected MPM from 2004 to 2013 were analyzed . The Registry of Malignant Mesothelioma (RMM) records were examined to crosscheck incident cases and to recognize misdiagnosed MPM. Sensitivity and specificity of the initial PB assessment versus the final classification of cases by RMM were evaluated. Overall survival (OS) was estimated using the Kaplan-Meier method and compared using log-rank test. **Result:**



Data of 552 patients were analyzed. Of those, MPM was diagnosed in 178 cases (32%) and no false-positive PBs were observed. Sensitivity and specificity were 93% and 100%, respectively. The number of false-negative PBs was 14 (2%). Of those, 10 (71%) had an initial diagnosis of chronic pleuritis, 3 (28.5%) of atypical mesothelial proliferation and 1 had reactive mesothelial proliferation. All of them reported a history of asbestos exposure and the correct diagnosis was reached after a median of 160 days (interquartile range 86-243) as follow: 9 (64%) after a further PB by VATS, 3 (22%) by cytology examination of a pleural effusion, 1 (7%) by fine-needle biopsy and 1 (7%) by open surgery . The median survival time of the patients with eventual MPM diagnosis was 13.8 months (CI 95%: 10.3-16.6).). One- and 4-year survival were 52% and 10% in MPM PB positive cases and 50% and 19% in false-negative cases (P=0.66) (Figure 1). **Conclusion:** When a history of asbestos exposure is reported and a strong clinical suspicion persists after a negative PB, iterative biopsy attempts should be considered. In high-volume centers, MPM misdiagnosis rate remains small and future advancement in diagnostic technologies could further increase the accuracy of diagnosis.

Keywords: Mesothelioma, Pleural biopsy, False negative

P2.06-24 MESOTHELIOMA SURVIVAL IN 2 HEALTH CENTRES IN SANTIAGO DE CHILE

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Background: Malignant pleural mesothelioma (MPM) is a rare but lethal tumour arising in the 5th – 7th decade of life of predominantly male industrial workers of developed countries. The prognosis is dismal because of early spreading and scarcity of therapies. Surgery (extrapleural pneumonectomy or pleurectomy/decortication) has shown some improvement in patient survival, even more important with the addition of radio or chemotherapy. Patients unfit or with advanced disease are treated with palliative chemotherapy or palliative care alone. Some centres (or countries) doesn't have the resources to embark in such aggressive and expensive managements, pondering the idea that in mesothelioma patients, complex therapies are only a futility exercise not worth the investment in herculean surgery or costly and patient-consuming radio or chemotherapy. The question if aggressive therapy is superior to nihilist approaches in terms of survival (SV) is difficult to answer but of critical importance in developing countries **Method:** Consecutive patients pathologically diagnosed with MPM of 2 health centres in the same city and time frame were assessed. Centre A is a public Hospital with an assigned population of 1 million, without thoracic surgeon and oncologic committee, and patients were seldom referred to palliative chemotherapy. Centre B is a terciary, referral academic university Hospital with Thoracic surgeons and oncologic committee. Centre A had 10 patients reviewed and centre B 20. Both cohorts were examined in terms of treatment and SV **Result:** The 2 series were comparable in terms of age (median=61,5) and sex (masculine: 70% for Centre A, 80% for Centre B). Centre A had 30% of patients with presence of metastasis at the time of diagnosis, while centre B had 10%. In centre A 2 of 10 patients received chemotherapy. In centre B: 9 patients had aggressive surgery, 7 patients received chemotherapy and 2 patients received radiotherapy. Kaplan Meier estimate showed 12-month SV of 51% (CI95% 16-79) in centre A and 59% (CI95% 35-77) in centre B, but there were no statistical differences between both groups **Conclusion:** Few patients were diagnosed (30 overall) in line with chilean epidemiology. The 2 centres had radically different resources and approaches to treat this illness, however, even though there is a tendency towards better survival in Centre B, there were no statistically differences between both groups. Differences could appear increasing the follow-up time or including more centres, alternatively, the rarity of this disease could produce oncologic teams with not enough experience dealing with it affecting survival outcomes.

Keywords: treatment, Mesothelioma, Survival

P2.06-25 MESOTHELIOMA UK ARMED FORCES PROJECT: ESTABLISHING A NATIONAL SUPPORT SERVICE FOR VETERANS / ARMED FORCES PERSONNEL WITH MESOTHELIOMA

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Background: In 2012 the UK Government announced that fines levied against banks for manipulating the London Inter-Bank Offered rate (LIBOR) rates would be used to support Armed Forces and emergency charities. In 2016 Mesothelioma UK (MUK) applied for a grant from this scheme to support a three year project to develop a specialist service for Armed Forces personnel and veterans affected by mesothelioma – the asbestos related cancer. **Method:** The aim of the project is to increase awareness and support for both serving and ex- military personnel who may have been exposed to asbestos. A work group which included representatives from MUK, patients/carers, advocacy groups and Veterans UK was established by MUK to set the fundamental elements of the project: • Provide a specialist mesothelioma nurse to lead the project • Provide a finance and benefits advisor specifically for Armed Forces personnel and veterans. • Work with multiple organisations and healthcare professionals, responsible for meeting the healthcare needs of Armed Forces personnel and veterans, to raise awareness about mesothelioma and available support. • Develop and deliver a range of information resources to raise awareness of the disease within the Armed Forces and military community. • A Facebook group Armed Forces patients, their family and friends and anyone interested in finding out more. • A comprehensive research programme will collate all available data to quantify and describe the mesothelioma burden among the Armed Forces explore the experience of Armed Forces personnel diagnosed with mesothelioma.• **Result:** The project group developed a range of written information specifically aimed at the Armed Forces community focusing on raising awareness of asbestos exposure within the military. Awareness events proved to be a major factor in the growth of the project providing excellent networking opportunities and resulting in invitations to speak and exhibit at other events. A list of organisations and relevant groups was developed in preparation for the national roll out. A range of social media is used to publicise the project and events. A research project - Military Mesothelioma Experience Study (MiMES) has been developed with University of Sheffield and is recruiting. **Conclusion:** .The development of this service has been very well received by the Armed Forces community and the project continues to gather momentum, widening the range of contacts and links made. We are planning a programme of roll out throughout the UK using the network of MUK funded mesothelioma nurse specialists to facilitate service delivery in their regions.

Keywords: Mesothelioma, Service Development, Armed forces/ veterans

P2.06-26 THE MILITARY MESOTHELIOMA EXPERIENCE STUDY (MIMES): INITIAL FINDINGS AND IMPLICATIONS FOR PRACTICE

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Background: Background Mesothelioma is one of the most challenging of cancers; it is incurable, has a long latency period, and is associated with extreme symptom burden. Mesothelioma mostly affects men over 65 years of age; It is linked to exposure to asbestos, normally 15-40 years prior to diagnosis. Its industrial nature diagnosis can mean navigating complex health, legal and welfare systems. Clinical experience and anecdotal evidence from health professionals indicate that this veterans encounter particular challenges in recognising and reporting early symptoms, getting a diagnosis and accessing care and support, including financial help. Little is known about mesothelioma amongst UK military veterans. Research is required to better understand the mesothelioma experience amongst UK military veterans and know how better to meet their needs. **Method:** Methods The Military Mesothelioma Experience Study (MiMES) is a qualitative interview based study that aims to identify the care and support needs of UK military veterans with mesothelioma from the perspective of veterans, family carers, and health professionals and support agency staff. This paper presents findings from the patient and carer data. Semi-structured interviews of up to 15 veterans with mesothelioma and 15 family carers are being conducted. Recruitment is via trusted charitable organisations including Mesothelioma UK and Asbestos Support Groups. Interviews are transcribed and analysed using Framework Analysis techniques. Interviews are being conducted between December 2018 and June 2019. 10 participants have been recruited to date (7 patients and 3 family carers). **Result:** Results The findings provide unique insight into the nature of asbestos exposure whist in the armed forces, as well as participant's diagnostic experience. The impact of military culture on how people respond to the diagnosis and how they navigate services is considered. Valued sources of support included specialist mesothelioma medical and nursing staff as well as mesothelioma/asbestos charities. Participants reported feeling 'in the middle' when it came to understanding legal and financial implications of their disease and asbestos exposure in the military. Being caught between civil and military claim systems and information services could create problems, especially when making a claim was time-pressured. This had an impact on people's quality of life over across the patient pathway. **Conclusion:** Conclusions MiMES is the first study to explore the experiences of UK military veterans with mesothelioma. Implication for practice and collaborative working are considered.

Keywords: Mesothelioma, epidemiology, patient experience

P2.08-01 OUTCOMES FOLLOWING GAMMA KNIFE RADIOSURGERY FOR OLIGOMETASTATIC BRAIN METASTASES IN PATIENTS WITH NSCLC AT LEEDS CANCER CENTRE

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Background: Gamma knife (GK) radiosurgery has increasingly been used for brain metastases from NSCLC in the oligometastatic setting. This study reports outcome results for patients with synchronous brain and new brain metastases from NSCLC at Leeds Cancer Centre (LCC). **Method:** 251 patients, who were treated with GK at LCC from 2009 until 2018 were analysed. Retrospective analysis of notes was performed using electronic patient records. Statistical analysis was performed using SPSS. Kaplan-Meier curves were performed to estimate time to intracranial progression, survival from diagnosis of brain metastases, and overall survival. **Result:** Median age was 65 years (range 33 – 90 years). For patients with new brain metastasis (147 patients), TNM stage at diagnosis was stage I (14 patients), stage II (42 patients), stage IIIA (26 patients) or stage IIIB/IV (65 patients). Histology was majority adenocarcinoma (59%), squamous cell carcinoma (16%) or NSCLC NOS (13%). Radical thoracic treatment (surgery, chemoradiotherapy or stereotactic ablative radiotherapy) was undertaken for 158 patients. 92% completed radical thoracic treatment. Median survival from diagnosis of brain metastases was 382 days (446 days for those with synchronous brain metastases (48 patients), and 325 days for those with new brain metastases (110 patients)). For all patients, median time to intracranial progression after GK was 242 days and overall survival after GK was 293 days. For patients with synchronous brain metastases at presentation (104 patients), median time for overall survival from date of diagnosis was 435 days. For all patients without brain metastases at presentation, median time to intracranial progression from date of diagnosis was 305 days and overall survival was 693 days. **Conclusion:** In conclusion, GK radiosurgery is an effective treatment for brain metastases in NSCLC, providing high rates of local control and improved survival. Beneficial effects are seen in patients with synchronous and new brain metastases, demonstrating its role in a wide subset of patients with advanced NSCLC. Use of GK, in combination with radical thoracic therapy, therefore has the potential to dramatically improve survival in patients who may not have previously been suitable for radical treatment.

Keywords: NSCLC, Brain metastases, oligometastatic disease

P2.08-02 OUTCOMES FOLLOWING STEREOTACTIC RADIOSURGERY FOR SYNCRONOUS BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER

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Background: Approximately 10% of non-small cell lung cancer (NSCLC) patients have brain metastases at presentation. The use of stereotactic radiosurgery (SRS) has enabled a proportion of patients with oligometastatic brain disease to be offered a radical treatment in conjunction with SRS. We evaluated the outcomes for patients presenting with synchronous brain metastases who received SRS to determine if radical treatment improves survival. **Method:** 164 patients with NSCLC received SRS for brain metastases between January 2012 and December 2017. This analysis focused on 71 patients who presented synchronously with brain metastases. Electronic patient records were accessed in March 2019 to determine initial extracranial disease treatment and date of death or last follow up. **Result:** 30 patients received radical treatment (18 radiotherapy alone, 11 chemo-radiotherapy and one surgery) and 24 received palliative treatment (17 chemotherapy, four radiotherapy and three tyrosine kinase inhibitor). 17 patients received no treatment following SRS, either due to death, deterioration in performance status or patient choice. Baseline demographics are presented in table 1.

	Radical	Palliative	No treatment
Mean age at diagnosis (+/-SD)	68.3 (8.9)	58.5 (14.5)	61.4 (10.4)
Male (%)	18 (60.0)	10 (41.7)	8 (47.1)
Female (%)	12 (40.0)	14 (58.3)	9 (52.9)
ECOG Performance Status			
0	9 (30.0%)	7 (29.2%)	7 (41.2%)
1	18 (60.0%)	17 (70.8%)	9 (52.9%)
2	3 (10.0%)	0 (0.0%)	1 (5.9%)
Mean number of brain metastases (+/- SD)	1.7 (1.1)	1.9 (1.6)	1.7 (0.9)
T stage			
1	3	5	1
2	14	8	9
3	8	6	4
4	5	5	3
N stage			
0	15	2	4
1	4	3	4
2	8	13	7
3	3	6	2

Table 1 Baseline demographics

Median overall survival for the radical, palliative and no treatment groups were; 7.9 (95% CI 5.5-14.0), 9.4 (6.6-14.4) and 1.4 (1.0-2.9) months, respectively. There was no significant difference in survival between the radical and palliative groups (p=0.43). Kaplan-Meier survival estimates at 12 and 24 months were 30.0% (95% CI 17.4-51.8%) and 10.0% (3.4-29.3%) for the radical and 33.3% (18.9- 58.7%) and 13.0% (4.1-41.4%) in the palliative group, respectively. **Conclusion:** Our results did not demonstrate the benefit for radical treatment, as expected based on published data. Potential reasons for this result include a lack of tools to select patients for radical treatment. Prospective studies are needed to identify the optimal treatment for extracranial disease in this patient group.

Keywords: Brain, synchronous, SRS

P2.08-03 CLINICAL OUTCOME OF PATIENTS WITH RECURRENT NON-SMALL CELL LUNG CANCER AFTER TRIMODALITY THERAPY

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Background: Trimodality therapy, consisting of induction chemoradiotherapy (CRT) followed by surgery, is a potential treatment option for patients with locally advanced (LA) non-small cell lung cancer (NSCLC), such as N2-3, bulky N1, or T3-4 stage disease. However, even after completing this intensive treatment, postoperative recurrence will develop in a subset of patients. Patients with distant metastatic recurrences are generally considered to have systemic disease, which is regarded as incurable. Nevertheless, some patients have a relatively good prognosis following this treatment, even after postoperative recurrence. **Method:** We analyzed the records of 182 patients with LA-NSCLC who were treated with trimodality therapy between 1999 and 2017 to review the clinical course of those patients and to identify the factors associated with favorable clinical outcome after recurrence. In this study, oligometastasis was defined as one to three metastatic lesions in the brain, or an isolated extracranial metastatic lesion. **Result:** In 182 patients patients who underwent trimodality therapy for LA-NSCLC, the median follow-up period after the beginning of CRT was 50 months, the median age was 61 years (range, 31–78 years), and Recurrence developed after trimodality therapy in 65 patients (35.7%). The median recurrence-free interval, being the period between the administration of trimodality therapy for the primary tumor and initial recurrence, was 11 months (range, 4.1–73.9 months). Of the 62 of these patients able to be assessed retrospectively, The brain was the most frequent location of recurrence (31%), followed by the lung (27%), lymph nodes (24%), and bone (15%). Twenty-eight had oligometastatic recurrence and 30 underwent local treatment with curative intent. Local treatment was most frequently given to patients with oligometastatic recurrence ($P < 0.001$). The median post-recurrence survival (PRS) was 15.1 months, and the 2-year

PRS rate was 57%. Patients who received local treatment showed better PRS (P = 0.004). The presence of liver metastasis (P = 0.003), bone metastasis (P = 0.034), or dissemination (P < 0.0001) were associated with worse PRS. **Conclusion:** The survival of patients who received aggressive local treatment for postoperative recurrence after trimodality therapy for LA-NSCLC was better than that of patients who did not.

Keywords: induction chemoradiotherapy, local treatment, oligorecurrence

P2.08-04 STEREOTACTIC ABLATIVE RADIATION THERAPY TO LUNG METASTASES ASSOCIATES WITH BETTER OUTCOMES IN OLIGOMETASTATIC LUNG CANCER: PROSPECTIVE STUDY

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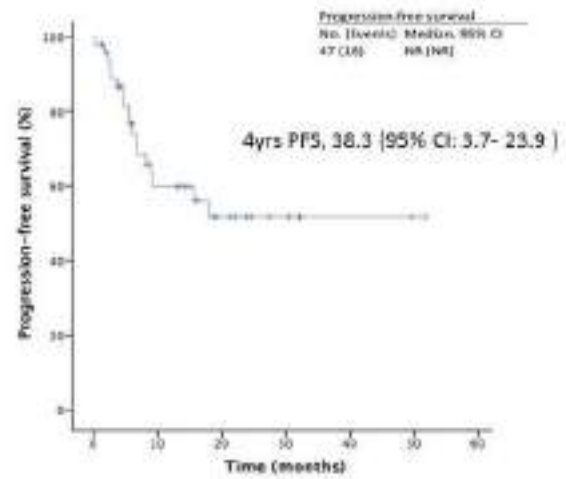
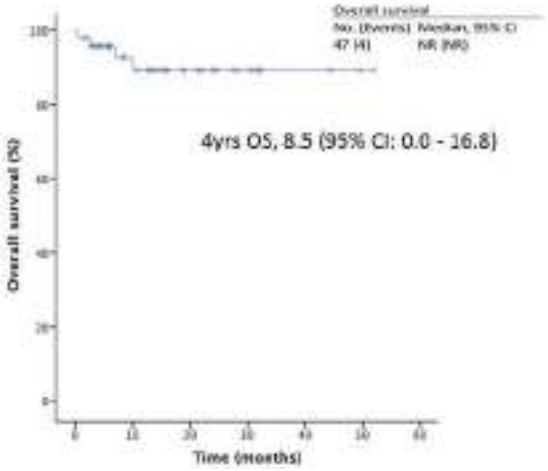
Background: Nearly 7% of stage IV Non-Small cell Lung Cancer (NSCLC) patients present oligometastatic disease at diagnosis. These patients can benefit from definitive treatment to primary tumour and loco-ablation of metastases. The use of stereotactic ablative radiotherapy (SABR) has demonstrated high rates of local control and survival improvement in early disease stage. The aim of this study is to evaluate Progression Free Survival (PFS), Overall survival (OS) and toxicity of patients with oligometastatic NSCLC treated with Stereotactic ablative radiotherapy (SABR) to lung metastases. **Method:** A prospective study was conducted with oligometastatic NSCLC patients. From August 2014 to April 2019, with a median follow up of 13 months, forty-seven patients were enrolled. All patients received systemic therapy according to international guidelines. Then, patients without progression to systemic treatment, received SABR to lung metastases (30-60 Gy in 2-8 fractions) to the thoracic lesion (primary or metastatic) depending on location, size and number of lesions, always keeping BED (Biologically Effective Dose) >100 Gy at isocenter. This study was approved by Ethic and Research comitees at Instituto Nacional de Cancerología (CEI/799)(013/014/ICI). **Result:** Most patients were women (59.6%), with a mean age of 58.9 years. Although two-thirds of patients were ever smokers (66.0%), most of them were light smokers. The most common histology was adenocarcinoma (87.2%). Contralateral lung was the most common metastatic site (40.4%). Half of the patient harbour at least one mutation, EGFR Exon 19 deletion was the most frequent mutation (38.3%). Patients received chemotherapy and EGFR-TKIs as 1st-line treatment in the 61.1% and 38.9%, respectively. All patients received SABR, response to treatment was as follows: disease control rate was 91.5%, partial response 14.9% and complete response 63.8%. Among those with disease progression, median time to systemic progression after SABR treatment was 5.4 months (95% 2.4-8.9 months). PFS since beginning of any treatment was not reached, since only 18 patients (38.3%) had disease progression. Until now only 4 patients (8.5%) had died, thus OS is not reached. Radiographic pneumonitis was observed in 72.2% (13 patients). Grade 1, 2 and 3 pneumonitis were observed in the 69.2% (9/13), 7.7% (1/13) and 23.1 (3/13) of the patients with pneumonitis.





Conclusion: SABR is a suitable and has a moderate toxicity profile. SABR is a therapeutic option for patients with oligometastatic NSCLC. SABR have shown to improve local control and increase progression-free survival. Future clinical trials are required to evaluate SABR against other treatment modalities.

Keywords: NSCLC, SABR, Lung Metastases

P2.08-05 THE ROLE OF SURGICAL TREATMENT FOR PATIENTS WITH NSCLC DEMONSTRATING LIMITED PLEURAL DISSEMINATION

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Background: Pleural dissemination or malignant pleural effusion confirmed during surgery generally indicates incurable disease and is a contraindication for lung resection. However, recent studies suggested that complete removal of the disseminated nodule in combination with lung resection is associated with long-term survival when dissemination is limited. This study investigated whether there is a curable subgroup of patients with NSCLC exhibiting limited malignant pleural disease (MPD). **Method:** Among 1966 patients who underwent lung surgery for primary lung cancer at our institution between 1986 and 2015, 61 patients were diagnosed with MPD during the operation. Excluding 3 patients who had other active malignancies and 2 patients who were lost to follow-up, we analyzed 59 patients, including 33 who had signs of MPD on preoperative CT. The type of surgery was biopsy only for 26, extrapleural pneumonectomy (EPP) for 17, lobectomy for 13, and wedge resection for 3. Macroscopic complete resection (MCR) was carried out for 24 patients. All but one patient were followed until December 2018 or death, and the follow-up period for surviving patients ranged from 48 to 361 months (median 158 months). **Result:**

Overall and progression-free survival					
Patients group	**Type of surgery**	**Number of patients**	**5yOS/PFS(%)**	**10yOS/PFS(%)**	**15yOS/PFS(%)**
All patients		59	28.1/10.1	18.1/6.7	13.8/6.7
	MCR	24	37.5/25.0	25.0/16.7	20.8/16.7
	EPP	17	41.2/29.4	35.3/23.5	29.4/23.5
No sigh of MPD preoperatively		26	34.6/15.4	19.8/11.5	19.8/11.5
	MCR	11	45.5/36.4	27.3/27.3	27.3/27.3
	EPP	5	60/60	60/60	60/60
Any sign of MPD preoperatively		33	23.1/6.0	13.2/3.0	9.9/3.0
	MCR	13	30.8/15.3	23.1/7.6	15.4/7.6
	EPP	12	33.0/16.6	25.0/8.3	16.7/8.3

Among the 59 patients, 4 patients survived without recurrence for more than 10 years. Furthermore, 3 out of the 4 patients were still alive at 361 months, 300 months, and 211 months, respectively. Among the 4 patients, 3 patients did not exhibit signs of malignant pleural disease preoperatively, and all 4 patients underwent EPP. The overall and progression-free survival rates at 5, 10, and 15 years for all 59 patients, the 26 not exhibiting signs of MPD preoperatively, and the 33 patients with signs of MPD according to the type of surgery are presented in the Table. Prognostic factors significantly associated with longer progression-free survival were early clinical stage, adenocarcinoma histology, absence of pathological mediastinal nodal metastasis, MCR, and EPP. **Conclusion:** A curable subgroup may exist among patients diagnosed with malignant pleural disease during surgery, especially among those without signs of pleural disease preoperatively treated by EPP.

Keywords: Non-Small Cell Lung Cancer, pleural dissemination, extrapleural pneumonectomy

P2.08-06 DEVELOPMENT AND VALIDATION OF A 18F-FDG PET/CT-BASED RADIOMICS MODEL FOR PROGNOSIS PREDICTION IN SYNCHRONOUS OLIGOMETASTATIC NSCLC

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Background: Oligometastatic non-small cell lung cancer (NSCLC) exists high heterogeneity with distinct outcome, and there is a lack of available biomarkers for patient stratification. In this study, we identified a positron emission tomography (PET)/computed tomography(CT)-based radiomics signature capable of predicting overall survival (OS) in patients with synchronous oligometastatic NSCLC. **Method:** A primary cohort consisted of 46 patients with synchronous oligometastatic NSCLC (≤5 metastases) between January 2012 and December 2017. Clinicopathologic data was acquired from medical records and database. A total of 20648 radiomic features were extracted from pretreatment CT and PET images, which were generated from the same PET/CT scanner. A radiomics signature was built by using the least absolute shrinkage and selection operator (LASSO) regression model. Multivariate Cox regression analysis was performed to establish the predictive model. A prospective internal validation cohort contained 14 patients from January 2018 to December 2018. The performance was evaluated with Harrell' concordance index (C-index). **Result:** 7 radiomics features were selected to build the radiomics signature. Smoking status (P=0.01) was the only independent clinicopathologic risk factor for overall survival prediction. Multivariate analysis indicated that the radiomics signature (P=0.007) was an independent prognostic factor, with a C-index of 0.810 and 0.900 for the primary and validation cohort. **Conclusion:** This study developed a radiomics model for predicting OS in synchronous oligometastatic NSCLC, which may serve as a predictive tool to identify individualized treatment strategy. Further external validation of the model are required. Support: 81572279, 2016J004, LC2016PY016, 2018CR033.

Keywords: Synchronous Oligometastatic NSCLC, radiomics model, individualized treatment

P2.09-01 CHARACTERISTICS OF DRIVER MUTATIONS IN EARLY LUNG ADENOCARCINOMA: FROM PREINVASIVE/ MINIMALLY INVASIVE TO INVASIVE ADENOCARCINOMA

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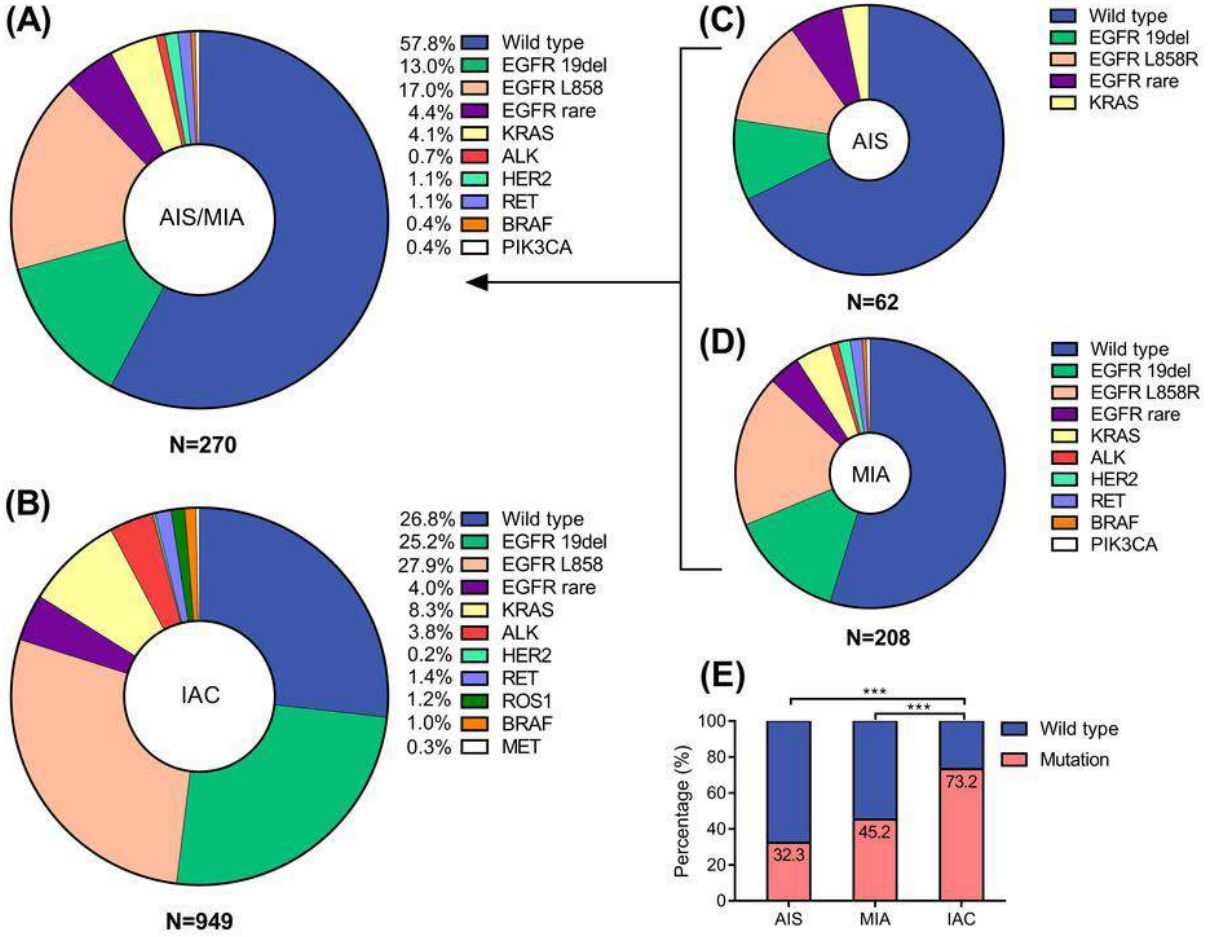
Background: It is still unclear when the gene mutation occurs during the carcinogenetic process, which progresses from preinvasive to invasive adenocarcinoma. We aim to investigate the driver gene alterations profile of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC). **Method:** A total of 1219 patients with pulmonary nodes smaller than 3 cm were selected for this study. Driver mutation testing was performed with NGS in all resected tumor tissues. The incidence of mutations was calculated and compared among different subtypes. Logistic regression was used to further identify factors that may independently correlate with IAC. **Result:** In all 1219 patients with lung adenocarcinoma, 62 were diagnosed as AIS, 208 as MIA and 949 as IAC. Mutations were found in 809 (66.4%) patients. The frequency of mutations increased with the progression of tumor invasiveness: AIS (32.3%), MIA (45.2%) and IAC (73.2%)(P<0.001 between IAC and AIS, P<0.001 between IAC and MIA). The results (Figure 1) also showed an increasing trend towards more driver mutations from AIS to MIA, and to IAC. Multivariate analysis revealed that driver mutations was a factor associated with IAC (OR: 2.39, P<0.001). Of the genetic factors, EGFR, KRAS and ALK alterations were significant indicators of IAC (all P<0.020), and were found increased in IAC compared with AIS/MIA.

Conclusion: Genetic alterations occurs early in the development of lung adenocarcinoma and can be detected even before tumor have acquired malignant potential. Driver mutations gradually increase in tumorigenesis and progression from AIS to MIA, and finally to overt IAC. A better understanding of carcinogenesis in preinvasive/ minimally invasive cases may allow the development of effective preventive, screening, and treatment strategies.

Keywords: Driver Mutations, Preinvasive/Minimally invasive Adenocarcinoma, Invasive Adenocarcinoma



POSTERS

P2.09-02 EXPLORING THE FEATURES OF THE SHORT AND LONG-TERM SURVIVORS FOR LUNG ADENOCARCINOMA: A SINGLE CENTER EXPERIENCE

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Background: The aim of this study was to identify an objective way to define a long-term survivors(LTS) and short-term survivors(STS) in patients with surgically resected lung adenocarcinoma (ADK), and secondly to find peculiar clinicopathological features in these two groups of patients. **Method:** all patients who underwent major lung resection for lung ADK from 2000 to 2015 were studied.LTS and STS were extrapolated considering the overall survival(OS) and pathological tumour stage:the first and the fourth quartile of those patients with cancer-related death were considered for statistical analysis. **Result:** from 600 ADK patients we found 79 STS and 77 LTS;clinico-pathologic baseline characteristics are presented in Table 1.Considering STS patients, smoking habit, histotype, tumour necrosis, pleural invasion and pathological stage were significantly associated with OS at univariate analysis (Fig.1). In LTS patients, smoking habit, neoadjuvant chemotherapy, tumour-infiltrated lymphocytes and pathological stage were significantly associated with OS (Fig.2).On multivariate analysis, smoking status, lymphoid infiltrate, pleural invasion and stage remained significantly associated with OS (Table 2).

Table 1

Variable	Full sample[a]	STS (N=79)[a]	LTS (N=77)[a]	p-value
Age at diagnosis (median)	68 (62-74)	68 (61-74)	69 (64-75)	0.301
Gender (M:F)	110:46 (70.5%:29.5%)	60:19 (24,1%:75,9%)	27:50 (35,1%:64,9%)	0.131
Smoking status				<0.001
Never smoker	23 (19,6%)	5 (6,8%)	18 (27,3%)	
Smoker + Former smoker	117 (81,4%)	69 (93,2%)	48 (72,7%)	
Other previous primary tumor				0.936
Yes	43 (27,6%)	22 (27,8%)	21 (27,3%)	
No	113 (72,4%)	57 (72,2%)	56 (72,7%)	
Side				0.079
Right	70 (44,9%)	30 (38,0%)	40 (51,9%)	
Left	86 (55,1%)	49 (62,0%)	37 (48,1%)	
Histotype				0.085
Lepidic	5 (3,2%)	0 (0,0%)	5 (6,5%)	
Papillary	21 (13,5%)	11 (13,9%)	10 (13,0%)	
Acinar	37 (23,7%)	16 (20,3%)	21 (27,3%)	
Micropapillary	18 (11,5%)	8 (10,1%)	10 (13,0%)	
Solid	75 (48,1%)	44 (55,7%)	31 (40,3%)	
Grade				0.034
G1	2 (1,3%)	0 (0,0%)	2 (2,6%)	
G2	23 (14,7%)	7 (8,9%)	16 (20,8%)	
G3	131 (84,0%)	72 (91,1%)	59 (76,6%)	
Lymphatic invasion				0.864
Yes	101 (64,7%)	51 (67,1%)	50 (65,8%)	
No	51 (32,7%)	25 (32,9%)	26 (34,2%)	
Blood invasion				0.128
Yes	47 (30,1%)	28 (36,4%)	19 (25,0%)	
No	106 (67,9%)	49 (63,6%)	57 (75,0%)	
Pleural invasion				0.439
PL0	78 (50,0%)	37 (46,8%)	41 (53,2%)	
PL1	41 (26,3%)	24 (30,4%)	17 (22,1%)	
PL2	20 (12,8%)	8 (10,1%)	12 (15,6%)	
PL3	17 (10,9%)	10 (12,7%)	7 (9,1%)	
Necrosis				0.419
Yes	70 (46,7%)	37 (50,0%)	33 (43,4%)	
No	80 (53,3%)	37 (50,0%)	43 (56,6%)	
Lymphoid infiltrate				0.787
Absent	57 (37,0%)	27 (35,1%)	30 (39,0%)	
Mild	63 (40,9%)	34 (44,2%)	29 (37,7%)	
Moderate	21 (13,6%)	9 (11,7%)	12 (15,6%)	
Marked	13 (8,4%)	7 (9,1%)	6 (7,8%)	
Neoadjuvant chemotherapy				0.371
Yes	11 (7,1%)	7 (8,9%)	4 (5,2%)	
No	145 (92,9%)	72 (91,1%)	73 (94,8%)	

Table 2

Variables	p-value.	HR	95% CI	
Smoking Habit	0,003	2,317	1,325	4,052
Histotype	0,817	,951	,620	1,459
Tumor Necrosis	0,065	,667	,434	1,025
Limphoyd Infiltrate	0,024	1,598	1,063	2,402
Neoadjuvant CHT	0,160	,502	,192	1,313
Pleural Invasion	0,021	,421	,201	,879
Stage	0,002	,480	,305	,755

Conclusion: Our findings suggest that the unexpected survival of STS and LTS ADK-patients is determined by a concert of clinical and pathological features. Biological characterizazion of these kind of patients will likely improve the understanding of their unusual course.

Keywords: long term survivors, short term survivors, lung adenocarcinoma

P2.09-03 PROGNOSTIC VALUE OF MUTATED KRAS IN CIRCULATING TUMOR DNA PRIOR TO THERAPY IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: Studies show an association between total tumor load and the amount of circulating cell-free tumor DNA (ctDNA) in blood, and that detectable ctDNA is a negative prognostic factor. *KRAS* mutations (mut*KRA*S) are the most common oncogenic drivers in lung adenocarcinomas (lungAC) and are found in 25-30 % of the patients. We hypothesized that the concentration of mut*KRAS* in plasma ctDNA is associated with outcomes in patients with lungAC harboring KRAS mutations, and aimed to investigate whether there was an association with disease stage, progression free (PFS) and overall survival (OS). **Method:** Blood samples collected prior to first treatment from 61 lungAC-patients with known mut*KRAS* in tumor DNA were analyzed. Digital droplet PCR was used for detection and quantification of mut*KRAS* in the plasma samples. The false positive rate for each mut*KRAS* assay was determined using cfDNA from healthy donors. A sample was defined as "positive" if the mut*KRAS* level was above the false positive rate. Mann-Whitney U test was used to compare PFS and OS between those with not-detectable and those with detectable mut*KRAS* ctDNA. Log-rank and Cox proportional hazard methods were used for survival analyses. One-way ANOVA was used to compare the concentration of mut*KRAS* between disease stages. **Result:** Median age was 68 years (range 47-83), all patients were former/current smokers, 39.3% were men; 39.3% had stage I, 18.0% stage II, 24.6% stage III and 18.0% stage IV; 55.7% had performance status (PS) 0, 39.3% PS 1, and 4.9% PS 2; 70.5% underwent surgery, 4.9% curative radiochemotherapy and 24.6% palliative treatment. Overall, 26.2% had detectable mutKRAS in ctDNA with a median of 119.68 (range:16.66-1208) copies/ml plasma.The proportion of patients with mutKRAS in plasma ctDNA increased with higher disease stage (stage I: 0%, II: 18%, III: 47%, and IV: 64 %; p=0.006). Patients with plasma mutKRAS had significantly shorter PFS (11.9 vs. 23.5 months; p=0.012) and OS (15.8 vs. 23.5 months; p=.0.010) than those without. The mutKRAS ctDNA concentration was significantly associated with both shorter PFS (HR 1.009, 95% CI 1.004-1.013; p<0.001) and OS (HR 1.007, 95% CI 1.003-1.011; p=0.001).The associations remained statistically significant in the multivariate analyses adjusting for baseline characteristics (gender, age, disease-stage, PS, treatment) for both PFS (HR 1.009, 95% CI 1.003-1.014; p=0.002) and OS (HR 1.008, 95% CI 1.002-1.015; p=0.008). **Conclusion:** The concentration of plasma mut*KRAS* increased with higher disease stage. Patients with detectable plasma mut*KRAS* had worse PFS and OS than patients without. The concentration of mutated *KRAS* was independently associated with worse PFS and OS.

Keywords: lung adenocarcinoma, circulating tumor DNA, KRAS mutation

P2.09-04 THE CLINICOPATHOLOGICAL CHARACTERISTICS AND PROGNOSIS OF LUNG CANCER WITH TUMOR SPREAD THROUGH AIR SPACES: A META-ANALYSIS

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Background: The clinicopathological characteristics of lung cancer with tumor spread through air spaces (STAS) has not been clearly characterized yet. Also, it is still not clear whether the presence of STAS correlated with worse prognosis in patients with lung cancer. Thus, we aim to systematically evaluate the clinicopathological characteristics and prognosis of the patients with or without STAS undergoing surgical resection for lung cancer. **Method:** Materials and Methods: A comprehensive search of online databases was performed. Clinicopathological characteristics, 5-year RFS and OS rate were compared between 2 groups. Cumulative meta-analysis was performed to evaluate the temporal trend of pooled outcomes. Specific subgroups according to different types of lung cancer are examined. **Result:** A total of 25 eligible studies including 8494 patients were recruited. STAS occurred in 2881 patients (34%) while non-STAS occurred in 5613 patients (66%). Overall, patients with STAS manifested significantly more aggressive characteristics, including lymphatic invasion (SMD=2.935; P=0.000), pleural invasion (SMD=2.329; P=0.000), vascular invasion (SMD=2.306; P=0.000) as well as lymph node metastasis (OR=3.510; P=0.000). Patients with STAS also correlated with significantly higher pathological stage (OR=2.216; P=0.003), T stage (OR=1.756; P=0.000), N stage (OR=2.395; P=0.000) and larger tumor size (OR=0.275; P=0.001). Meanwhile, the incidence of STAS was significantly associated with the micropapillary (OR=9.792; P=0.000) and solid patterns (OR=2.451; P=0.000). Moreover, the presence of STAS was related to male sex (OR=1.493; P=0.000), smoking history (OR=1.637; P=0.000) and necrosis (OR=2.300; P=0.000). As for the outcomes of the prognosis, patients with STAS linked with significant worse prognosis than those without STAS, including both 5-year RFS (HR=0.585; 95% CI: 0.486–0.684; P=0.000) and 5-year OS rate (HR=0.788; 95% CI: 0.596–0.980; P=0.000). **Conclusion:** The presence of STAS was associated with several invasive pathological characteristics, which might explain the worse prognosis in patients with STAS compared with those without STAS.

Keywords: Lung cancer, tumor spread through air spaces, clinicopathological characteristics

POSTERS

P2.09-05 CLINICAL AND BIOLOGICAL CHARACTERIZATION OF LUNG ENTERIC ADENOCARCINOMA

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Background: Lung Enteric Adenocarcinoma (LEA) is a rare and poorly characterized variant of Lung Adenocarcinoma (LA), defined by an intestinal differentiation in ≥50% of tumor and ≥1 colorectal biomarker at Immunohistochemistry. **Method:** We retrospectively identified the cases of LEA diagnosed at Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy between 01/2013 and 12/2018. Next Generation Sequencing was performed with IonTorrent (ThermoFisher Scientific, Life Technologies) by using the commercial Hot Spot Cancer Panel (HCP) on DNA derived from formalin-fixed paraffin-embedded tissues. ALK and ROS-1 status was assessed with fluorescent *in situ* hybridization. PD-L1 expression was determined with DAKO22C3 assay. Biological data obtained from our cases were compared with those reported in Tumor Cancer Genome Atlas (TCGA) for LA, restricting the comparison only to the genes targeted by HCP. **Result:** We identified 38 LEA cases. Main clinical and biological characteristics of the two populations are detailed in the table.

Variable/ gene mutation	INT LEA (N=38)	TCGA LA (N=660)
	%	%
Gender		
Female	34.1	51.9
Male	65.9	47.9
Unknown	0	0.2
Smoking status		
Former/current	76.3	78.9
Never	15.8	14.1
Unknown	7.9	7.0
Disease stage		
I	2.6	51.6
II	2.6	23.0
III	28.9	16.4
IV	65.9	4.7
Unknown	0	4.3
TP53	52.6	54.1
KRAS	34.2	32.4
STK11	23.7	15.8
CDKN2A	15.8	3.9
APC	7.9	4.8
CTNNB1	7.9	3.8
EGFR	7.9	15.8
KIT	5.3	2.1
PI3KCA	5.3	5.9
SMAD4	5.3	4.1
ATM	2.6	8.9
BRAF	2.6	8.2
FGFR	2.6	0.8
GNAS	2.6	3.8
NRAS	2.6	0.6
PDGFRA	2.6	7.4
RB1	2.6	5.8
SMO	2.6	2.7

Neither ALK nor ROS-1 rearrangements were detected in our case series. PD-L1 was negative in 23 cases, 1-49% in 9 cases, not evaluable in 6 cases. Microsatellite were stable except for 3 cases with low instability and 3 not evaluable cases. **Conclusion:** Our series of LEA was small and differed from TCGA LA for a higher proportions of males and metastatic disease. Given these limitations, our LEA genetic profile showed some difference from that of TCGA LA. In particular, LEA showed a higher incidence of *STK11, CTNNB1, FGFR, NRAS, KIT* and *CDKN2A* mutations, and a lower incidence of *ATM, BRAF, PDGFRA, RB-1* and *EGFR* mutations. PD-L1 expression, ALK and ROS-1 rearrangements were lower than literature data in LA. Most cases were microsatellite stable. In conclusion, further research is needed to understand the biology of LEA, which seems partially different from common LA.

Keywords: Lung Enteric Adenocarcinoma, Biological characterization, Rare NSCLC

P2.09-06 EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION SPECTRUM IN PULMONARY ADENOCARCINOMAS: INDIAN EXPERIENCE

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Background: Incidence of lung cancer is rising in India, which is the major cause of mortality worldwide. The identification of *EGFR* mutations and *ALK* fusions in lung cancer has changed the treatment paradigm. The use of tyrosine kinase inhibitor (TKI) is now well established in clinical practice as it improves treatment outcomes. Molecular testing using tumor tissue is the gold standard for targeted therapies. The aim of the present study is to analyze the exact frequency of *EGFR* activating, rare and coexisting mutations in pulmonary adenocarcinoma (ADC). **Method:** A total of 783 ADC (755 biopsies and 28 cytology aspirate smears) cases were studied. The male: female ratio was 1: 0.3 with age ranging from 20 to 78 years. During grossing, two tumor blocks were made, one for immunohistochemistry studies and other for mutation testing. In high- cellularity, low- tumor fraction cases, tumor enrichment was done by manual microdissection. We used more than one aspirate smears/biopsy blocks in cases with low- cellularity, high- tumor fraction. Probe-based real-time PCR (RT-PCR) technique was used to analyze *EGFR* hotspots mutations (exons 18 to 21). Before proceeding for molecular testing, histo/cytomorphology, tumour content and DNA quality were determined. For checking the quality of DNA, RT-PCR was done using wild type *EGFR* exon 2 primers. **Result:** About 99% cases passed through the quality check of DNA and only 1.02% (8/783) cases failed. Overall, 234 patients (29.8%) were positive for *EGFR* mutations. The distribution of different types of *EGFR* mutations is shown in the Table 1. The common *EGFR* mutations were Exon 19 del and Exon 21 L858R which were equally distributed between both the genders. The *EGFR* mutations were more in non-smokers. T790M was present at baseline in around 3% TKI naive cases and it coexisted mostly with Exon 19 del. Cytological smears also showed *EGFR* mutations in the same pattern as tissue biopsies and a concordance was seen in cases where matched tissue and cytology smears were available. Table1: EGFR mutation spectrum in pulmonary adenocarcinomas

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EGFR Exon	Percentage
Single Mutations = 89.7% (210/234)	
EGFR most common mutations	
Exon 19 del	61.5%
Exon 21 L858R	29.1%
EGFR TKI resistant mutation at baseline	
Exon 20 T790M	2.8%
Rare EGFR Single Mutations	
Exon 18 G719X	2.4%
Exon 20 S768I	1.4%
Exon 21 L861Q	1.4%
Exon 20 Ins	1.4%
EGFR double mutations = 10.2% (24/234)	
Common double mutations	
Exon 19 del: Exon 20 T790M	11
Exon 19 del: Exon 21 L858R	5
Rare double mutations	
Exon 18 G719X: exon 20 S768I	2
Exon 21 L858R: exon 20 S768I	2
Exon 20 T790M: Exon 18 G719X	1
Exon 20 T790M: Exon 20 Ins	1
Exon 19 del: Exon 21 L861Q	1
Exon 19 del: Exon 18 G719X	1

Conclusion: With judicious use and triaging of lung cancer diagnostic specimens, it is possible to perform successful mutation testing in >98% cases. *EGFR* mutation was positive in about a third of ADC including rare, TKI resistant and coexisting mutations in approximately 10% cases which may have significant therapeutic implications. In patients with limited amounts of tissue, cytology samples can be used for *EGFR* mutation testing as a promising alternative.

Keywords: Lung cancer, EGFR, mutation

P2.09-07 MULTIPLE IMMUNOHISTOCHEMISTRY OF NON-SMALL CELL LUNG CANCERS REVEALS DISTINCT IMMUNE CONTEXT

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Background: Immune checkpoint blockade improves survival in a subset of patients with non-small cell lung cancer (NSCLC). Though increased tumor infiltrating lymphocytes (TILs) correlate with better outcome in many human cancers, biomarkers that predict response to PD-1 pathway inhibitors remain largely unknown. Therefore, a comprehensive evaluation of the composition and distribution of TILs is necessary to demonstrate their roles. **Method:** To determine the predictive significance of specific immune cells in the tumor microenvironment, we used multiples IHC. Multiplex IHC is a powerful investigative tool which provides objective quantitative data describing the tumor immune context in both immune subset number and location. To evaluate the immune context broadly we used the OPAL staining panel contains CD8, CD4, CD20, CD68, FOXP3, and panCK. **Result:** Pathologic tumor specimens from 101 patients with recurred or metastatic NSCLC were analyzed. Tumors exhibited a high degree of heterogeneity in the immune infiltrate and there was no significant difference when immune infiltrates were compared by tumor histology. Furthermore, there were no significant immune cell differences in EGFR mutant tumors or tumors that did not harbor mutations in adenocarcinoma. We observed increased Tregs (CD4+/FOXP3+) in PD-L1-positive tumors as compared with PD-L1-negative tumors. Our results showed that the infiltration levels of most T-cell subpopulations within tumor did not significantly associated with survival. However, high infiltration of B cells significantly correlated with overall survival. **Conclusion:** Increased infiltration of B cells into tumor regions is an independent predictor of better overall survival in NSCLC. These findings suggest that tumor-infiltrating B cells could act as a clinical factor in anti-PD-1 immunotherapy for NSCLC.

Keywords: tumor microenvironment, multiplex IHC, Non-Small Cell Lung Cancer

P2.09-08 CORRELATION BETWEEN HORMONE RECEPTOR EXPRESSION AND EGFR GENE MUTATION IN LUNG CANCER PATIENTS WITH SIMULTANEOUS PRIMARY BREAST CANCER

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Background: Double primary breast cancer (BC) and lung cancer (LC) is not uncommon but research is limited. To decipher the inner pathogenesis, relationship between hormone receptor (HR) protein expression and EGFR gene mutation was explored in the present study. **Method:** Clinicopathological characteristics of 400 female patients with double primary BC and LC were analyzed, while another 114 patients with single LC were compared correspondingly. Tissue samples were obtained from enrolled subjects to detect EGFR mutation status by gene sequencing analysis, and estrogen receptor (ER) and progesterone receptor (PR) expression was determined by immunohistochemistry. **Result:** Among 169 patients, synchronous and metachronous double primary BC-LC cases accounted for 39.1% and 61.0%, respectively. For most female LC patients with simultaneous primary BC, adenocarcinoma was the dominant subtype (95.1%). The positivity rates were 13% for ER and 13% for PR in lung tumor tissues of 200 double BC-LC patients, slightly higher than those in single LC patients. Among BC-LC patients with mutant EGFR, 48.2% were either ER-positive (30.6%) or PR-positive (30.6%). But for those without EGFR mutation, both ER and PR could not be detected in lung tumor tissue samples. $\chi 2$ testfurther confirmed a significantly positive correlation between ER, PR expression and EGFR mutation in lung tumor tissues in double primary patients ($P < 0.05$). However, such relationship could not be similarly observed in single LC cases. Besides, the presence of family tumor history was associated with the onset time of the two primary cancers. **Conclusion:** Double primary BC-LC patients have distinctive clinicopathological features. Expression of HRs (both ER and PR) significantly correlated with EGFR mutation status in their lung tumor tissues.

Keywords: Breast cancer, Double Primary, Lung cancer

P2.09-09 EGFR IS HIGHLY MUTATED IN LUNG ADENOCARCINOMA PATIENTS WITH HISTORY OF BREAST CANCER

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Background: EGFR gene mutation has been reported to be frequent in the patients with specific clinical features such as female, adenocarcinoma, and East-Asian ethnicity. The mutation rate in lung adenocarcinoma is approximately 50% in Japan. Currently, the molecular mechanism which cause EGFR mutation has not been clarified. If the EGFR mutation in lung adenocarcinoma correlates with specific type of malignancy in the other organ, it could be a clue to find a mechanism which promote carcinogenesis of lung adenocarcinoma. In the current study, we focused on breast cancer. **Method:** Patients with lung adenocarcinoma who underwent pulmonary resection in our hospital from January 2011 to December 2018 were analyzed. We retrospectively reviewed clinical information such as past illness, radiological findings, pathological diagnosis, and EGFR mutation status. Correlation was tested by chi-square test and p value of less than 0.05 was regarded as statistically significant. **Result:** A total of 21 patients of lung adenocarcinoma had history of treatment for breast cancer. All patients were female. Among them, EGFR mutation was detected in 20 patients (95%). One patient who were negative for EGFR mutation had history of not only breast cancer but also cervical cancer of uterus and gastrointestinal stromal tumor, and developed angiosarcoma of the skin. Detected EGFR

mutation types in 20 patients were as follows; deletion in exon 19 for 9 patients, L858R for 7 patients G719X for two patients, and L861Q for one patient. One patient showed multiple mutation (G719X and L861). In the same period, among 203 lung adenocarcinoma patients without other organ malignancy, 115 showed EGFR mutation (56.7%). There was significant difference in EGFR mutation rate between breast cancer group and no malignancy group (p=0.00058). **Conclusion:** Patients of lung adenocarcinoma with history of breast cancer showed extremely high positive rate for EGFR mutation in Japan, suggesting underlying common oncogenic molecular mechanism between lung adenocarcinoma and breast cancer. Elucidation of the mechanism may contribute to the diagnosis and treatment of carcinogenesis of breast cancer and lung cancer.

Keywords: EGFR, adenocarcinoma, Breast cancer

P2.09-10 INSM1 IS A GOOD MARKER FOR DIAGNOSIS OF SMALL CELL LUNG CARCINOMA EVEN WHEN NEUROENDOCRINE MARKER NEGATIVE

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Background: To diagnose small cell lung carcinoma (SCLC), neuroendocrine (NE) phenotype markers such as chromogranin A, synaptophysin and CD56 are helpful. However, because they are dispensable, SCLCs occur without neuroendocrine phenotypes. Insulinoma-associated protein 1 (INSM1) is a transcription factor for neuroendocrine differentiation and has emerged as a single practical marker for SCLC. **Method:** Using the surgical samples of 141 NE tumors (78 SCLCs, 44 large cell neuroendocrine carcinomas (LCNECs), and 19 carcinoids), and 246 non-NE carcinomas, we examined the immunohistochemical expression and prognostic relevance of INSM1 in association with NE phenotype markers in each histologic type. We evaluated its sensitivity and specificity for SCLC diagnosis, as well as its usefulness to diagnose SCLC without NE marker expression and to estimate the prognosis of the subgroups of SCLC stratified by the expression levels of the NE markers. Those of 13 lung cancer cell lines (9 SCLCs and 4 ADCs) were also evaluated. **Result:** INSM1 was expressed in SCLCs (92%, 72/78), LCNECs (68%, 30/44), and carcinoids (95%, 18/19). Additionally, among SCLCs with no expression of NE phenotype markers (n=12), 9 (75%) were positive for INSM1. These data suggest the superiority of INSM1 to the phenotype markers. SCLC with low INSM1 expression (n=28) had a significantly better prognosis (*P*=0.040) than the high-INSM1 group (n=50). Only 7% of adenocarcinomas (9/134) and 4% of squamous cell carcinomas (4/112) were positive for INSM1. In cell lines, most SCLCs were positive for INSM1 (7/9), whereas all ADCs were negative (0/4). **Conclusion:** Our study revealed that INSM1 is highly sensitive to detect SCLC, is positive in most phenotype marker-negative SCLCs and can estimate prognosis. INSM1 will be a promising marker for SCLC.

Keywords: insulinoma-associated protein 1 (INSM1), small cell lung carcinoma (SCLC), Neuroendocrine marker

P2.09-11 GENOMIC PROFILING OF PULMONARY LYMPHOEPITHELIOMA-LIKE CARCINOMA (PLELC)

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Background: PLELC, a rare and distinct type of primary lung cancer, is characterized by Epstein-Barr virus (EBV) infection. Histologically, it resembles undifferentiated nasopharyngeal carcinomas (NPC). Only a few hundred cases have been reported since its discovery. Due to the extreme rareness, its genomic landscape remains elusive. **Method:** Tissue samples of 27 PLELC patients (13 males and 14 females) with various stages (Ib to IV) were subjected to targeted sequencing using a panel consisting of 520 cancer-related genes, spanning 1.6Mb of human genome. **Result:** Collectively, we identified 184 somatic mutations spanning 109 genes, including 107 SNVs, 12 insertions or deletions (INDELs) and 65 copy-number amplifications (CNAs). Approximately, 50% of patients had CNAs. One patient had no mutation detected from this panel. Except for 2 patients, 1 with *HER2* amplification and another with *KRAS* mutation, no other classic NSCLC driver genes were detected. The most frequently mutated genes were *CCND1, TP53*, *DAXX* and *NFkBIA*, occurring in 30%, 26%, 22% and 22% of patients, respectively. Interestingly, 78% (21/27) patients had mutations in epigenetic regulators. Of the 184 mutations identified, 51 occurred in epigenetics-related genes. Pathway analysis also revealed an enrichment of genes participating in chromatin remodeling and organization. Next, we compared the genomic profile of PLELC with lung adenocarcinoma and EBV positive NPC. The frequency of *TP53* mutations was significantly higher in lung adenocarcinoma (68% vs 26%, p=0.021). Comparing to NPC, PLELC had significantly more mutations in epigenetic regulators. TMB analysis revealed a median TMB of 1.6/Mb, significantly lowered than lung adenocarcinomas (p<0.01). We also assessed PD-L1expression and revealed that 67% had an overexpression of PD-L1. Interestingly,*TP53*-mutant patients were more likely to associated low PD-L1 expression (p<0.01). **Conclusion:** In this study, we elucidated a distinct genomic landscape associated with PLELC with no classic NSCLC driver mutation but an enrichment of mutations in epigenetic regulators. The observation of high expression of PD-L1 and lack of canonical druggable driver mutation raises the potential of immunocheckpoint blockade therapy for PLELC.

Keywords: pulmonary lymphoepithelioma-like carcinoma, genomic profiling

P2.09-12 NEXT-GENERATION SEQUENCING OF 7 CASES WITH DIFFUSELY COEXPRESSED TTF-1 AND P40 REVEALS A NEW MOLECULAR ENTITY IN RESECTED NSCLC

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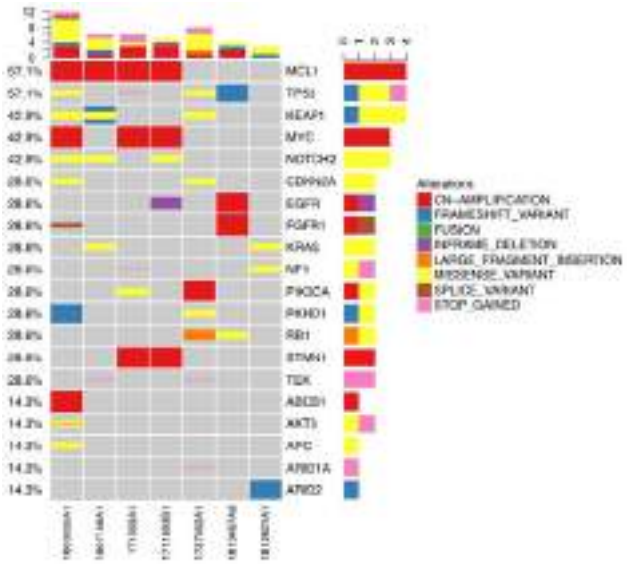
Background: Non-small cell lung cancer (NSCLC) histological and molecular subtypes played a pivotal role in management and treatment of patients. We reported unusual 7 NSCLC cases with diffuse coexpression of TTF-1 and p40 in surgical NSCLC specimens. The clinicopathological features and molecular profile of these cases were investigated in this study. **Method:** NSCLC tumors and paired normal lung tissues were performed targeted next-generation sequencing of 425 cancer genes related to treatment, genetic risks and tumorigenesis. Comprehensive immunohistochemistry and clinical information were analyzed. Genomic data was compared with TCGA database of different lung cancer subtypes. **Result:** In the 7 tumors, the most frequent genomic alterations were MCL1 amplification (confirmed by FISH) and TP53 mutations (57.1%, 4/7), KEAP1 and NOTCH2 mutations (42.9%, 3/7) and MYC amplification (42.9%, 3/7), KRAS and CDKN2A mutations (28.6%, 2/7), and EGFR mutation (14.3%, 1/7). 4 cases with MCL1 amplification were frequently along with NOTCH2 mutations (3 cases) and MYC amplification (3 cases), KRAS (1 case) and EGFR mutation (1 case). Two or three genes amplification co-existed in 4 cases. KRAS mutation was detected to be mutually exclusive from both EGFR and TP53 mutation. 5 cases with tumor mutation burden were more than 10/MB. There was no microsatellite instability found in 7 cases. All tumors were centrally located, with no morphological squamous and glandular differentiation. Diffuse and strong nuclear immunopositivity for TTF-1 (clone 8G7G3/1) and p40 expressed on the same tumor cells and were confirmed by double immunofluorescence. Napsin A was negative in all cases and CK5/6 was positive for 5 cases. 5 of 6 male patients were non-smokers. One was female with no smoking history.



Conclusion: Our results illustrated that poorly differentiated NSCLC with diffuse co-expression of TTF-1 and p40 showed an unique molecular subtype compared with other lung cancer subtypes. Therapies combined with MCL1 inhibitor may be eligible for these MCL1-amplification entities.

Keywords: Non-Small Cell Lung Cancer, MCL1 amplification, Molecular subtype

P2.09-13 HISTOLOGICAL AND MOLECULAR EVALUATION OF MULTIPLE LUNG CARCINOMA WITH SYNCHRONIC PRESENTATION. SINGLE-CENTER STUDY IN ARGENTINA

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Background: The simultaneous presence of more than one tumor nodule in lung cancer patients requires histological assessment to classify them as synchronous or metastatic tumors, allowing correct staging. In certain cases, the distinction based only on histological features is challenging. **Method:** An observational study was performed including 22 lung cancer cases with more than one nodule (17 of them with 2 nodules, 1 with 4 nodules and 2 with more than 4 small nodules). 21 cases corresponded to surgical specimens, and only 1 case corresponded to needle core biopsy. Only 2 nodules per patient were studied, selected according to histological or sizing criteria. Both nodules of each case was assessed histologically according to both WHO 2015 and comprehensive histologic assessment (CHA). Tumors were classified according to both histological criteria into 3 categories: Synchronous, metastatic or undefined. Gene mutations and fusions were assessed using Oncomine Focus Assay (Thermo Fisher) in Ion PGM platform (Thermo Fisher). Cases sharing at least 1 somatic mutation or fusion were considered metastatic tumors. Cases with different somatic mutations/fusions were considered synchronous tumors and those showing no mutations/fusions were classified as undetermined. **Result:** Tumor nodule size in surgical specimens varied between 0,3 and 4 cm, whereas the biopsy case corresponded to an 8-cm mucinous adenocarcinoma. According to the WHO 2015 classification, 20 cases were adenocarcinomas (ADC), 1 was a squamous cell carcinoma and 1 was a large cell carcinoma. On WHO 2015 criteria-based histologic assessment, 10 cases were classified as metastatic (same features), 9 cases were considered synchronous (different features), whereas 3 cases remained undefined. Using CHA criteria, 7 cases were classified as metastatic (same features), 13 cases were considered synchronous (different features), whereas 2 cases remained undefined. Based on molecular testing, we found 6 (27,27%) related and 14 (63,64%) non-related tumors, whereas only 2 cases (9,09%) remained undetermined. Molecular testing was helpful classifying 2 CHA-undefined patients as synchronous, whereas 1 patient could not be re-classified due to the lack of mutations or fusions recognized by our panel. The combination of the WHO, CHA and molecular results helps solving discrepancies in undefined cases. **Conclusion:** The combination of WHO 2015 and CHA criteria improves the accuracy of synchronous or metastatic tumors. The addition of molecular testing is useful to define discrepancies in challenging cases

Keyword: pathology molecular multiple

P2.09-14 EVALUATION ON INTER-ASSAY CONSISTENCY AND INTER-READER PRECISION FOR PD-L1 ASSAYS: VENTANA SP263 AND DAKO 22C3 IN NON-SMALL CELL LUNG CANCER

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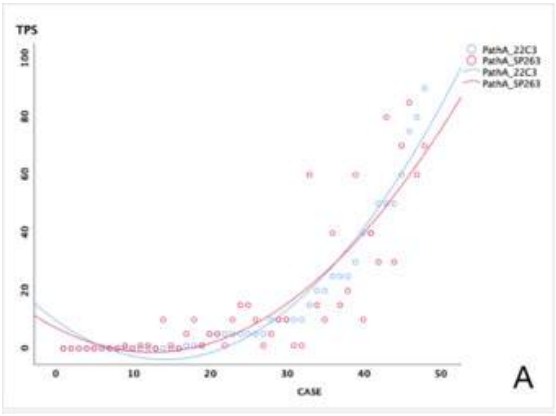
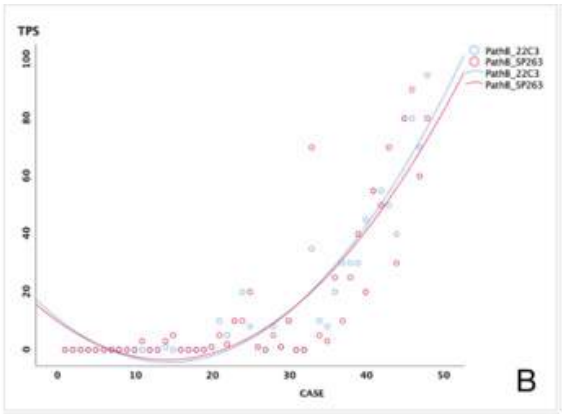
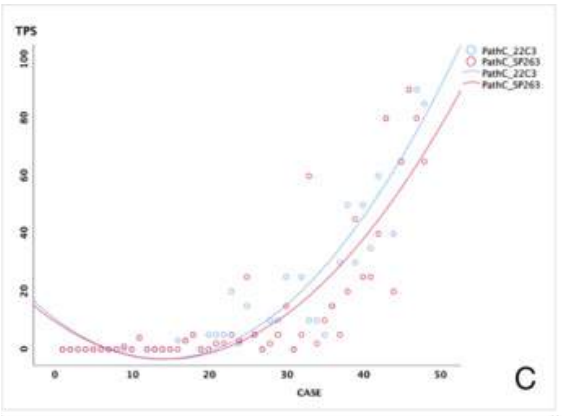
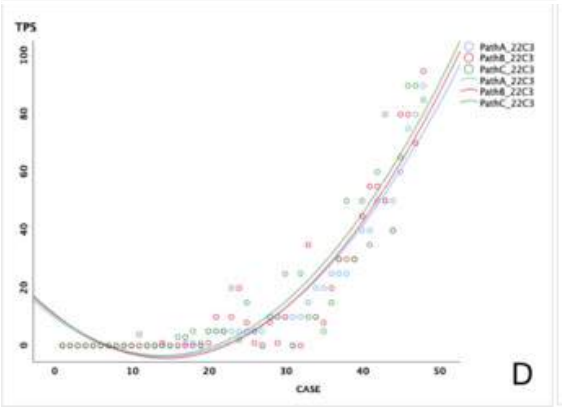
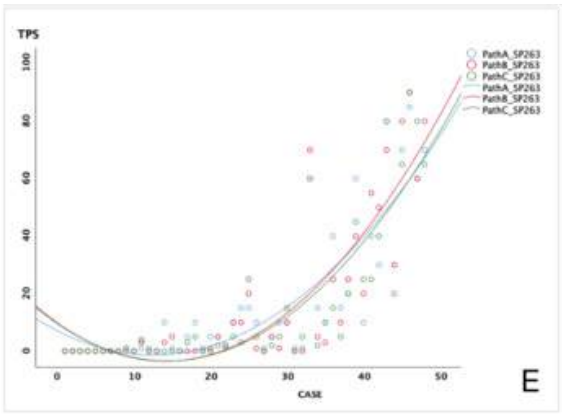
Background: FDA has approved several anti-PD1/PD-L1 checkpoint inhibitors for the treatment of a variety of cancers. It has been shown the expression level of PD-L1 in NSCLC tumor cells is associated with the response to anti-PD-1/PD-L1 treatment. Currently, five anti-PD1/PD-L1 inhibitors have been approved for either as a companion diagnostic (e.g., pembrolizumab) or as complementary diagnostic (e.g., nivolumab, atezolizumab and durvalumab). The blueprint studies and several others have reported the concordance on different PD-L1 IHC assays, however, few Chinese samples were included for assay consistence study; in addition, it remains unclear how these two assays perform in inter-reader variability of pathologists in China. **Method:** Surgical specimens from 48 NSCLC patients were selected for PD-L1 IHC by Ventana SP263 and Dako 22C3. Tumor proportion scores (TPS) were interpreted by three pathologists from three centers. Inter-assay consistency were evaluated by Kappa test at different cut-off value (1%, 25%, and 50%) for each pathologist; and inter-reader precision were performed by Kendall's W test for Ventana SP263 and Dako 22C3, respectively. **Result:** 1) Inter-assay consistency: When TPS were categorized as <1%, 1% to 24%, ≥25%, the overall agreement percentage (OPA) between two IHC assays was 81.25% observed by Pathologist A(κ=0.710), 89.6% observed by Pathologist B (κ=0.84) and 79.2% observed by Pathologist C (κ=0.684); If the TPS were categorized as <1%, 1% to 50%, ≥50%, the OPA were 81.25%, 93.75% and 85.4% (κ= 0.675, 0.899 and 0.760), respectively. 2) Inter-reader precision: The interpretation results on Ventana SP263 by three pathologists were consistent, when TPS was categorized as <1%, 1% to 49%, ≥50% (p=0.017) or <1%, 1% to 24%, ≥25% (p=0.047) respectively; the consistency was not optimal, when TPS was further categorized with narrower groups as <1%, 1% to 24%, 25% to 49%, ≥50% (p=0.065). The interpretation results of Dako 22C3 were inconsistent among three observers in all categories above, with all p values greater than 0.05.











Conclusion: 1) The inter-assay consistency of PD-L1 assays is high between Ventana SP263 and Dako 22C3; 2) The interpretation results of Ventana SP263 is more consistent among different observers.

Keywords: PD-L1 Assays, TPS, Non-Small Cell Lung Cancer

P2.09-15 PD-L1 EXPRESSION AND LYMPHOCYTE INFILTRATION IN RESECTED STAGE IIIAN2 NSCLC: PRELIMINARY DATA FROM A LUNG ART ANCILLARY STUDY

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Background: Patients with resectable stage IIIA N2 NSCLC, are at high risk of both systemic and loco-regional relapse following surgical resection, necessitating neo-adjuvant or adjuvant treatments. Prognostic biological markers are needed. Parameters from the immune microenvironment, including PD-L1 expression and lymphocytic infiltration, have been poorly described in this group of patients. Thus we assessed simultaneously PD-L1 expression and TIL density in a cohort of stage IIIA N2 Lung ART patients, and correlated the results with clinical and pathological features before adjuvant treatment. **Method:** Formalin fixed paraffin-embedded tumor surgical specimens from 247 patients included in the Lung Adjuvant Radiotherapy Trial (NCT00410683) were studied. PD-L1 immunohistochemistry was performed centrally on whole slides using a validated clinical PD-L1 assay. Expression of PD-L1 in tumor cells (TC) and immune cell (IC) was scored by a trained pathologist. Morphological assessment of TIL density (percentage of tumor area) was performed on whole hematoxylin-eosin stained slides. Surgical and pathology reports were reviewed by an independent expert committee for tumor staging. Association between immune parameters and baseline clinical characteristics were assessed in exploratory analyses in order to provide insights on immune activity in resected NSCLC patients. **Result:** PD-L1 expression in ≥1% TC, ≥50% TC, ≥1% IC, ≥10% IC was observed in 47.8%, 21.9%, 61.5%, 7.3% of patients, respectively. In univariate analysis, high PD-L1 expression in both tumor cells and immune cells for all cut points correlated strongly with a higher TIL density (p-values ≤0.001). In 41 (16.6%) patients with preoperative chemotherapy (CT), a higher TIL density was observed (mean 28.1 vs. 17.5%, p=0.0018) as compared to patients without preoperative CT, but no difference was noted for PD-L1 expression in both TC and IC,. Skip N2 metastases were associated with a higher TIL infiltration (mean 22.9% vs. 17.4% p=0.014). We found no significant correlation between PD-L1 or TIL infiltration with the number of mediastinal lymph nodes stations involved on pathological examination and with histological tumor subtypes (squamous cell carcinoma vs. adenocarcinoma). **Conclusion:** PD-L1 expression levels in TC and IC appeared similar in stage IIIA N2 NSCLC as compared to other stages. Expression in both TC and IC strongly correlated with TIL infiltration, suggesting a prominently immune-induced expression mechanism. Preoperative chemotherapy was associated with a higher TIL infiltration but not higher PD-L1 expression. Patients with skip N2 metastases harbored a higher level of TIL density, a finding consistent with a more active immune microenvironment in this group of patients with better prognosis. These data will be subsequently updated on a larger number of patient and correlated to clinical follow-up.

Keywords: PD-L1, stage IIIA NSCLC, tumor infiltrating lymphocytes

P2.09-16 ASSESSMENT OF PD-L1 AND CD8 EXPRESSION IN LUNG CANCER USING RNA IN SITU HYBRIDISATION

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Background: PD-L1 is routinely assessed using immunohistochemistry (IHC) as a companion-diagnostic test. However, patients may be missing out on therapy as issues exist in determining PD-L1 positivity. This is partly due to the use of different antibodies, staining platforms and positivity cut-offs. The use of RNA *in-situ* hybridisation (RISH) for the detection of *PD-L1* levels may be a way to address this; particularly as *PD-L1* mRNA expression levels are

associated with better overall survival in NSCLC. It is well established that PD-L1 expression is associated with increased numbers of Tumour Infiltrating Lymphocytes (TILs) including those which are CD8+. Therefore, it may also be worthwhile to combine PD-L1 testing with additional marker testing such as CD8. The aim of this study is to investigate the expression of PD-L1 and CD8 by RISH in a cohort of NSCLC samples and correlate with clinical outcome. **Method:** RISH protocols (RNAScope® 2.5 HD assay, Advanced Cell Diagnostics, Inc.) were initially optimised on a well annotated cell line TMA (low, moderate and high expression) and compared with standard IHC (DAKO - clone 22C3). Following successful optimisation of the technique, a test cohort of 35 full-face FFPE NSCLC samples were examined for PD-L1 expression by both RISH and IHC. All slides were scored independently by a pathologist. RISH slides were scored as per ACD guidelines (0-4; based on number of positive dots per cell and number of dot clusters). IHC was scored using the standard tumour proportion score system. Image analysis (IA) was subsequently performed by Visiopharm®. Currently, a further cohort of 200 FFPE samples is being assessed, in addition to 50 FFPE samples from patients who received an anti-PD-1 therapy. Optimisation is on-going for dual CD8/PD-L1 RISH staining. **Result:** In the initial 35 samples, PD-L1 was detected in 20% of cases by IHC (≥50% positivity) with mRNA expression identified in 14% of cases by RISH (≥2). In contrast with other recently published studies, issues were identified between IHC and RISH. There were 3 cases which scored positive by IHC, which were negative by RISH. Additionally, 1 case was positive by RISH but negative by IHC. The comparison between both assays produced a 'moderate agreement' as assessed using Cohen's kappa coefficient (κ=0.528, p=0.002). IA undertaken on both assays could not be statistically compared using Cohen's kappa coefficient due to the use of a composite scoring matrix to quantify RISH mRNA signals. However, IHC stained sections scored by IA showed similarity to IHC scored by a pathologist. Further optimisation is required on the RISH IA scoring algorithm. A comparison of PD-L1 IHC with RISH, combined with dual CD8/PD-L1 staining in a larger cohort of clinical samples is on-going, which will further determine the clinical utility of this technique. **Conclusion:** Data from our test cohort of samples have shown that PD-L1 detection by RISH is feasible and compares well to IHC. Preliminary data would also suggest that IA may be better than a pathologist alone, particularly in borderline cases. RISH may be a suitable method for improved detection of *PD-L1* in NSCLC.

Keywords: PD-L1, RISH, CD8

P2.09-17 REAL-WORLD CONCORDANCE ACROSS PATHOLOGISTS FOR PD-L1 SCORING IN NON-SMALL CELL LUNG CANCER: RESULTS FROM A LARGE NATIONWIDE INITIATIVE

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Background: PD-L1 immunohistochemistry (IHC) is an important routine biomarker in patients with metastatic and locally advanced non resectable non-small cell lung cancer (NSCLC). Currently, the thresholds of ≥1% and ≥50% of tumor cells stained are clinically relevant. Scoring concordance across pathologists was reported only in small groups of pathologists or across thoracic pathology experts. Here, we provide real-world concordance data in a large group of pathologists (n=161) with various experience of PD-L1 testing and practice in thoracic pathology. **Method:** Twenty-nine NSCLC samples, mostly biopsies, stained in routine clinical pathology practice with PD-L1 IHC standardized assays (22C3, 28-8 and SP263), were selected to represent various PD-L1 expression levels. Slides were digitalized and scored for the percentage of tumor cells with membranous staining by 161 pathologists using an online digital platform. A consensus score was defined for each case by a group 15 expert pathologists. Data regarding experience, training and practice of PD-L1 testing were also collected for each pathologist. **Result:** Consensus score determined by the expert group highly correlated with the median of scores for each case (correlation coefficient=0.992). Overall concordance across pathologists was moderate, higher for the ≥50% cutoff (K=0.64) than the ≥1% cutoff (K=0.58). A higher concordance was achieved in the expert group (15 pathologists) as compared to the other pathologists (146 pathologists), in particular for the ≥1% cutoff. Concordance across pathologists correlated with training to PD-L1 scoring as well as the number of PD-L1 tests evaluated weekly. No correlation was found with the number of years of thoracic pathology practice or the type of pathology practice (private laboratory, community hospital, university hospital). The issues observed in the most discrepant cases were evaluated and described. **Conclusion:** Concordance across pathologists for PD-L1 scoring in NSCLC was higher in the expert group of pathologists as compared to other pathologists, in particular for the ≥1% cutoff. Training to PD-L1 scoring and experience in routine pathology practice correlated with higher concordance. These data emphasize the importance of training to achieve a high concordance across pathologists in the real-world setting.

Keywords: PD-L1, Biomarker

P2.09-18 LYMPHOCYTE INFILTRATION PATTERN AND STING EXPRESSION IDENTIFY DIFFERENT PROGNOSTIC GROUPS IN EARLY STAGE NSCLC

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Background: Lymphocyte infiltration has been described has a potential biomarker of lung cancer patients' survival. Different studies de-convoluted immune cell compartment (i.e. stromal CD8 density) trying to identify clinically relevant immune patterns. **Method:** A series of 178 early-stage (IB-IIIA) NSCLC has been retrospectively collected at Department of Oncology, San Luigi Hospital (Orbassano, Italy). From Formalin-Fixed and Paraffine-Embedeed (FFPE) tumor blocks, Tissue Microarrays (TMA) were constructed (4 cores were selected for each case). Lymphocyte infiltration pattern was determined by light-microscopy on Hemathoxylin-Eosin (HE) whole slides. Immunohistochemistry was performed as follow: CD8 (SP57) and STING (D2P2F) antibodies were tested with Ventana Benchmark and PD-L1 (22C3) with Dako Autostainer. Infiltration pattern has been clustered in 4 different categories: brisk-diffuse, non-brisk multifocal, non-brisk focal and none. CD8 was quantified as positivity percentage, PD-L1 through TPS (<1%, 1-49% and ≥50%) and STING taking advantage of H-score. Overall survival (OS) and Progression Free Survival (PFS) were estimated using the Kaplan-Meier method and compared using log-rank test. **Result:** Most represented patients had following features: male (119-71%), current or previous smokers (145-82%), stage II (94-53%) and adenocarcinoma histology (119-67%). Distribution of lymphocyte infiltration pattern was: 110 cases with brisk-diffuse (62%), 56 with non-brisk (multi-focal and focal) (31%) and 12 with none pattern (7%). CD8 positivity was distributed in 3 categories: high (66 - 37%), intermediate (75 - 42%) and low (37 -21%) density. For PD-L1 TPS analyses 111 cases (62%) had <1%, 39 cases (22%) 1-49% and 28 cases (16%) >50%. STING high-expressors were 88 (49%) and low-expressors 90 cases (51%). Lastly, were identified 81 samples (45%) with STING positivity at high-density on immune cells (IC) and 97 samples (55%) with low-density. As expected, Brisk-infiltrated samples presented an higher CD8 density (p=0.015). At PFS analyses, STING IC resulted associated (p=0.05) with a worse PFS for high-density patients. At OS analyses, brisk lymphocyte infiltration pattern appeared to have a negative impact (p=0.05) and STING higher-expressors on tumor cells had a worse prognosis (p=0.04). **Conclusion:** NSCLC with wider lymphocyte infiltration and expression of immune activation markers (as STING) appeared to be associated with a worse prognosis (PFS and OS). These date need further validation at multivariate analyses.

Keywords: immunoscore, CD8 density, STING

P2.09-19 EFFECT OF NEOADJUVANT (RADIO) CHEMOTHERAPY ON PD-L1 EXPRESSION IN RESECTED NON-SMALL CELL LUNG CANCERS

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Background: Programmed cell death ligand 1 (PD-L1) expression has been established as a predictive biomarker for checkpoint-inhibitor treatment in advanced non-small-cell lung carcinomas (NSCLC). Inclusion of PD1/PD-L1 inhibitors into existing neoadjuvant regimens is currently evaluated in clinical trials. However, data on the impact of neoadjuvant regimens on tumoral PD-L1 expression is rare. We aimed to assess the PD-L1 expression in NSCLC before/after neoadjuvant treatment, including its prognostic relevance. **Method:** Our single-center, retrospective study cohort comprised 131 consecutive patients with NSCLC resected after neoadjuvant therapy, diagnosed 2000-2016, including 63 available pretreatment biopsies. Tumor types comprised 59 squamous cell carcinomas (SQCC), 66 adenocarcinomas (ADC) and 7 others. The pathological slides and clinical records were reevaluated assessing tumor-size according to current IASLC-recommendations by multiplying the vital tumor percentage with the macroscopic tumor bed. Biologically matched cohorts of 60 locally advanced (pN2) primary resected ADC and 54 SQCC served as controls. PD-L1 was immunohistochemically stained using the Ventana SP263 KIT and tumoral expression was assessed on whole slides by two investigators using the increments: <1%, 1-<25%, 25-<50%, ≥50%. The results were correlated with clinico-pathological parameters. **Result:** PD-L1 could be evaluated in 112 specimens after neoadjuvant chemotherapy, including 24 following neoadjuvant radiochemotherapy: 53 cases scored <1%, 31 1-<25%, 4 25-<50% and 24 ≥50%. In pre-treatment biopsies, 50/63 (79.4%) cases scored <50%, 13/63 (20.6%) ≥50%. Eight/63 (12.7%) cases were discordant regarding the clinically relevant cut-off 50%, 4 cases (2 ADC, 2 SQCC) having a higher expression and 4 cases (2 ADC, 2 SQCC) with lower expression after neoadjuvant radiochemotherapy. PD-L1 expression was significantly higher in primary resected SQCC (n=53) compared to neoadjuvantly treated SQCC (n=52, p=0.014; n=41 neoadjuvant chemotherapy only, p=0.033), with 14 cases scoring <1%, 21 1-<25%, 4 25-49% and 14≥50%. There was no significant difference regarding PD-L1 expression for the paired ADC-groups. In neoadjuvantly treated NSCLC, there was no correlation between PD-L1 expression (increments or 50% cut-off) and ypT, ypN, UICC/AJCC-stage, histological tumor regression, tumor size or the size of the tumor bed. PD-L1 expression was not associated with overall survival nor progression free survival in any cohort. **Conclusion:** We document a discordance of 12.7% regarding the cut-off 50% between pre-treatment biopsies and resections after neoadjuvant therapy, which may be due to tumor-heterogeneity. The higher PD-L1 expression in primary resected SQCC compared to SQCC resected after treatment provides evidence that the influence of neoadjuvant therapy on PD-L1 expression might depend on the histological tumor type.

Keywords: PD-L1 expression, Neoadjuvant therapy

P2.09-20 THE POSSIBLE CLINICAL SIGNIFICANCES OF INFILTRATION OF CD8+ LYMPHOCYTES IN NON-SMALL CELL LUNG CANCERS

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Background: Understanding of the immune contexture of tumor microenvironments might provide knowledge predicting the effect of immunotherapies and prognosis. The amount of CD8+tumor-infiltrating lymphocytes (TILs) seems to be a promising candidate as positive prognostic factor in non-small cell lung cancer (NSCLC). However, few details are understood. Hence, we investigated the prognostic significance of CD8+TILs in NSCLC. **Method:** Of the NSCLCs surgically resected in our institution between 2011 and 2013, those with more than 10% of their tumor cells growing in a solid pattern were immunohistochemically studied to evaluate the CD8+TILs in both tumor parenchyma and stroma. The number of CD8+TILs in tumor parenchymal elements and the percentages of stromal CD8+TILs compared with the total amount of nucleated cells in stromal elements which means "density" were assessed by a digital pathology scoring software. Data were analyzed with Kaplan-Meier survival analysis and Cox proportional hazards models. The primary endpoint of this study was relapse-free survival (RFS). **Result:** Eighty-four patients were included in this study. The median age was 69 (range 31-81) years and the majority of patients were men (85%). Histologically, 52 cases were squamous cell carcinomas, 19 adenocarcinomas, 9 pleomorphic carcinoma and 4 other types. In univariate analysis, the density of stromal CD8+TILs was a significant poor prognostic factor (P=0.0053), while the number of intraparenchymal CD8+TILs showed no prognostic significance. In addition, the multivariate analysis also indicated that the density of stromal CD8+TILs was a significant poor prognostic factor (HR, 3.62; 95% CI, 1.37-9.55; P=0.0094). **Conclusion:** Our data showed that a high density of stromal CD8+TILs might be associated with patient's shorter RFS. Further studies are needed to verify the presenting findings.

Keywords: Lung cancer, CD8+tumor-infiltrating lymphocytes, Immune contexture

P2.09-21 A PROSPECTIVE STUDY OF THE CONCORDANCE FOR PD-L1 STATUS IN CORE NEEDLE BIOPSY AND CORRESPONDING RESECTION SPECIMEN IN NSCLC

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Background: Some studies have demonstrated a relatively poor concordance of PD-L1 IHC expression between biopsies and corresponding resection specimens. To address this central and relevant issue having a significant impact on treatment stratification for patients with NSCLC, we evaluated a novel method to compare and evaluate PD-L1 status in biopsies and resection samples. **Method:** Randomly core needle aspiration biopsy was performed in 170 resected NSCLC samples with 1 to 2 biopsies per centimeter in *longest* diameter of tumor. Among these 170 cases, a total of 52 cases were selected for the study. 41 cases were characterized as PD-L1 positive as a PD-L1 TPS≥ 1%), 1 case which the TPS<1% resected specimen with obvious stained tumor area and randomly 10 specimens being PD-L1 negative. In total 221 biopsies were available for the 52 resection cases. The PD-L1 expression in resected specimens and corresponding biopsies were evaluated by the PD-L1 IHC 22C3 pharmDx assay (Agilent) on the Dako Autostainer. **Result:** In our investigation, the concordance of PD-L1 status in biopsy and resection was not influenced by number of tumor cells at 1% and 50% cut-off's. The length of biopsy improves concordance of PD-L1 status but is not statistically significant (table 1). In figure 1. under 1% cut-off, the PD-L1 status in biopsy and resection is concordant irrespective of biopsies density, whereas the density of biopsies improves the concordance for 50% cut-off. The threshold was 1 per centimeter in longest diameter of tumor.

Table 1. Relevance trend between different length of biopsy and consistency ration in 1% and 50% cutoffs.

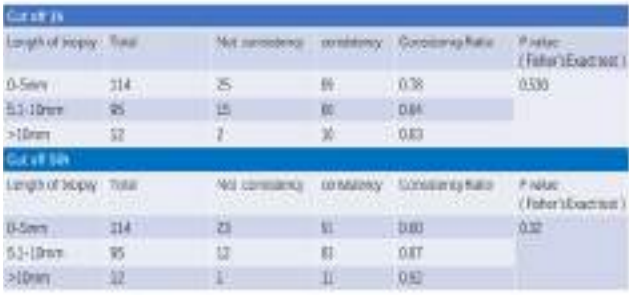
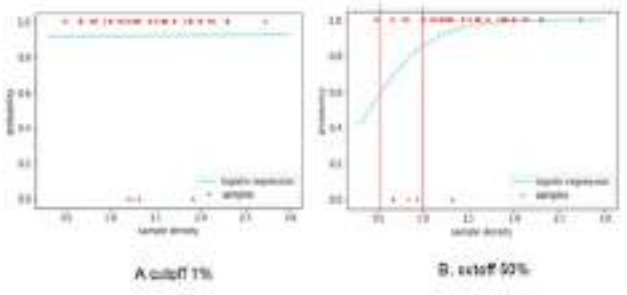


Figure 1. Correlation between PD-L1 accuracy and biopsy density through logistic regression at a cutoff of 1% and 50%.



Conclusion: The concordance between biopsy and resected specimen is related to the length, density of biopsy and the clinical cutoff. Increasing the biopsy density will improve accuracy of PD-L1 detection.

Keywords: PD-L1, core needle biopsy, resection specimen

P2.09-22 MOLECULAR AND IMMUNOLOGICAL PROFILES OF LUNG CARCINOMA: ARE THEY ASSOCIATED?

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Background: Lung cancer, usually related to tobacco and other exposures, has also risk factors that suggest a genetic susceptibility. Thus, there has been increasing interest in the definition of oncogenic changes that allow targeted therapy. On the other hand, immunological checkpoint inhibitors have been shown to be increasingly effective, regardless tumor histology or expression of PD-L1. We aimed to characterize the presence of predictive response mutations to target therapies and the immunological profile of non-small cell lung cancer (NSCLC), and to study possible associations between them. **Method:** Retrospective study of NSCLC cases submitted to the determination of PD-L1 by the Pathology Service since January 2017 until March 2019 and, in those patients, description of the predictive response mutations in the EGFR, ALK and ROS1 genes. Data were analyzed using simple descriptive statistics methods. To test hypotheses, we used the chi-square test, and the predictive factor search was performed through logistic regression. **Result:** A total of 794 patients were identified, 73.8% male (n=586), with a median age of 67 years (IQR, 13). The histological type was classified as adenocarcinoma in 69.3% of cases (n=550) and squamous cell carcinoma in 22.8% (n=181). Among the adenocarcinomas, we found predictive mutations in the EGFR gene in 17.6% of the patients (n=97), translocation in the ALK gene in 4.9% (n=27), and rearrangement in the ROS1 gene in 0.9% (n=5). PD-L1 expression was positive in 54.2% of the cases (n=430), and superior to 50% in 22.9% (n=182). Overall, the association between PD-L1 expression and EGFR status was not statistically significant. However, there was an association between PD-L1 expression and EGFR mutation in females (p=0.013). There was also an overall association between PD-L1 expression and ALK translocation (p<0.001), and this association was maintained in the gender analysis for the male patient group (p=0.003). In the multivariate analysis, the ALK translocation was a predictor of PD-L1 expression. **Conclusion:** The molecular profile of lung carcinoma was similiar to what is described in the literature. In our study, there was a statistically significant association between ALK translocation and PD-L1 expression in the global population. It would be interesting to understand the biological behavior of this group of tumors and, in the future, to study the role of eventual therapeutic associations.

Keywords: molecular profile, immunological profile, Lung cancer

P2.09-23 PD-L1 EXPRESSION OF PAIRED PRIMARY RESECTED NON SMALL CELL CARCINOMA AND METASTATIC LYMPH NODE FINE NEEDLE ASPIRATES

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Background: Small biopsy or cytology samples may present with a different level of PD-L1 expression compared to resected samples (which usually entail scoring of a much greater number of cells) resulting in relatively increased or reduced tumour proportion scores (TPSs). Many PD-L1 results are based on cytology fine needle lymph node aspirates (FNLNAs), encompassing analysis of metastatic disease and the substitution of cytology for histology samples. We compared the PD-L1 TPS of metastatic FNLNAs with that of resected non small cell carcinoma. **Method:** The pathology archive at Wythenshawe Hospital was searched for cases with adequate material over a period spanning 2010-2016. The Ventana SP263 PD-L1 clone was used to stain blocks select from 50 resected NSCCs and matched FNLNA cell blocks from each individual, along with a fresh H&E and negative PD-L1 control section. **Result:** Four of the cell block sections were inadequate for TPS assessment. The remaining 46 cases comprised 21 adenocarcinomas, 3 large cell carcinomas, 1 large cell neuroendocrine carcinoma, 1 atypical carcinoid tumour, and 20 squamous carcinomas. 34 cell block PD-L1 TPSs (68%) were in broad agreement with the corresponding resection block TPS, based on cut-off levels of 1% and 50%. Of the 12 (32%) cases in which differences occurred, 6 (50%) reflected an increase in TPS from resection to FNA, while 6 reflected a decrease causing a change in therapeutic cut-off. Nine of the FNLNAs were sampled after the resection, favouring the presence of recurrent disease.

TABLE 1. PD-L1 expression of resections versus FNLNAs across TPS categories								
	Resection Tumour Proportion Scores n, (%)				FNLNA Tumour Proportion Scores n, (%)			
		0 / <1%	1 - 49%	≥ 50%	*p*	0 / <1%	1 - 49%	≥ 50%
Total n = 46	12 (26)	15 (33)	19 (41)		16 (35)	7 (15)	23 (50)	0.14
Median age at diagnosis (yrs)	63	64	64		62	69	64	
Adenocarcinoma Squamous ca. Other[a]	2 (4) 7 (15) 3 (7)	8 (20) 6 (11) 1 (2)	10 (22) 8 (17) 1 (2)	0.132	2 (4) 10 (22) 4 (9)	5 (11) 2 (4) 0 (0)	13 (28) 9 (20) 1 (2)	0.035
Discrepant cases n = 12	1 (8)	9 (75)	2 (17)		4 (33)	2 (17)	6 (50)	

[a] Includes large cell carcinoma, large cell neuroendocrine carcinoma, atypical carcinoid

Conclusion: The majority of metastatic TPS FNLNAs are in broad agreement with a primary resected carcinoma TPS. FNLNAs tended to score less in the 1-49% category, possibly due to limits of cellularity. In addition to heterogeneity of expression, sampling of recurrent rather than residual disease may contribute to discrepancies.

Keywords: resection, PD-L1, metastatic

P2.09-24 IASLC GLOBAL SURVEY FOR PATHOLOGISTS ON PD-L1 TESTING FOR NON-SMALL CELL LUNG CANCER

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Background: PD-L1 immunohistochemistry (IHC) is now performed for advanced non-small cell lung cancer (NSCLC) patients to examine their eligibility for pembrolizumab treatment, as well as in Europe for durvalumab therapy after chemoradiation for stage III NSCLC patients. Four PD-L1 clinical trial validated assays (commercial assays) have been FDA/EMA approved or are *in vitro* diagnostic tests in multiple countries, but high running costs have limited their use; thus, many laboratories utilize laboratory-developed tests (LDTs). Overall, the PD-L1 testing seems to be diversely implemented across different countries as well as across different laboratories. **Method:** The Immune biomarker working group of the IASLC international pathology panel conducted an international online survey for pathologists on PD-L1 IHC testing for NSCLC patients from 2/1/2019 to 5/31/2019. The goal of the survey was to assess the current prevalence and practice of the PD-L1 testing and to identify issues to improve the practice globally. The survey included more than 20 questions on pre-analytical, analytical and post-analytical aspects of the PDL1 IHC testing, including the availability/type of PD-L1 IHC assay(s) as well as the attendance at a training course(s) and participation in a quality assurance program(s). **Result:** 344 pathologists from 310 institutions in 64 countries participated in the survey. Of those, 38% were from Europe (France 13%), 23% from North America (US 17%) and 17% from Asia. 53% practice thoracic pathology and 36%, cytopathology. 11 pathologists from 10 countries do not perform PD-L1 IHC and 7.6% send out to outside facility. Cell blocks are used by 75% of the participants and cytology smear by 9.9% along with biopsies and surgical specimens. Pre-analytical conditions are not recorded in 45% of the institutions. Clone 22C3 is the most frequently used (61.5%) (59% with the commercial assay; 41% with LDT) followed by clone SP263 (45%) (71% with the commercial assay; 29% with LDT). Overall, one or several LDTs are used by 57% of the participants. A half of the participants reported turnaround time as 2 days or less, while 13% reported it as 5 days or more. Importantly, 20% of the participants reported no quality assessment, 15%, no formal training session for PD-L1interpretation and 14%, no standardized reporting system. **Conclusion:** There is marked heterogeneity in PD-L1 testing practice across individual laboratories. In addition, the significant minority reported a lack of quality assurance, formal training and/or standardized reporting system that need to be established to improve the PD-L1 testing practice globally.

Keywords: global survey, NSCLC, PD-L1 immunohistochemistry

P2.09-25 TUMOR SPREAD THROUGH AIR SPACES (STAS) WAS CORRELATED WITH MULTIPLE ADVANCED CLINICOPATHOLOGICAL FACTORS

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Background: Tumor spread through air spaces (STAS) has been reported as a form of tumor invasion having a poor prognosis mainly in lung adenocarcinoma. However, STAS appears not only in adenocarcinoma but in squamous cell carcinoma and neuroendocrine carcinoma. The aim of this study was to analysis STAS in recent resected lung cancers. **Method:** This study included 103 patients with assessment of STAS of 163 NSCLC who underwent complete surgical resection at Osaki Citizen Hospital between April 2017 and March 2019. STAS were assessed tumor edges to find floating tumor cells or clusters. A statistical analysis was performed to determine the impact of clinicopathologic parameters on STAS and to clarify the relationship between STAS and recurrence. **Result:** STAS was present in 34 of 103 cases (33.0%). Cases with STAS contained 28 of adenocarcinoma, 4 of squamous cell carcinoma and 2 of small cell carcinoma. STAS was correlated with the value of carcinoembryonic antigen (CEA), tumor size, invasion size, pathological T factor (pT), pathological N factor (pN), pleural invasion (pl), intrapulmonary metastasis (pm), lymphatic invasion (ly) and blood-vessel invasion (v). Although this study has short-term follow up periods, there was a significant association between presence of STAS. In a multivariate Cox proportional hazards model, no significant predictor of RFS was defined. **Conclusion:** We found STAS in 33% of resected lung cancers. Presence of STAS was correlated with multiple advanced clinicopathological factors and recurrence, but not significant in multivariate analysis.

Keywords: Lung cancer, STAS

P2.09-26 INADEQUATE SURGICAL MARGINS AT VIDEO-ASSISTED THORACOSCOPIC WEDGE RESECTION OF GROUND-GLASS OPACITY LUNG ADENOCARCINOMA

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Background: Limited resection is now indicated for more patients with ground-glass opacity (GGO) lung cancer, supported by advances in histological analysis and prognostic assessment of this disease. This study involved pathological examination of the possibility of inadequate surgical margins at video-assisted thoracoscopic (VATS) wedge resection of GGO lung cancer. **Method:** Among 12 patients with GGO lung cancer who underwent VATS wedge resection in a 4-year period (April 2012-March 2016), 4 (12%) had local recurrence detected by follow-up computed tomography (CT). Surgical margins determined intraoperatively in these 4 patients were reexamined pathologically. The median proportion of GGO component determined by preoperative CT was 78.75%. In principle, percutaneous CT-guided lung needle marking of the center of a lesion was performed immediately before surgery, and the lesion was excised with 1-cm margins from the collapsed lung under one-lung ventilation. VATS wedge resection was selected based on the patient's decision and was performed with the intention of complete removal of the lesion with adequate margins in each case. **Result:** Mean follow-up duration was 55 months in the 12 patients, and median time to local recurrence was 27 (range, 15-60) months after surgery in the 4 patients. Pathological re-examination in the 4 patients revealed a diagnosis of adenocarcinoma with a mean invasion zone size of 0.68 (range, 0.18-1.4) cm. The distances of margins determined pathologically were shorter than those intended perioperatively; margins were positive in 3 of the 4 specimens. Although the edges of the 0.6-cm margins around the primary lesion were negative, numerous tumor cells were observed in the remaining 1 specimen. **Conclusion:** In wedge resection, it is difficult to identify accurate surgical margins of the GGO lesion and to detect multiple lesions near the surgical margin without palpation. Thus, surgical margins at VATS wedge resection determined solely by visual inspection can be inadequate and may result in incomplete removal of the lesion.

Keywords: ground-glass opacity (GGO) lung cancer, limited resection, surgical margin

P2.09-27 CORRELATION BETWEEN DIFFERENT ROS1 CLONES (SP384 & D4D6) AND CONSISTENCY WITH ROS1 FLUORESCENCE IN SITU HYBRIDIZATION (FISH) RESULTS

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Background: Since treatment options for ROS1 translocated Non-Small Cell Cancer cases has been revealed, ROS1 testing was included in NSCLC guidelines. FISH method is essential for the detection of these cases. Immunohistochemically ROS1 testing in the guidelines is recommended as an aid to the FISH method. The most commonly used commercial ROS1 clone is D4D6. Recently a new immunohistochemical (IHC) clone which has higher sensitivity and specificity (SP384) is available. The aim of this study is to compare these ROS1 antibodies and to interpret with FISH results. **Method:** Twenty-three patients (fourteen ROS1 FISH-positive, nine ROS1 FISH-negative) were included for this study. The material available for all tumors had been formalin-fixed and paraffin-embedded (FFPE). D4D6 clone from Cell Signaling Technology and SP384 clone were provided by Ventana Medical Systems, which were used for ROS1 expression. The staining study was performed according to previously published methodology. ROS1 expression was evaluated by intensity scoring. IHC staining patterns of tumor cells was also interpreted as cytoplasmic or membranous and/or both pattern predominantly. All samples of FISH testing has been performed with LSI ROS1 Break Apart Probe; Abbott Molecular probe. Incompatible cases according to FISH and IHC results AmoyDx gene fusions detection kit testing has been used as confirmatory RT-PCR method. **Result:** Table 1. The immunhistochemical and FISH results of the cases

Cases	Sp384 İntensity	Staining Pattern	Tumor Cell Staining Pattern		D4D6 İntensity	Staining Pattern	Tumor Cell Staining Pattern		FISH Pattners
			Cy.	Mb.			Cy.	Mb.	
1	2	heterogeneous	+	+	1	heterogeneous	+	+	b.a*.
2	3	heterogeneous	+	+	1	heterogeneous	+	-	b.a*.
3	2	heterogeneous	+	-	1	heterogeneous	+	-	b.a*.
4	3	homogeneous	+	-	2	homogeneous	+	-	iso 3'
5	3	heterogeneous	+	-	1	homogeneous	+	-	iso 3'
6	2	heterogeneous	+	+	1	heterogeneous	+	-	b.a*.
7	3	homogeneous	+	-	2	homogeneous	+	-	iso 3'**
8	-	-	-	-	-	-	-	-	n***
9	3	homogeneous	+	+	2	heterogeneous	+	-	b.a*.
10	3	homogeneous	+	+	2	homogeneous	+	+	b.a*.
11	3	homogeneous	+	-	1	homogeneous	+	-	b.a*.
12	3	homogeneous	+	+	1	homogeneous	+	-	b.a*.
13	3	heterogeneous	+	-	1	heterogeneous	+	-	b.a*.
14	3	homogeneous	+	-	2	homogeneous	+	-	b.a*.
15	3	homogeneous	+	-	2	homogeneous	+	-	iso 3'
16	-	-	-	-	-	-	-	-	n***
17	-	-	-	-	-	-	-	-	n***
18	-	-	-	-	-	-	-	-	n***
19	-	-	-	-	-	-	-	-	n***
20	3	homogeneous	+	-	-	-	-	-	n***
21	-	-	-	-	2	homogeneous	+	-	n***
22	1	heterogeneous	+	+	2	heterogeneous	+	+	n***
23	3	homogeneous	+	+	3	homogeneous	-	+	n***

*Break apart, **İsolated 3', *** Negative -The immunhistochemical and FISH results of the cases are presented on Table1. -The study included 14 FISH positive, 6 FISH negative and 3 incompatible cases by FISH and IHC results -All ROS1 FISH rearrenged cases were also positive for both D4D6 and SP384 clones but the intensity was mostly higher; SP384 showed almost always higher intensity except in two cases (case22 and 23). -Incompatible 3 cases (Case 20, 21 and 23) FISH results were confirmed by RT-PCR but IHC results were variable. -Break apart pattern FISH positive cases did not showed membranous staining in both immunhistochemstry clones

Conclusion: -ROS1 SP384 is more feasible then D4D6 for ROS1 protein evaluation. However, both clones may rarely be incompatible with FISH results. -We recommend that the IHC and FISH study should be done together. -In incompatible cases, the RT-PCR study will be determinant with the FISH study.

Keywords: ROS1 Immunohistochemistry, SP384, D4D6, FISH

POSTERS

P2.09-28 PROGNOSTIC IMPACT OF LKB1 EXPRESSION IN ADVANCED NON-SMALL-CELL LUNG CANCER

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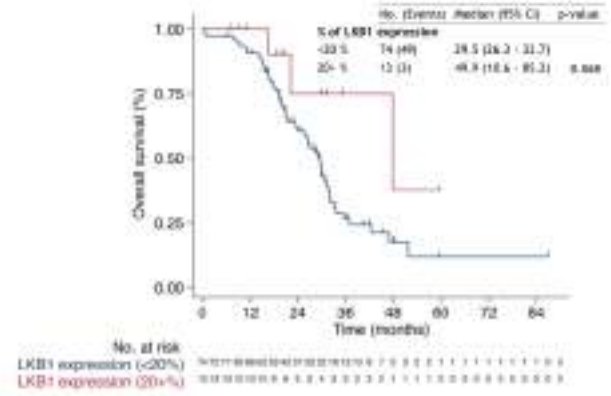
Background: LKB1 is a tumor suppressor gene that regulates cell energy homeostasis, cell polarization, and apoptosis. Within lung cancer, LKB1 ranks as the third most common mutation found in lung adenocarcinoma, both alleles are somatically inactivated in 30%. LKB1 mutations are linked to smoking history, moreover, it have been associated with more aggressive clinical phenotype in KRAS-mutant NSCLC patients, according to preclinical models. Additionally, LKB1 has been associated with primary resistance to PD-1 axis inhibitors in lung adenocarcinoma. However, its expression and clinical implication has not been extensively studied. The aim of the study was to evaluate LKB1 expression in patients with advanced NSCLC. **Method:** In retrospective way patients with advanced NSCLC with and without *EGFR* mutations from México and Colombia were analyzed. Patients received therapy according *EGFR* status (TKI anti-EGFR or chemotherapy). Inclusion criteria were a histopathological confirmed diagnosis, adequate tissue to determine the expression of LKB1 by immunohistochemistry through the clone HPA017254 (Sigma®). The primary outcome was overall survival (OS). **Result:** A total of 87 patients were included in the analysis, 25.3% of them had *LKB1* positive expression. Median score intensity was 20%. There was a significant association of *LKB1* positive expression with wood-smoke exposure (76.9 vs 23.1%, p=<0.001), *EGFR* mutation (54.5 vs 45.5%, p=<0.001) compared to *LKB1* negative. Global Median OS was 29.7 months. Median OS for *LKB1* positive was 33.3 months (CI 95%, 8.9 - 57.6) and 29.5 months (CI 95%, 26.1 - 32-8) for LKB1 negative (p=0.42). After stratifying patients by percentage of LKB1 expression, cut-off of 20% showed a tendency to increase OS in patients with ≥20% expression (figure 1); 49.9 months (IC 95%, 10.6 - 85.2 months) vs 29.5 months (IC 95%, 26.3 - 32.7 months), (p=0.068). Furthermore, a similar trend in OS was observed in patients with ≥50% expression, median OS was not reached compared with 29.5 months (IC 95%, 26.2 - 32.7 months) in patients with <50% expression (p=0.091).



Conclusion: We found a trend to higher OS in patients with *LKB1* expression >20%. This data should be confirmed in prospective study in order to determine the role of *LKB1* as biomarker in NSCLC patients.

Keywords: LKB1, NSCLC, biomarkers

P2.09-29 CORRELATION OF TUMOR SPREAD THROUGH AIR SPACES AND CLINICOPATHOLOGICAL CHARACTERISTICS IN SURGICALLY RESECTED LUNG ADENOCARCINOMAS

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Background: Tumor spread through air spaces (STAS) has recently been reported as a novel invasive pattern in lung adenocarcinoma, but the correlation between other clinicopathological and genetic profiles has not been well studied. The aim of this study was to investigate these correlations in patients with surgically resected lung adenocarcinoma. **Method:** Five hundred consecutive patients with lung adenocarcinoma who underwent curative lung tumor resection and with available STAS profile were reviewed retrospectively from January to December 2016. The correlations of STAS presence and clinicopathological and genetic characteristics were analyzed. **Result:** One hundred thirty-four patients (26.8%) had positive STAS. The pathological stage of these patients was adenocarcinoma in situ, IA, IB, II, and III in 25 (5%), 343 (68.6%), 63 (12.6%), 29 (5.8%), and 40 (8%), respectively. Multivariate analysis showed that the presence of STAS was significantly correlated to higher T (p=0.001) and N (p=0.032) stages, moderate/poor differentiation (p=0.001), and the presence of lymphovascular invasion (p=0.001). Although positive epidermal growth factor receptor mutation and non-lepidic histologic subtypes were correlated with the presence of STAS in the univariate analysis, they were not significantly correlated with the presence of STAS in the multivariate analysis (p=0.676 and 0.286, respectively).

Multivariate analysis of the correlation among clinicopathological characteristics, genetic mutation, and presence of STAS.

	No.	STAS +	OR	95% CI	p Value
Age (years)					
≤65	336	77 (22.9)	1.000		
> 65	164	57 (34.8)	1.218	0.731–2.031	0.449
Sex					
Female	337	73 (21.7)			
Male	163	61 (37.4)	1.705	0.964–3.016	0.067
Smoking status					
Nonsmoker	425	100 (23.5)			
Smoker	75	34 (45.3)	1.451	0.710–2.965	0.308
CEA					
Normal	418	102 (24.4)			
Abnormal	61	28 (45.9)	1.107	0.537–2.281	0.783
Differentiation					
Well	155	8 (5.2)			
Moderate/poor	345	126 (36.5)	5.416	2.690–14.035	0.001
Visceral pleural invasion					
Negative	430	99 (23.0)			
Positive	70	35 (50.0)	0.954	0.494–1.841	0.888
Lymphovascular invasion					
Negative	417	83 (19.9)			
Positive	83	51 (61.4)	2.994	1.583–5.663	0.001
Predominant subtype					
Non-lepidic	362	123 (34.0)			
Lepidic	138	11 (8.0)	0.601	0.236–1.532	0.286
T stage					
Tis-T1a	189	12 (6.4)			
T1b-T4	311	122 (39.2)	3.799	1.762–8.192	0.001
N stage					
N0	448	101 (22.5)			
N1-2	52	33 (63.5)	2.309	1.073–4.969	0.032
EGFR					
Positive	269	86 (32.0)			
Negative	187	44 (23.5)	0.891	0.519–1.529	0.676

Values are presented as n (%), OR, or 95% CI.
Abbreviations: *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *EGFR*, epidermal growth factor receptor; *OR*, odds ratio; *SD*, standard deviation; *STAS*, spread through air spaces.

Conclusion: STAS was significantly correlated with several invasive clinicopathological characteristics, including higher T and N stages, moderate/poor differentiation, and the presence of lymphovascular invasion in surgically resected lung adenocarcinoma. The correlation may lead to poor clinical outcomes in patients with positive STAS. Based on our results and current evidence, the presence of STAS may be considered as a staging profile in future staging system.

Keywords: lung adenocarcinoma, spread through air spaces

POSTERS

P2.09-30 PD-L1 TESTING AND CLINICAL BENEFIT IN PATIENTS TREATED WITH CPI

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Background: PD-L1 expression in tumor cells should predict better response rate in lung carcinoma patients treated with immune checkpoint inhibitors. **Method:** Retrospective analysis of 46 NSCLC lung cancer patients with cytology/pathology samples from primary tumor/metastasis tested for PD-L1 expression and comparing the PD-L1 testing results with clinical benefit. Follow-up period was 6 to 24 months. Samples were stained with PD-L1 mouse monoclonal antibody (clone 22C3, DAKO, Denmark) or with rabbit monoclonal antibody (clone SP263, Ventana/Roche, USA) on an automated staining platform (Benchmark ultra, Ventana/Roche, USA). Samples were divided into four categories: Cytology, histology, primary tumor and metastasis. Number of positive tumor cells was assessed semiquantitatively and divided into three categories: 0%, 1 to 49% and 50 to 100%. We compared PD-L1 expression with clinical course of patients treated with immune checkpoint inhibitors (nivolumab, pembrolizumab and atezolizumab), considering complete response, partial response and stable disease (RECIST criteria) as clinical benefit. Progress of the disease was considered as no clinical benefit. **Result:** We had 37% cytological and 63% histological samples. Overall PD-L1 expression was present in 76% of all samples (1 to 49% and 50 to 100% categories, 13% and 63%, respectfully). We observed clinical benefit in 33 patients (5, 5 and 23 with 0%, 1 to 49% and 50 to 100%, respectively). Progress of the disease was observed in 13 patients (6, 1 and 6 with 0%, 1 to 49% and 50 to 100%, respectively). Out of 29 patients with histological samples, 22 had clinical benefit (2, 5 and 15 with 0%, 1 to 49% and 50 to 100%, respectively). Progress of the disease was observed in 7 patients (5, 0 and 2 with 0%, 1 to 49% and 50 to 100%, respectively). Out of 17 patients with cytological samples 11 had clinical benefit (3, 0 and 8 with 0%, 1 to 49% and 50 to 100%, respectively). Progress of the disease was observed in 6 patients (1, 1 and 4 with 0%, 1 to 49% and 50 to 100%, respectively). We had 29 samples from primary tumor and 17 samples from metastasis. 23 patients with primary tumor sample (2, 4 and 16 with 0%, 1 to 49% and 50 to 100%, respectively) and 10 with metastasis sample (3, 0 and 7 with 0%, 1 to 49% and 50 to 100%, respectively) had clinical benefit. Progress of the disease was observed in 6 patients with primary tumor sample (4, 0 and 2 with 0%, 1 to 49% and 50 to 100%, respectively) and in 7 patients with metastasis sample (2, 1 and 4 with 0%, 1 to 49% and 50 to 100%, respectively) . **Conclusion:** Histological samples from primary tumors seem to have the best, while cytological samples from metastases the poorest predictive value for assessment of clinical benefit for NSCLC patients treated with immunotherapy.

Keyword: PD-L1, CPI, NSCLC

P2.09-31 HIGH CONCORDANCE OF PD-L1 ANTIBODY BETWEEN CLONE 22C3 AND CLONE E1L3N IN NON-SMALL CELL LUNG CANCER BIOPSY SAMPLES

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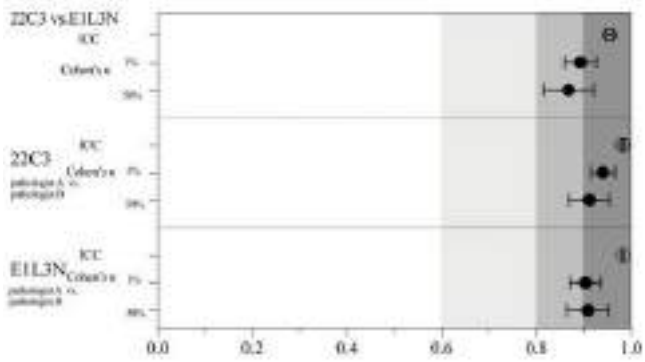
Background: PD-L1 22C3 pharmDx was approved as a companion diagnostics for predicting response to pembrolizumab of advanced non-small cell lung cancer (NSCLC) patients. However, the laboratory developed tests (LDTs) for PD-L1 immunohistochemistry were widely available and urgently be standardized in clinical routine practice. We compared the concordance between PD-L1 antibody clone E1L3N and clone 22C3 expression on the DaKo AutostainerLink48 platform in NSCLC biopsy samples. **Method:** 171 non-small cell lung cancer (NSCLC) biopsy samples were recruited in this study, Serial sections of FFPE blocks were used for IHC staining. The staining protocol was performed according to the standard of PD-L1 IHC 22C3 pharmDx package. **Result:** PD-L1 clone E1L3N and 22C3 distributed a similar pattern in NSCLC biopsy samples. The two assays scoring of E1L3N and 22C3 were highly concordant (lower Kappa value was 0.868 for two cutoff). There was very strong reliability among two pathologists in evaluating PD-L1 scoring with two assays (the lowest PPA was 88.9% for two cutoff). The PPA range was 85.7%-96.3% for all samples. In the Bland-Altman analysis, the mean difference in percentage of tumor cells positively stained for PD-L1 between the paired assay findings was 1.36% for all samples, and 0.57%, -0.66% between the two pathologists for 22C3 and E1L3N assay, respectively.



Conclusion: The results indicated that clone E1L3N assay has a high concordance with 22C3. PD-L1 clone E1L3N assay is reliable and cost-effective, which could be used as a primary screening agent for PD-L1 IHC staining in the pathological laboratory.

Keywords: Non-Small Cell Lung Cancer, PD-L1, immunohistochemistry

P2.09-32 HIGHER PREVALENCE OF EGFR MUTATIONS SIGNIFICANTLY CORRELATES WITH LOWER PD-L1 EXPRESSION IN CHINESE LUNG ADENOCARCINOMA

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Background: *EGFR* mutations are more prevalent in lung adenocarcinoma compared with other non-small cell lung cancer and are more prevalent in East Asians compared with the other populations. At the same time, we observed lower PD-L1 Tumor Proportion Score (TPS) in Chinese lung adenocarcinoma patients (pts) compared with that in Chinese lung squamous cell carcinoma pts and we also observed the proportion of PD-L1 positive (TPS >= 1%) in Chinese lung adenocarcinoma pts was lower than that in other multicenter cohorts. Then we hypothesize that the higher prevalence of *EGFR* mutations in Chinese lung adenocarcinoma pts correlates with lower PD-L1 expression. **Method:** The Origimed-based lung adenocarcinoma cohort was a retrospective cohort consisted of more than one thousand Chinese lung adenocarcinoma pts who underwent both NGS panel sequencing and PD-L1 immunohistochemistry (IHC) in a College of American Pathologists (CAP) certified and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory during the year 2017 and 2018. Antibodies used in the PD-L1 IHC assay included 28-8 (sample size = 883) and 22C3 (sample size = 158). Tumor Proportion Score (TPS) was applied. All the slides were reviewed by the same senior pathologist. All the *EGFR* mutations were manually reviewed in Integrated Genomics Viewer for confirmation. After confirmation, each pts was assigned to *EGFR* positive group or *EGFR* negative group. Fisher' s exact test and Student' s t-test were applied. **Result:** For antibody 28-8, PD-L1 IHC was positive (TPS >= 1%) in 18% (66/370) *EGFR* positive pts and was positive in 35% (180/513) *EGFR* negative pts (fisher exact test p value = 1.6e-5). For antibody 22C3, PD-L1 IHC was positive (TPS >= 1%) in 14% (9/64) *EGFR* positive pts and was positive in 45% (42/94) *EGFR* negative pts (fisher exact test p value = 3.8e-3). And we observed a significantly lower PD-L1 TPS in *EGFR* positive pts for both antibodies (t-test p value = 3.5e-11 for PD-L1 antibody 28-8; t-test p value = 6.0e-5 for PD-L1 antibody 22C3). **Conclusion:** The observation demonstrated that lower PD-L1 TPS in Chinese Lung Adenocarcinoma pts was significantly correlated with East-Asian-specific high prevalence of *EGFR* mutations. The observation reassured that *EGFR* mutation status should be examined simultaneously with PD-L1 IHC in lung adenocarcinoma pts because it was a confounding factor for predicting immunotherapy outcome using PD-L1 TPS. The observation partly explained the generally higher PD-L1 TPS in Chinese lung squamous carcinoma pts compared with that in Chinese lung adenocarcinoma pts.

Keywords: EGFR, IHC, PD-L1

P2.09-33 PREVALENCE OF ROS1 (SP384)-REACTIVE TYPE II PNEUMOCYTE STAINING IN LUNG TISSUE

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Background: Availability of a positive control sample is important to ascertain that specimen preparation and immunohistochemistry (IHC) processes are performed correctly. Lack of proper control tissue may result in an invalid IHC interpretation. Given the low prevalence (1-2%) of *ROS1* gene fusions (which leads to overexpression of ROS1) in non-small cell lung cancer (NSCLC), the feasibility of using *ROS1*-fusion positive NSCLC tissue as a control sample is challenging. ROS1 wild-type (WT) protein expression has been shown to be absent in normal lung tissue; however, ROS1 reactivity has been observed in reactive type II pneumocytes in non-neoplastic lung tissue. Hence, we sought to characterize the prevalence of VENTANA ROS1 (SP384) Rabbit Monoclonal Primary Antibody (ROS1 (SP384)) reactive type II pneumocytes in normal or benign lung tissue in order to assess the feasibility of using type II pneumoctyes as a control tissue for ROS1 (SP384). **Method:** One hundred seventy-seven (177) formalin-fixed, paraffin-embedded (FFPE) normal or benign lung tissue samples were randomly procured. Tissues sectioned at 4 µm were stained with hematoxylin and eosin (H&E), Rabbit Monoclonal Negative Control Ig, and ROS1 (SP384) IHC. ROS1 (SP384)-stained specimens were evaluated for presence of type II pneumocytes. If present, type II pneumocytes were evaluated for reactivity based on a 0 to 3-point stain intensity scale. Reactivity was defined as any staining greater than 0. Data was analyzed for percent distribution for a range of stain intensities. **Result:** Out of the 177 specimens evaluated, 165 ROS1 (SP384)-stained slides were evaluable (12 cases were unacceptable due to tissue loss or were identified as neoplastic lung tissue). Type II pneumocytes were present in all 165 evaluable samples. Forty-seven type II pneumocyte samples (28.5%, 47/165) demonstrated no staining with ROS1 (SP384) while 71.5% of the type II pneumocyte samples (118/165) demonstrated reactivity with ROS1 (SP384). In addition, 23.0% (38/165) of the type II pneumocyte samples demonstrated a stain intensity of at least 2. **Conclusion:** Herein, this cohort demonstrates a high prevalence of ROS1 reactivity in type II pneumocytes, with a range of stain intensities, in normal or benign lung tissue with VENTANA ROS1 (SP384) Rabbit Monoclonal Primary Antibody. This finding suggests that use of reactive type II pneumocytes in normal or benign lung tissue as a control tissue for ROS1 (SP384) is feasible.

Keywords: ROS1, Type II pneumocytes, immunohistochemistry

P2.09-34 NEXT-GENERATION SEQUENCING IMPLEMENTATION IN NON-SMALL CELL LUNG CANCER MOLECULAR DIAGNOSIS

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Background: Currently, all patients with advanced non-small cell lung cancer (NSCLC) require *EGFR, ALK, ROS1* and *BRAF* molecular characterization. Next-generation sequencing (NGS) allows the simultaneous analysis of these biomarkers optimizing both the sample and the economic cost. The purpose of this study was to compare NGS results with those obtained using single gene analysis in a prospective clinical setting. **Method:** During 12 months, 50 paraffin-embedded samples from patients with advanced NSCLC (46 adenocarcinomas and four NSCLC-NOS) were prospectively analyzed in our institution. Molecular characterization was carried out using the NGS Oncomine Solid Tumor DNA and Fusion Transcript Kits for hotspot mutations and gene fusions (Thermo Fisher) and results were compared with Therascreen *EGFR* RGQ PCR Kit (Qiagen), and Vysis *ALK* and *ROS1* Break Apart FISH Probe Kits (Abbott Molecular, ZytoVision). **Result:** All samples studied by NGS for hotspot mutations were assessable and we detected pathogenic alterations in 90% (n= 45). Regarding targetable alterations, we identified nine patients harboring *EGFR* mutations (18%), in agreement with real-time PCR (except for one case which had an exon 20 insertion not interrogated by Therascreen), and one patient with a *BRAF* mutation (2%). We highlight the presence of *TP53* mutations in 27 cases (54%), *KRAS* in 16 cases (32%) and *STK11* in three cases (6%). *TP53* mutations were concomitant with other alterations in 70% of the cases (n= 19), without being significantly associated with any of them. Gene fusion analysis by NGS was assessable in 80% of the samples (n= 40): six samples had insufficient RNA quality and four had not enough material. We detected only one case with an *ALK* rearrangement (2%), confirmed by FISH. **Conclusion:** NGS technology for NSCLC molecular diagnosis could be considered as the initial screening test although the success rate in gene fusion assessment is closely related to RNA paraffin-embedded evaluation. NGS also detected other genomic alterations that allowed referral of patients to clinical trials.

Keywords: Molecular diagnosis, Next-generation sequencing, Biomarker's detection

P2.09-35 PROPOSAL TO REVISE VENTANA ALK SCORING INTERPRETATION GUIDE FOR NON-SMALL CELL LUNG CARCINOMA: INTERPRETATION OF ALK HETEROGENEITY

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Background: A small number of non-small cell lung cancer (NSCLC) cases showed heterogeneity of anaplastic lymphoma kinase (ALK) by VENTANA immunohistochemistry (IHC) in clinical practice. According to the ALK Scoring Interpretation Guide for VENTANA anti-ALK (D5F3), the presence of strong granular cytoplasmic staining in tumor cells (any percentage of positive tumor cells) is called positive for ALK. However, we know little about ALK heterogeneous cases. Multiple detection platforms are used to analyze molecular variability and pathological features in anticipation of clinical treatment decisions for such cases. **Method:** A total of 2228 NSCLC cases with successful ALK IHC (VENTANA, D5F3, Roche) detection in Guangdong Provincial People`s Hospital were recruited between January 2012 and April 2018. Positive and negative system control and a negative agent control were established for each case. ALK IHC positivity was defined as the presence of strong granular cytoplasmic staining in 100% tumor cells; ALK IHC heterogeneity as the presence of strong granular cytoplasmic staining in 1-99% tumor cells; ALK IHC negativity as no tumor cells show strong granular cytoplasmic staining. Fluorescence *in-situ* hybridization (FISH) (Vysis ALK Break Apart FISH Probe Kit, Abbott) and next-generation sequencing (NGS) (OseqTMLung Cancer Gene Detection, BGI, China) was performed for cases showed ALK (D5F3) IHC heterogeneity. **Result:** ALK (D5F3) double-blind review analysis showed 201 (9.0%) ALK-positive cases, 10 (0.4%) ALK-heterogeneous cases, and 2017 (90.5%) ALK-negative cases. The heterogeneity cases included 2 large cell neuroendocrine carcinomas, 1 lymphoid epithelioid carcinoma, and 7 squamous cell carcinomas. The percentages of tumor cells with strong granular cytoplasmic staining were 1% to 30%. The *ALK* FISH break apart signal of these ten cases were 0% to 12%, indicating *ALK* FISH negativity. Nine ALK-heterogeneous cases were successfully detected by NGS, and no *ALK*gene variations (including gene fusion, copy number variation, insertion/deletion or single nucleotide variation) were found. Immunohistochemical staining showed that some ALK-heterogeneous cases showed neuroendocrine differentiation.

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Table. Comparison of IHC, FISH and NGS results of the ALK-heterogeneous cases.

						ALK IHC	ALK FISH	ALK FISH	ALK NGS	ALK NGS	
Case No.	**Gender**	**Age**	**Biopsy/ surgery**	**Diagnosis**	**Tumor cell content**	**Strong positive staining tumor cells**	**Break apart signal**	**Interpretation result**	*ALK* **fusion**	*ALK* **INDEL/ SNV/CNV**	**8th TNM**
1	M	69	Wedge resection	Large cell neuroendocrine carcinoma	70%	2%	0%	Negative	Negative	Negative	pT1bN0M0
2	M	55	Lobectomy	Large cell neuroendocrine carcinoma	85%	20%	4%	Negative	Negative	Negative	pT2bN0M0
3	F	33	Lobectomy	Lymphoid epithelioid carcinoma	60%	5%	0%	Negative	Negative	Negative	pT3N0M0
4	M	68	Lobectomy	Squamous cell carcinoma	70%	5%	6%	Negative	Negative	Negative	pT3N0M0
5	M	69	Lobectomy	Squamous cell carcinoma	70%	5%	12%	Negative	Negative	Negative	pT2aN0M0
6	M	52	Lobectomy	Squamous cell carcinoma	80%	1%	0%	Negative	Negative	Negative	pT2aN1M0
7	M	73	Lobectomy	Squamous cell carcinoma	90%	5%	2%	Negative	Negative	Negative	pT3N0M0
8	M	70	Lobectomy	Squamous cell carcinoma	80%	5%	4%	Negative	Negative	Negative	pT2bN1M0
9	M	69	Biopsy	Squamous cell carcinoma	85%	15%	0%	Negative	Negative	Negative	sT3N1M0
10	M	60	Biopsy	Squamous cell carcinoma	85%	30%	0%	Negative	NA	NA	cT2bN3M0

Abbreviations: INDEL, insertion and deletion; SNV, single nucleotide variation; CNV, copy number variation; NA, NGS was not performed due to insufficient tumor tissues.

Conclusion: Multi-platform detection of ALK-heterogeneous cases did not show evidence of *ALK*gene variation, and the effect of ALK-TKI treatment was unknown. therefore, the VENTANA ALK scoring interpretation guide for non-small cell lung carcinoma should be revised. It is recommended that ALK-heterogeneous cases be defined as ALK (D5F3) uncertain equivocal cases. The molecular pathology report should clearly state that the clinical significance is unclear, and it is recommended to conduct further testing by FISH or NGS.

Keywords: Non-Small Cell Lung Cancer, VENTANA ALK, Heterogeneity

P2.10-01 ANALYSIS OF HUMAN PAPILLOMA VIRUSES (HPV) AND HUMAN POLYOMA VIRUSES (HPYV) IN LUNG CANCER FROM SWEDISH NEVER-SMOKERS

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Background: A possible role for oncogenic infections in the etiology of lung cancer has been investigated in a large number of studies, with contradictory results. High-risk mucosal human papillomaviruses (HPV), recognized as being associated with cervical cancer and oropharyngeal cancer, has been suggested as a causative factor also in lung cancer [1,2], whereas other studies found no, or at most very limited, involvement of HPV in lung cancer [3,4]. To investigate human papillomaviruses (HPV) and human polyomaviruses (HPyV) as possible causative factors behind lung cancer in never-smokers, we analyzed the presence of these viruses in a subset of tumors within a larger Swedish cohort of never-smoking lung cancer patients [Swedish Molecular Initiative against Lung cancer, SMIL; Salomonsson et al. Abstract WCLC 2019]. **Method:** Eighty-seven surgically resected lung cancer samples from never-smokers, diagnosed 2005-2014 in Stockholm, Sweden, were analyzed by Luminex assays for the presence of 27 HPV types (including all HPV types currently regarded as high-risk types) and for 10 HPyV species (BKPyV, JCPyV, KIPyV, WUPyV, TSPyV, MWPyV, HPyV6, 7, 9, and 10). **Result:** All samples were positive for the β-globin gene, confirming the presence, amplification and detection of cellular DNA. All samples were negative for the HPV types included in the assay. The only viral DNA detected in the tumors were low amounts of Merkel cell polyomavirus (MCPyV) DNA, of unknown significance, in 15 samples. **Conclusion:** Our study shows no evidence for neither HPV nor HPyV in the etiology of lung cancer in Swedish never-smokers. References 1. Syrjanen, K. Detection of human papillomavirus in lung cancer: Systematic review and meta-analysis. *Anticancer Res* 2012, *32*, 3235-3250. 2. Ragin, C.; Obikoya-Malomo, M.; Kim, S.; Chen, Z.; Flores-Obando, R.; Gibbs, D.; Koriyama, C.; Aguayo, F.; Koshiol, J.; Caporaso, N.E.*, et al.* Hpv-associated lung cancers: An international pooled analysis. *Carcinogenesis* 2014, *35*, 1267-1275. 3. Koshiol, J.; Rotunno, M.; Gillison, M.L.; Van Doorn, L.J.; Chaturvedi, A.K.; Tarantini, L.; Song, H.; Quint, W.G.; Struijk, L.; Goldstein, A.M.*, et al.* Assessment of human papillomavirus in lung tumor tissue. *J Natl Cancer Inst* 2011, *103*, 501-507. 4. Tang K.W.; Alaei-Mahabadi B.; Samuelsson T.; Lindh M.; Larsson E. The landscape of viral expression and host gene fusion and adaptation in human cancer. *Nat Commun* 2013, *4*, 2513. 5. Swedish Molecular Initiative against Lung cancer, SMIL; Salomonsson A. *et al.* Lung cancer in never-smokers: A nationwide population based mapping of targetable alterations. *20th World Conference on Lung Cancer* (Barcelona, 7-10 Sept, 2019)

Keywords: never-smoker, polyomavirus, human papillomavirus HPV

P2.10-02 SMOKING HABIT IN LUNG CANCER IN SPAIN

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Background: Tobacco is the leading cause of lung cancer. The fight against the smoking habit is essential and should be continuous, to detect the national situation that makes it possible to design health care policies against this consumption. To do so, the *Grupo Español de Cáncer de Pulmón* (Spanish Lung Cancer Group) made this analysis within the context of the Thoracic Tumor Registry (TTR). **Method:** The TTR is an observational cohort multicenter study in Spain. The study is conducted according to the Declaration of Helsinki and approved by the institutional review board of each participating site. The registry was approved by the Spanish Drug Agency, as a non-post-authorization, non-interventional study. **Result:** We collected data from 6,600 patients diagnosed of lung cancer from 58 different Spanish hospital sites. A total of 3,039 patients were former smokers (46%), 2,611 were active smokers (39%) and only 866 (12%) patients stated to be non-smokers; the status in 2% is unknown. If we make a comparison by gender regarding the presence of this habit, large differences (p-valor < 0.001) are observed, with a greater number of non-smokers in women (37 % vs. 4.5% in males), while the percentage of former smokers is much higher in the males (53.4% vs. 27.9% in women) and a minor difference in active smokers (42.1% vs. 34.4% in women). Significant differences were observed in the study on the distribution of the smoking habit by gender and year of diagnosis. An increase is also observed in the last two years regarding the percentage of patients who were active smoked, both for the total population as well as for each one of the two genders separately. The increase is greater among the women and, also, the number of women who are active smokers is greater in recent years. Mean age of onset of the smoking habit is 18.2 years. Significant differences are observed between both genders (p-valor < 0.001), with a mean age of initiation of 17.9 years in the men (95%CI 17.6-18.2 years) and 19.2 years in the women (95%CI 18.5-19.8 years). Significant differences between Regional Communities were also found in the mean age at onset of the habit, with much lower levels in the Valencian Community (16.6 years) or Navarra (16.9 years) regarding other communities, such as the Region of Murcia (22.9 years) or the Balearic Islands (21.6 years) **Conclusion:** Lung cancer in Spain is associated to tobacco consumption in 85% of the cases diagnosed. Consumption has shown an increase in both genders in recent years and is especially rapid and worrisome in women. Anti-smoking campaigns should be reactivated and the causes of the regional differences analyzed in depth

Keywords: smoking habit, tobacco consumption

P2.10-03 PREVALENCE OF TOBACCO USE DISORDER IN PATIENTS DIAGNOSED WITH LUNG CANCER AND THEIR TOBACCO USE CHARACTERISTICS

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Background: Tobacco use disorder (TUD), previously termed as nicotine dependence, was associated with increased risk of lung cancer. However, little is known about the prevalence of TUD and symptom manifestation in smokers with lung cancer. The aim of the present study was to investigate the prevalence of TUD using DSM-5 diagnostic criteria in patients diagnosed with lung cancer and determine their tobacco use characteristics. **Method:** A total of 200 histologically confirmed lung cancer patients who used tobacco within prior 12-month period at the time of diagnosis were recruited for this study. Participants were assessed with interviewer-administered questionnaires on symptoms of TUD and smoking-related behaviors and self-administered Fagerstrom Test for Nicotine Dependence (FTND). **Result:** The prevalence of DSM-5 TUD was 92.0% (n = 184). Of a total of 200 subjects, 23 (11.5%), 35 (17.5%), and 126 (63.0%) were classified as mild, moderate, and severe TUD, respectively. A total of 19 (81.3%) moderate TUD and 98 (77.8%) severe TUD patients had attempted smoking cessation.

Of these subjects, 21 (21.4%) severe TUD patients and 12 (63.2%) moderate TUD patients had tried more than three times. The number of satisfied criteria of DSM-5 TUD was positively correlated with FTND score, cumulative lifetime smoking amount, and daily smoking amount. **Conclusion:** Smokers diagnosed with lung cancer had high prevalence of DSM-5 TUD. Their heavy and consistent tobacco use characteristics might be less motivated to maintain abstinence and make them to be less stick to quit.

Keywords: Tobacco, Lung cancer, Tobacco use disorder

P2.10-04 PREDICTING NON-COMPLIANCE IN ROUTINE LUNG CANCER SCREENING FOR HIGH-RISK ADULTS

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Background: Lung cancer is the most common cause of cancer-related deaths, which can be effectively reduced by routine screening. To detect lung cancer early, annual screening in high-risk adults aged 55-74 years using low-dose computed tomography (LDCT) is recommended by the Canadian Medical Association guidelines. High-risk adults are recommended an annual screen within 11-15 months of their baseline scan. However, screening compliance is a challenging area influenced by a series of complex biopsychosocial, behavioral and cognitive processes. This study aims to describe the participants and identify predictors of noncompliance in the Lung Cancer Screening Pilot for People at High Risk Program (HR LCSP) conducted in Ontario, Canada. **Method:** During 2017-18, HR LCSP has recruited over 5,999 high-risk adults from 3 sites in Ontario, with 5,502 adults undergone risk assessment for screening eligibility, and 2,997 baseline scans conducted. Baseline and follow-up participant experience surveys assess satisfaction especially around test result communication. During risk assessment, all individuals who identify as current smokers are referred to smoking cessation services irrespective of their eligibility. The clinical data are collected using an internationally accepted standard, the Resident Assessment Instrument Minimum Data Set at each site. We hypothesize that participant compliance is predicted by the satisfaction of their first screening experience in additional to socio-demographic and clinical factors. A multivariable logistic regression model will be conducted to predict non-compliance, which is defined by a return interval >15 months or missing. The model will contain individual level factors including age, sex, aboriginal status, education, income estimates, geographic distance; system level factor includes physician-referral/self-referral status; clinical factors include the risk prediction by PLCOm2012, which assesses smoking status including intensity and duration; other clinical factors include personal and family history of cancer, history of lung disease, body mass index; psychosocial/behavioral factors include smoking cessation program participation, baseline screening results including the presence of actionable incidental findings and appropriate follow-up of the abnormal results. Data linkage is under way and results will be presented at the conference. **Result:** This study will provide a granular view on the predictors of routine screening compliance among high-risk adults, which will be used to improve the program recruitment and retention especially when designing targeted messages. Findings will have implications for health care professionals when communicating with high-risk individuals about routine screening for lung cancer. **Conclusion:** Section not applicable.

Keywords: non-compliance, organized screening program, predictors

P2.10-05 INDOOR RADON AND LUNG CANCER RISK. A POOLING STUDY ON THE SECOND RISK FACTOR FOR LUNG CANCER

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Background: Residential radon is the second risk factor of lung cancer following tobacco consumption, according to WHO (World Health Organization) and United States EPA statements. It is recognized as the first cause of lung cancer in never-smokers by both organizations. Nevertheless, case-control studies performed in radon prone areas are still scarce and with limited sample sizes. We aim to know the relationship between residential radon and lung cancer risk in a study performed in a radon-prone area, and where inhabitants live for a long time in the same dwelling. **Method:** We have pooled results from 5 different case-control studies performed in the same geographical area to assess the relationship between indoor radon and lung cancer. One of these studies was focused specifically in never smokers and other in Small Cell Lung Cancer. All cases and controls were older than 30 and cases had a confirmed diagnosis of lung cancer. Controls were selected for attending hospital for trivial surgery. Controls were selected through a frequency-based sampling based on age and gender distribution of cases. The information and questionnaires collected was the same in all studies, with special focus on tobacco consumption. Radon devices of an alpha track type were placed at the participants' homes for at least three months. Odds Ratios of lung cancer due to radon exposure have been calculated adjusted by age, gender, and tobacco consumption. **Result:** We included 1691 cases and 1698 controls. Median age was 63 and 67, respectively, and females comprised 33% of both cases and controls. Adenocarcinoma was the most frequent histology (43%) and participants lived a median of 30 years in the same dwelling. The table show the risk of lung cancer due to radon exposure.

Table. Residential radon and lung cancer.

Variable	Cases n (%)	Controls n (%)	OR[a] (95% CI)	OR[b] (95% CI)
Residential radon exposure, Bq/m³				
≤50	219 (14.9)	346 (24.1)	1 (---)	1 (---)
51-100	352 (24.0)	350 (24.4)	1.61 (1.28-2.02)	1.66 (1.28-2.15)
101-148	265 (18.1)	235 (16.4)	1.75 (1.37-2.25)	1.89 (1.43-2.50)
149-200	194 (13.2)	162 (11.3)	1.86 (1.41-2.45)	2.00 (1.48-2.72)
>200	435 (29.7)	343 (23.9)	2.00 (1.60-2.52)	2.32 (1.80-3.00)
Tobacco consumption				
Never-smokers	523 (33.4)	900 (54.5)		1 (---)
1-33	205 (13.1)	423 (25.6		1.51 (1.17-1.94)
34-66	425 (27.2)	223 (13.5)		6.19 (4.78-8.02)
>66	412 (24.4)	104 (6.3)		12.1 (8.96-16.4)

[a]Adjusted by age and sex [b]Adjusted by age, sex and tobacco consumption.

Conclusion: Residential radon is a relevant risk factor for lung cancer, even below concentrations established as safe by USEPA and WHO.

Keywords: Indoor radon, case-control study, ionizing radiation

P2.10-06 SMOKING PREVALENCE AND PERCEPTIONS AMONG HEALTHCARE PROFESSIONALS: A SURVEY IN AN ITALIAN CLINICAL CANCER CENTRE

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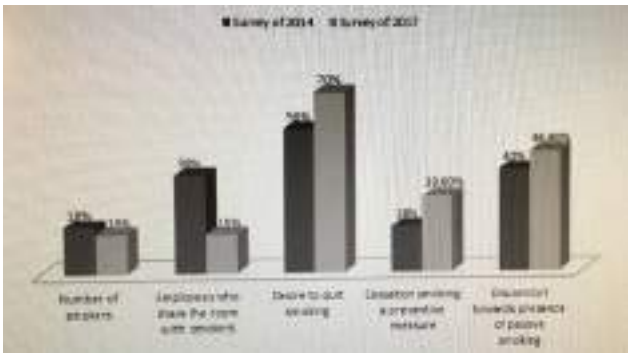
Background: A survey has been conducted on employees of our Clinical Cancer Centre about the smoking prevalence and knowledge of the smoking-related harms. The results have been compared to those emerged from a previous survey when the current smoke-free-hospital policies (national and internal) were not yet active. **Method:** In June 2017, during two weeks, 400 subjects received an anonymous questionnaire (36items) investigating demographics, smoking-habits, secondhand-smoke exposure, knowledge of Italian smoke-free legislation. **Result:**



104 subjects (26%) returned the self-completed form (M=45.34years, SD=10.5; 67.3%women). 17,8%of responders were smokers, 26,2%former smokers, 56% no smokers, while in 23,8% the data were missing. Among the former smokers, the mean age of smoking cessation was 33,3 years (sd=10,2), without drugs in 77,3% of cases, for the following reasons: preventive health purposes (29,6%),a child birth (26%),suggestions from family members (3,%); no one stopped on medical advice. The ex-or never smokers share the working room with one (23,2%) or more (8,5%) smokers, pointing out the smoke exposure in hospital (30%), and feeling intense uneasiness (46,8%). The smoke-free-hospitals policy is not fully accepted, indeed only 40% declared that the smoking ban is observed and 63,2% said to smoke during the working-time. Regarding the policies that prohibit smoking inside and outside the hospital, the responders perceived it as a good way to protect the health (65,4%), to reduce the prevalence of smokers in hospital (20%), to protect non-smokers (46,1%) and to decrease tobacco-related disorders (37,5%) (p<0,001). The implementation of Italian smoke-free policies has favoured the reduction of the number of smoked cigarettes (55%), but did not increase the desire of a complete cessation (63%). A comparison of the surveys conducted in 2014 and 2017 is showed in Figure. **Conclusion:** The adopted strategies are partially efficient; among personnel there is a large prevalence of smokers and interventions aimed at the development of a culture of health promotion are needed.

Keywords: Survey, Smoking prevalence, Antismoking in-hospital policy

P2.10-07 DOES SHORT-TERM CESSATION OF SMOKING BEFORE LUNG RESECTIONS REDUCE THE COMPLICATION RISK?

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Background: Smoking cessation is one of the most important preoperative preparatory acts before thoracic surgery; however, the optimal timing for preoperative smoking cessation has not been clarified. In this study, we examined the effect of short-term smoking cessation before pulmonary resection for preventing postoperative pulmonary complications (PPCs). **Method:** We enrolled 753patients who underwent curative surgical resection for thoracic malignancies from 3institutions. We instructed patients with a smoking history to quit smoking by at least four weeks prior to surgery in order to reduce the incidence of pulmonary events. We collected information on the preoperative smoking status, duration of smoking cessation before surgery, and occurrence of postoperative pulmonary complications. Study subjects were classified into three groups based on their smoking status. Recent smokers were defined as any who had smoked within two months before surgery, and former smokers were defined as those who had abstained from smoking for more than two months prior to the operation. Never-smokers were defined as those who had never smoked. We examined the relationship between the duration of the preoperative smoke-free period and the development of PPCs. **Result:** The mean age of the patients was 68 years old, including 426 males and 327 females. Former smoker accounted for 48% (n =361) of the cases, followed by never smokers (n=287, 38%) and recent smokers (n=105, 14%). Surgery was performed for 660 primary lung cancer and 93 metastatic lung tumor. The types of procedures performed included lobectomy (n=542), pneumonectomy (n=11), wedge resection (n=167) and segmentectomy (n=33). PPCS were observed 62 cases (8%) among all patients. The incidence of PPCS among recent, former and never-smokers was 15%, 8% and 6%, respectively (p=0.01). The mean duration of post-operative chest tube drainage among recent, former and never-smokers 3.2, 2.2 and 2.2 days, respectively (p=0.04). The mean post-operative hospital stay among recent, former and never-smokers was 12.1, 10.6 and 10.2 days, respectively (p=0.07). There were no cases of 30-day mortality.

Table Relationship between characteristics of the patients, outcome and smoking status

Factor	Never smokers (n=287)	Former smokers (n=361)	Recent smokers (n=105)	p-value
Mean age	68.4 (38-90)	67.6 (21-92)	65.6 (28-86)	0.15
Gender				
male	67 (23%)	280 (78%)	79 (75%)	<0.01
female	220 (77%)	81 (22%)	26 (24%)	
%VC	106.2%	103.1%	102.3%	0.02
FEV1.0%	76.7%	72.8%	71.5%	<0.01
Surgical procedure				
partial resection	57 (20%)	93 (26%)	17 (16%)	0.08
segmentectomy	15 (5%)	15 (4%)	3 (3%)	
lobectomy	214 (75%)	245 (68%)	83 (79%)	
pneumonectomy	1 (1%)	8 (2%)	2 (2%)	
PPCs				
No	270 (94%)	332 (92%)	89 (85%)	0.01
Yes	17 (6%)	29 (8%)	16 (15%)	
Mean hospital stay	10.2 (1-23)	10.6 (2-73)	12.1 (1-73)	0.07
Mortality	0 (0%)	0 (0%)	0 (0%)	1.00

Conclusion: Cigarette smoking was associated with PPCS such as respiratory failure, pneumonia, empyema, atelectasis and prolonged air leakage. In addition, cigarette smoking generated a harmful effect for post-operative short-term outcome. Smoking abstinence for at least 2 months prior to surgery was not shown to reduce the incidence of PPCs.

Keywords: smoking cessation, surgical resection, post-operative pulmonary complication

P2.10-08 ASSOCIATION BETWEEN SMOKING AND ANXIETY/DEPRESSION IN RESPIRATORY TRACT CANCERS

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Background: Several studies have shown that depression can reduce patients' immune and endocrine functions. The prevalence of depression and anxiety is the highest among respiratory tract cancers, which in turn has a negative impact on treatment outcomes. Interestingly, patients with lung cancer have the highest rates of depression when compared to those with other types of cancers. We believe one possible reason for this is that they may suffer from the stigma that lung cancer is self-induced by smoking. Society has shifted perspectives greatly on how smoking is viewed. From widely disseminated anti-smoking ads to increased political campaigns and regulations to ban smoking in public spaces, lung cancer has now become almost synonymous with a disease of smoking. In this study, we analyzed the association between PHQ-4 scores and smoking status in lung and head and neck cancer patients. **Method:** Medical records for 395 lung and head and neck cancer patients (never smokers=83, former smokers=142, and current smokers=170) at University of Illinois Hospital were assessed using the validated Patient Health Questionnaire (PHQ-4) scale, a four-item health questionnaire that measures anxiety and depression. Patient data from the two-year time May 2016 to Aug 2018 was matched for important demographics like age, race, sex, and cancer diagnosis. Multivariate analyses examined correlations between PHQ-4 score, smoking status (based on CDC definitions), and other characteristics including: insurance, pain level, fatigue level, level of physical concern, level of physical activity, **Result:** Being a current smoker demonstrated a very strong correlation with elevated anxiety and

depression levels (p = 0.0003), while being a former smoker did not have the same effect. Insurance also had a significant positive correlation, with Medicaid patients having the highest average PHQ-4 score (p = 0.02). As expected, pain, fatigue, physical concerns, and physical activity scores were also highly correlated with depression and anxiety with p < 0.0001 for all of these measures. A multivariate model adjusting for the most salient patient parameters affecting PHQ-4 distress scores was generated and found that being a smoker had a significant increase on PHQ-4 score of on average 0.84 points over non-smokers (p = 0.03). In this model, pain, fatigue, and physical concerns also had increases of 0.14, 0.22, and 0.25 respectively in PHQ-4 scores (p = 0.0046, p < 0.0001, and p < 0.0001). **Conclusion:** Our findings show that there is a correlation between smoking status, and PHQ-4 scores in lung and head and neck cancer patients. Distress and anxiety can interfere with a patient's ability to effectively cope with cancer, its physical symptoms, and its treatment. Thus, screening for anxiety and depression, identifying it, and referring patients to smoking cessation clinics and other supportive services is an integral part of cancer treatment. Since lung and head and neck cancers are associated with smoking, patients feel that their smoking is the culprit of the disease, and this in turn can lead to self-inflicted stigma. We are currently investigating whether higher PHQ-4 scores in lung and head and neck cancer patients are correlated with higher levels of perceived cancer-related stigma.

Keywords: Distress Screening, Treatment care concerns, Psychosocial aspects of lung cancer

P2.10-09 ENVIRONMENTAL POLLUTION IN THE CITY OF MEXICO AS A RISK FACTOR FOR LUNG CANCER AND ITS PROGNOSTIC IMPACT

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Background: Lung cancer is the leading cancer in incidence and mortality worldwide. Smoking is the main risk factor, however, in Mexico up to 40% of the population has no history of smoking and its development has been associated with other risk factors such as chronic exposure to wood smoke and environmental pollution. Mexico City and the Metropolitan Area of the State of Mexico have high levels of environmental pollution. In this work, we analyze the prognostic impact of environmental pollution in lung cancer among patients diagnosed with lung cancer who live in those highly polluted areas. **Method:** We retrospectively analyzed patients diagnosed with non-small cell lung cancer (NSCLC) treated at the National Institute of Cancer, who lived in Mexico City or in the State of Mexico within 10 years before diagnosis of NSCLC. We correlated pollution indexes according with the Atmospheric Monitoring System of the Goverment of Mexico City (http://www.aire.cdmx.gob.mx/default.php?opc=%27YqBhnmU=%27), with the coordinates of their home (Google Maps / Earth R Studio program) to analyze the intensity of contamination with survival. In addition, we correlated the contamination indexes with the degree of differentiation, molecular profile, gender and with the stage at the time of diagnosis. **Result:** We analyzed the information of 422 patients diagnosed with NSCLC treated in the period between 2011 and 2018. The median age was 62.4 years (SD ± 12.5), 56.6% were women, 41.5% were non-smokers. At the time of diagnosis, 80% were stage IV and 15% stage III. The histology was adenocarcinoma (83%), squamous (10.4%) and small cells (4%). EGFR mutation was detected in 26.5% of the patients and PD-L1 was positive in 2.6% (analyzed 128/422, clone SP263). At the time of this analysis, 43% of the patients had died. The risk of death was higher among patients with the combination of smoking and living in highly polluted areas (RR 9.3), followed those living in highly polluted rates (RR 6.1). Patients living in highly polluted areas showed an increased incidence of poorly differentiated tumors than those who lived in different areas (72% vs 23%); also, a lower incidence of EGFR mutations was detected. **Conclusion:** High pollution rates are associated with more aggressive tumors and poor prognosis. According with our results, combination of high levels of environmental pollution and smoking had a significant impact in decreased survival. More studies are required to confirm the association between pollution and survival outcomes, also, this study established a baseline to new analysis like massive sequencing of genes to identify associations between NSCLC diagnosis and smoking versus NSCLC and environmental pollution, which could have prognostic and therapeutic implications (eg, response to immunotherapy).

Keywords: contamination, NSCLC, environmental pollution

P2.10-10 IMPACT OF SCHOOL BASED ANTI-TOBACCO EDUCATION FOR KNOWLEDGE ENHANCEMENT AMONG HIGH SCHOOL CHILDREN OF ERNAKULAM CITY, INDIA

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Background: Tobacco is considered to be the single largest cause of premature death, which kills more than 6 million people globally every year. The mortality due to tobacco is more than that associated with tuberculosis, HIV/AIDS, and malaria combined. The state of Kerala, located in the south west corner of India, also suffers from the tobacco menace in spite of its high literacy and better health care systems. The Global Adult Tobacco Survey reports that the prevalence of any form of tobacco use in Kerala among the adult male population is 35.5%. GYTS also pointed out that second hand smoke exposure was found among one in five students at homes, where others smoked. This study was conducted to understand the extent of knowledge pertaining to tobacco before and after conducting awareness programs in schools of Ernakulam city of central Kerala, India. **Method:** The study was conducted in the Ernakulam city of Ernakulam District located in the central part of Kerala, India. A multistage cluster sampling design was adopted for selecting the study units. In Ernakulam Educational District, there are 27 Government, 57 Private aided and 14 private unaided schools. In the initial phase, giving an adequate representation, from these 18 schools was selected randomly (5 Government, 10 private aided and 3 private unaided schools). From each school, 2 divisions were randomly selected in the next stage. A cross-sectional study was conducted in these 18 schools (36 divisions with a sample population of more than 1000 high school children) using a pretested semi structured questionnaire where in, students tobacco use, knowledge on tobacco hazards before and after delivering anti-tobacco messages, were collected. The data obtained was subjected to statistical analysis using SPSS software version 16. **Result:** The overall prevalence of students who reported users of tobacco in the current academic year was 7.2% (95% CI 5.74–8.72). Knowledge assessment scores revealed a statistically significant increase in the mean knowledge scores after post training evaluation (mean score = 9.84) when compared to pre training evaluation (mean score = 7.85). The age-wise comparison of knowledge scores during both pre and post evaluations showed significant difference between the age groups (p>0.05). **Conclusion:** Adolescent health education, targeting tobacco in particular, should be implemented in schools and has to be continued systematically. Apart from anti-tobacco awareness programs, strict monitoring of tobacco products trade near educational institutions has to be conducted consistently to curb this tobacco menace.

Keywords: anti-tobacco education, high school children, knowledge assessment

P2.10-11 THE RELATIONSHIP AND SIGNIFICANCE OF ASBESTOS BODIES AND FIBERS IN THE LUNG FOR THE COMPENSATION OF ASBESTOS-RELATED LUNG CANCER IN JAPAN

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Background: From the Helsinki criteria 1997, for the criteria of asbestos in the lung tissues for asbestos-related lung cancer patients is more than 5,000-15,000 asbestos bodies or more than 5 million asbestos fibers(more than 1 micrometer) per 1gram of dry lung tissues. Therefore, we examined the relation between numbers of asbestos bodies and fibers in the same patients was studied and also checked the kind of asbestos fibers and verified the validity. **Method:** Total 201 lung tissues from lung cancer patients obtained by surgery or autopsy were examined by the method of Kohyama using sodium hypochlorite. The number of asbestos bodies were counted by phase-contrast microscopy and numbers and kinds of asbestos fibers were counted by transmission electron microscopy

using metal analyzer. The number of asbestos bodies was classified into 4 divisons for asbestos –related lung cancer whose asbetos bodies are more or less than 5,000 asbestos bodies and more than 1 micrometer asbestos fibers are more or less than 5 million per 1 gram of dry lung tisses. **Result:** The number of asbestos bodies and fibers are positive co-relation with a correlation coefficient of 0.703. There are 21 cases whose more than 1 micrometer asbestos fibers are more than 5 million in spite of lower than 5,000 asbestos bodies per 1 gram. As the main component of asbestos fibers, 10 cases are crocidolite, 6 chrysotile, 4 tremolite/actinolite and one amosite. For the occupational histories, 6 cases are construction workers 4 cases are asbestos material producer and each 2 cases are shipbuilder and steel maker. **Conclusion:** The number of asbestos bodies and fibers in the lung are positive co-relation. There are 21 cases whose asbestos bodies in the lung are less than 5,000, but more than 1 micrometer asbestos fibers are more than 5 million. who should be compensated as asbestos-related lung cancer in Japan. Occupational histories are important for these cases approval of compensation of asbestos-related lung cancer and the count of asbestos fibers in the lung is important in spite of the lack of the count of asbestos bodies approved compensation criteria.

P2.10-12 CLINICOPATHOLOGICAL ANALYSIS OF THE LUNG CANCER PATIENTS WHO HAVE HISTORY OF ASBESTOS EXPOSURE

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Background: Because of the delayed cessation of the asbestos use in industry, the malignant pleural mesothelioma patients are increasing in Japan. Simultaneously, lung cancer patients, who have history of asbestos exposure, is increasing in our hospital. **Method:** We analyzed the characteristics of the lung cancer with the history of asbestos exposure. This study enrolled 1216 patients operated on in our department with a diagnosis of lung cancer since January 2003 to March 2018. Among them, 153 patients (12.6%) had the history of asbestos exposure. **Result:** The patients were 145 men and 8 women, the age were 47 to 83 (mean 70) years old, shipyard workers were 22 men. 64 patients pointed out by the regular medical checkup, 61 were in the middle of detailed examination for other disease, 10 had hemoptysis, and 9 patients were suffering from cough. The affected sites were right 92, left 61. The operative procedures were pneumonectomy 2, lobectomy 116, segmentectomy 8 and wedge resection 21. Postoperative complications were 49 episodes in total, such as bronchopleural fistula, pneumonia, ALI. 30 days mortality was 3cases (0.02%). The histology were adenocarcinoma 87, Squamous cell carcinoma 49, adenosquamous cell carcinoma 5, small cell carcinoma 4, Large cell carcinoma 2, and LCNEC 4. The postsurgical stage (UICC ver,6, UICCver.7) were StageIA(33%,33%),IB(29%,33%),IIA (7.8%,5.8%), IIB(9.8%,8.1%),IIIA(3.9%,17.4%),IIIB(5.9%,0%),IV(2.0%,1.2%), respectively. Over all 5 years survival rate was 62.1%. Asbestos bodies count (by Smith method) were analyzed for 51 cases. The numbers were 3 to 718041 AB/g dry lung. **Conclusion:** The characteristics of the lung cancer patients who have history of asbestos exposure were not unique, and no very special issues, in the aspects of symptom, histology and prognosis.

Keywords: Lung cancer, asbestos

P2.10-13 EFFECTS OF THE ADVANCED TOBACCO CONTROL TRAINING (ATCT) ON HEALTHCARE PROFESSIONALS' SMOKING CESSATION KNOWLEDGE AND COUNSELING

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Background: Smoking is the major threat to health and it may cause cancer and many chronic illnesses. Due to nature of nicotine dependence, it is not easy to quit smoking. Trained health care personnel play important roles in helping people in smoking cessation (SC). This study is part of a national project. The purpose of the study is to (1) explore the influencing factors related to providing SC counseling interventions among healthcare professionals; and (2) examine the effects of an "advanced tobacco control (ATC) in healthcare professionals of its effects on their SC knowledge, attitudes and providing SC counseling. **Method:** It is a health outcome research with pretest-post-test design. Eligible subjects were health care professionals with basic knowledge of tobacco control. In Taiwan, a national advanced tobacco control training (ATCT) was applied for them and examine of its further effects. A total of 383 subjects participated the study (combining from four groups of trainings). The self-report questionnaire was used before the ATCT as baseline data (T0). The 3 and 6 months post-training examination were again delivered (T1 & T2). A generalized estimating equation (GEE) was used for data analyses. **Result:** Several important findings were found. (1) Subjects with more knowledge, more positive attitude, less barriers, and higher self-efficacy reported to provide more smoking cessation counseling to smokers. (2) Subjects had significantly higher scores in knowledge, more positive attitudes and increasing providing smoking cessation counseling in 3 and 6 month post-training compared to before training the basic point. **Conclusion:** The advanced tobacco control training (ATCT) has short-term (3 month) and lasting effects (6 months) on providing smoking cessation counseling to smokers. It suggests that the ATCT is effective and worthwhile to implement nationally and internationally to enhance the effect the tobacco control.

Keywords: Tobacco Control, Smoking Cessation Counseling

P2.10-14 PREVALENCE, PATTERN, AND INTENTION TO QUIT USE OF SMOKED TOBACCO IN A RURAL COMMUNITY IN SOUTH EASTERN NIGERIA

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Background: Introduction Prevalence studies have consistently reported higher rates of tobacco use in the South-Eastern parts of Nigeria but little is known about the pattern and intention to quit use of smoked tobacco in these parts of the country. The aim of this study was to determine the prevalence, pattern, and intention to quit use of smoked tobacco, among residents of Ukpo community of southeastern Nigeria. **Method:** A cross-sectional descriptive study was carried out among 490 residents of Ukpo community selected using a two-stage sampling method. Data was collected using anonymous pre-tested interviewer-administered questionnaires adapted from the Global Adult Tobacco Survey. Odd ratios and 95% confidence intervals were computed and P values of < 0.05 were considered statistically significant. **Result:** The results showed that there were male respondents 300(61.2%) than females 190(38.8%). The age range was 20-70 years with a mean of 42.18 ± 15.412 years. About one quarter, 116 (23.7%) were ever-users of smoked tobacco with 69 (14.8%) remaining as current users. Cigarette 93 (80.2%) was the most common form used. Majority 41(59%) use within 5 minutes after waking up, 11 (15%) within 6-10 minutes, 3 (4%) within 31-60 minutes. The highest prevalence was among the age group 81-100 with 4 people (66.7%) followed by age group 71-80 with 4 people (36.4%). More males 105(35.0%) than females 11(5.8%) were ever users. For marital status, the highest prevalence was among widowed with 36 people (83.7%). Of 116 smokers who visited the hospital, only 36(16.7%) were asked if they use smoked tobacco and 29 (25%) were advised to stop and 68 (58.6%) were willing to quit. Majority of people tried to quit through counseling at a cessation clinic 22 (10.2%), followed by nicotine replacement therapy 15 (6.9%). Age (p<0.055) male gender (p<0.0001), tribe (p<0.003), and low educational attainment (p<0.003) were significantly associated with smoking. **Conclusion:** Efforts targeted at raising community awareness of the health effects of smoked tobacco use are needed in rural communities where tobacco use is disproportionately high. Programs should be directed at older males with lower levels of education.

Keywords: Prevalence, Pattern, Intention to quit use of smoked tobacco

POSTERS

P2.10-15 LUNG CANCER AND SMOKING RELATED MYTHS AMONG GENERAL POPULATION: DO WE NEED TO MAKE PEOPLE MORE AWARE?

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Background: With increasing incidence of lung cancer, there are various myths regarding lung cancer and smoking related facts among general population. Myths in present digital era spread like wildfire and can be harmful to people. This study was conducted to know general population perception about myths and facts related to smoking and associated lung cancer. **Method:** This survey was conducted at various places in Delhi-NCR about the various facts and myths about smoking and associated lung cancer among general public. People were asked to complete the survey with response from strongly agree to strongly disagree. There were 18 questions on general myths regarding smoking and lung cancer in the questionnaire. **Result:** Among 2571 participants, 67.9% and 57.6% people accepted that radiation from mobile tower and tea in plastic cups can cause lung cancer respectively. Smoking cannot cause lung cancer if diet rich in anti-oxidants is consumed was strongly agreed by 62.8% people because it prevent lung cancer. Almost 25% people strongly agreed that Hukka & E-Cigarettes are less harmful than normal cigarettes. Participants aged 50 year and above strongly agreed that cancer treatment has more side effects then benefits (0.016), Food cooked in microwave oven can cause cancer (p= 0.001), Smoking once and twice in a month don't cause Cancer (p= 0.029). Less educated people strongly agreed with most of the myths such as smoking once and twice in a month don't cause Cancer (0.02), Sugar makes cancer worse (0.008), E-Cigarettes are less harmful then cigarettes (0.002), Hukka is safe as smoke get filtered by water (0.001). However, participants with family history of cancer knows about these myths and they don't believe that E-Cigarettes are less harmful then cigarettes (p= .006), Sugar makes cancer worse (0.001), only smokers get lung cancer (0.038), no family history of cancer makes you safe from cancer (p= 0.002). **Conclusion:** There is an urgent need to make people aware regarding smoking related facts and myths along with lung cancer risk factors, symptomatology, screening, diagnosis and treatment. There is a need of more frequent population based lung cancer awareness program to make general population more informed about the lung cancer.

Keywords: Lung cancer, Myths, smoking

P2.10-16 LUNG CANCER OCCURRENCE ATTRIBUTABLE TO PASSIVE SMOKING AMONG NEVER SMOKERS IN CHINA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Quantifying lung cancer occurrence due to passive smoking is a necessary step for policy makers. The aim of this study is to estimate the proportion of lung cancer cases attributable to passive smoking among never smokers in China. **Method:** A systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. We comprehensively searched six databases up to July 2019 for original observational studies in both English and Chinese languages. Studies that reported relative risks (*RR*) or odds ratios (*OR*) for lung cancer occurrence associated with passive smoking in Chinese never smokers were included. For each selected publication, two reviewers assessed publications in English and Chinese independently and assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS). Any disagreements encountered were settled through a consensus. The population attributable fraction (PAF) was calculated using the combined proportion of lung cancer cases exposed to passive smoking and the pooled *OR* yielded from meta-analysis under the assumption of homogeneity. **Result:** Thirty-one studies (all designed as case-control) were identified, comprising 9,614 cases and 13,093 controls. The overall proportion of lung cancer cases among never smokers attributable to passive smoking was estimated at 20.5% (95% CI: 16.0% - 24.7%), based on the proportion of lung cancer cases exposed to passive smoking (61.6%) and the pooled *OR* for passive smoking and lung cancer risk of 1.50 (95% CI: 1.35-1.76).). The PAF was 15.5% (95%CI: 9.3%-21.0%) based on population-based studies and was 22.7% (95%CI: 16.6%-28.0%) based on hospital-based studies. The subgroup analysis (Table 1) showed that the PAF was similar in non-smoking men (20.9%) and women (21.3%). The proportion of lung cancer cases attributable to household passive smoking was much higher than workplace passive smoking (19.2% vs 10.5%).

Table 1 Population attributable fraction (PAF) of lung cancer caused by passive smoking among never smokers in subgroups											
subgroup	No. of studies	NOS score	cases	cases_ exposed	cases-exposed(%)	Pooled OR	95%CI	I^2	P	PAF	95%CI
Study year											
before 2000	13	6.23	2600	1639	63.04%	1.70	1.43-2.03	48.40%	0.025	25.96%	18.96% - 31.99%
after 2000	20	5.57	7000	4348	62.11%	1.50	1.31-1.72	67.60%	<0.001	20.70%	14.70% - 26.00%
Gender											
men	9	6.22	809	473	58.47%	1.55	1.10-2.19	62.00%	0.007	20.75%	5.32% - 31.77%
women	26	5.77	7248	4803	66.27%	1.49	1.34-1.66	47.80%	0.004	21.79%	16.81% - 26.35%
Region											
mainland	23	5.83	6468	3925	60.68%	1.55	1.35-1.79	67.60%	<0.001	21.53%	15.73% - 26.78%
non-mainland*	10	5.80	3132	2062	65.84%	1.61	1.36-1.90	49.00%	0.039	24.94%	17.43% - 31.19%
Exposure age											
childhood/ adulthood	5	6.40	1219	972	79.74%	1.50	1.14-1.96	52.70%	0.078	26.58%	9.79% - 39.06%
childhood	4	6.50	654	315	48.17%	1.50	1.08-2.10	43.30%	0.152	16.06%	3.57% - 25.23%
adulthood	5	6.60	835	517	61.92%	1.65	1.05-2.58	69.70%	0.010	24.39%	2.95% - 37.92%
Cancer type											
all types	28	5.89	7642	4759	62.27%	1.62	1.44-1.82	59.80%	<0.001	23.83%	19.03% - 28.06%
adenocarcinoma	10	6.10	2485	1627	65.47%	1.52	1.20-1.91	67.80%	0.001	22.40%	10.91% - 31.19%
squamous cell carcinoma	3	6.67	101	57	56.44%	1.36	0.80-2.32	0.00%	0.400	14.94%	-14.11% - 32.11%
Publication language											
EN	22	5.87	7082	4633	65.42%	1.40	1.27-1.54	35.40%	0.049	18.69%	13.91% - 22.94%
CN	11	5.72	2518	1354	53.77%	1.99	1.63-2.42	55.90%	0.012	26.75%	20.78% - 31.55%
Source of passive smoking											
household/ workplace	19	5.73	5183	3668	70.77%	1.70	1.46-1.99	72.20%	<0.001	29.14%	22.30% - 35.21%
household	7	6.14	1170	595	50.85%	1.67	1.32-2.10	41.40%	0.115	20.40%	12.33% - 26.64%
workplace	5	6.40	1178	245	20.80%	2.01	1.62-2.50	0.00%	0.514	10.45%	7.96% - 12.48%
Study setting											
hospital-based	24	5.60	7428	4767	64.18%	1.67	1.47-1.9	68.50%	<0.001	25.75%	20.52% - 30.40%
population-based	9	6.44	2172	1220	56.17%	1.31	1.14-1.51	0.00%	0.464	13.29%	6.90% - 18.97%

Conclusion: Around 20% of lung cancer cases in never smokers, both men and women, are potentially attributable to passive smoking in China. These lung cancer cases in never smokers might be potentially prevented by eliminating exposure to passive smoking, in particular with regards to household passive smoking.

Keywords: Environmental Tobacco Smoke, Lung cancer, Population attributable fraction

P2.11-01 NOVEL FLEXIBLE LONGITUDINAL MACHINE LEARNING COUPLED WITH PATIENT DEMOGRAPHICS IMPROVES LUNG CANCER RISK PREDICTION USING WHOLE SCREENING CTS

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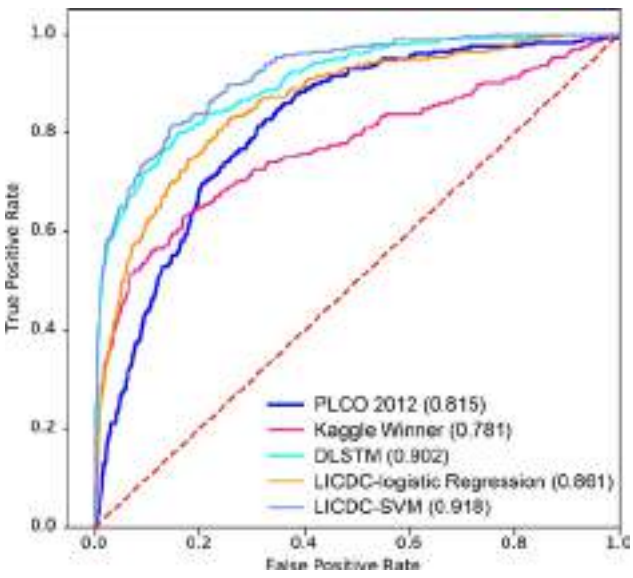
Background: The inherent variability of screening scans in clinical practice limits existing machine and deep learning techniques, who have difficulty accessing all available information. As a result, cohorts are less generalizable or require integrating human intervention to initiate data definition. We created a deep learning prediction model for lung cancer screening that could define temporally static and time varying imaging features and combine them with common epidemiological factors collected at the time of shared decision making. We propose a new longitudinal lung cancer detection method, called longitudinal imaging and clinical data co-learning (LICDC), which integrates the temporally flexible deep imaging features and clinical features from the PLCO model. **Method:** 722 individuals with cancer and 1072 random participants without cancer with more than one scan were selected from the NLST. We initiated the deep learning model using Kaggle contest algorithm discovered features for cancer using each CT scan (n=4781) in its entirety as an independent observation (temporally varying features are not created). We then applied our flexible long and short-term temporal memory methodology to extract additional longitudinal features and generate a neural network model. This training for the LICDC model used NLST participants (n=829) and scans (n=3588) and 826 participants (367 had multiple scans) with 1193 scans from our local screening program. Ten-fold cross-validation was performed on a participant basis. Cancer risk probabilities from imaging-only deep learning model (DLSTM) were combined with PLCO model predictions and regressed together (LICDC-Logistic Regression). Additionally, individual variables from the PLCO model and the cancer probability from DLSTM were fitted with support vector machine (SVM) method using linear kernels (LICDC-SVM) and their area under the receiver operating curve was estimated (AUC). All AUC curves were calculated from the same 1655 patients (829 from NLST and 826 from our local screening program). **Result:** PLCO's predicted risk and basic imaging features (Kaggle winner) had similar accuracy with AUC of 0.815 and 0.781, respectively. Combining risk estimates from the full longitudinal deep learning and PLCO model in a simple logistic regression increased AUC to 0.861. Re-estimation of PLCO and imaging features LICDC-SVM further increased AUC to 0.918. **Conclusion:**



Risk prediction for lung cancer in patients who are eligible for screening is improved by combining longitudinal machine learning CT imaging data with demographic information. These methods allow for risk prediction based on a complete CT imaging data set with varying time between scans and across participants without relying on a segmented nodule.

Keywords: machine learning, Lung Screening, Risk prediction

P2.11-02 INDIVIDUALIZED RISK-BASED LUNG CANCER SCREENING INCORPORATING PAST SCREENING FINDINGS AND CHANGES IN SMOKING BEHAVIORS

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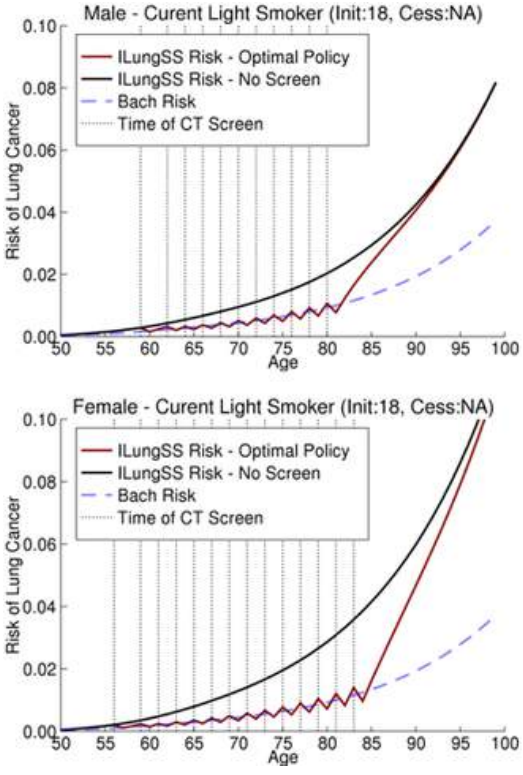
Background: Risk-based lung cancer screening guidelines are actively being pursued as an alternative to existing guidelines. However, current risk-based approaches do not capture the dynamic nature of the risk and ignore information collected from past screening findings. **Method:** We develop and apply a novel decision tool, the Individualized Lung Screening Scheduler (ILungSS), to optimize lung cancer screening for asymptomatic ever-smoked individuals by maximizing the expected quality-adjusted life years (QALYs) gained from screening. The ILungSS models health progression and smoking behavior of US ever-smokers as a dynamic and stochastic process using a partially observable Markov decision process (POMDP). A POMDP is typically used to model sequential decision making under uncertainty and provides a well-suited framework to optimize screening decisions. Screening decisions are based on the personal lung cancer risk of individuals, which is updated leveraging on information obtained from past screening exams and changes in smoking behaviors. **Result:** The ILungSS offers personalized optimal screening policies for ever smoked individuals that include the optimal screening starting and stopping ages, and screening frequency. The ILungSS offers fully dynamic screening policies and age-specific risk thresholds that define screening eligibility. The ILungSS yields higher QALYs and lung cancer-specific mortality reduction, recommends extending screening coverage to current light smokers but increases the number of screening exams as compared to the US Preventive Services Task Force (USPSTF) strategy. Upon smoking cessation, the ILungSS adjusts future screening decisions recommending less screens as compared to the USPSTF guidelines. The clear presentation of the health benefits associated with smoking cessation, in terms of personal lung cancer risk and number of recommended future screening exams, could support a smoking cessation program supplementing screening.



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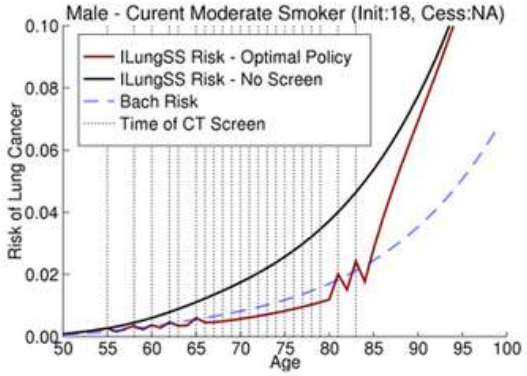

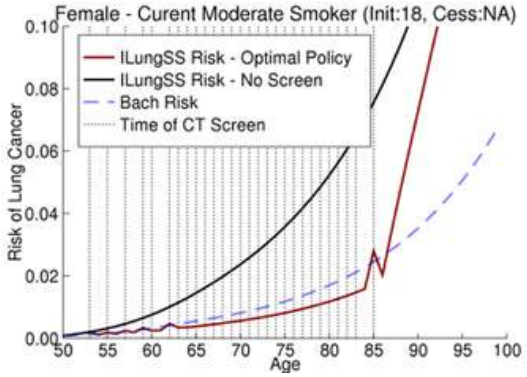

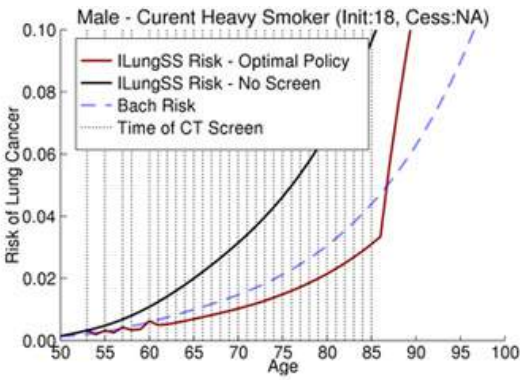

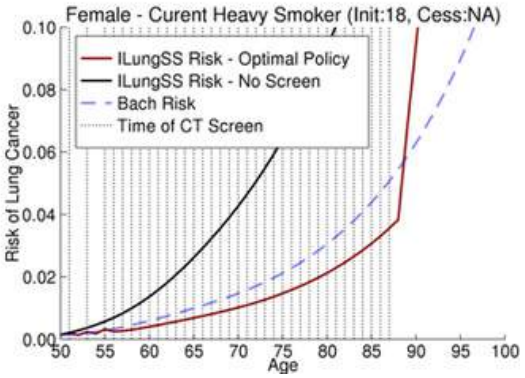

Conclusion: Personalized, dynamic risk-based lung cancer screening could improve the effectiveness of lung cancer screening. The ILungSS integrates screening with a smoking cessation program that could further improve the effectiveness of screening.

Keywords: health policy, medical decision making, lung cancer screening

P2.11-03 IMPLEMENTING PHYSICIAN EDUCATION TO INCREASE LUNG CANCER SCREENING COMPLIANCE

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. The USPSTF recommends annual low-dose CT chest (LDCT) for lung cancer screening in adults who meet the appropriate criteria: age 55-80, current smokers or former smokers who quit within 15years, with a 30 pack-year smoking history. Even with these recommendations, screening rates in these patients remain low. We created a study to assess compliance in an outpatient Internal Medicine clinic to assess the barriers for obtaining LDCT. We hypothesized that by providing an educational program, overall compliance would increase. **Method:** The study was divided in two arms: a pre-intervention arm and a post-intervention assessment. Initially, 35 physicians completed a questionnaire on their attitudes to LDCT screening and their reasons for not screening high risk patients. We created a lung cancer screening education program, which consisted of lectures provided to physicians. Following the lectures, consecutive patient visits were reviewed to assess compliance with screening. **Result:** In the first arm, 678 visits were reviewed. 115 patients met USPSTF criteria of whom 26% underwent screening. 29/546 (5%) underwent LDCT without meeting criteria. The most common reasons for not ordering LDCT scans in patients meeting criteria included: poor knowledge of criteria (22%), failure to determine if patients qualified (13%), and patient refusal (8%). Following the education, 208/955 patients reviewed met USPSTF criteria, of which 78% underwent LDCT and 27/738 (3.6%) who did not meet criteria were screened for lung cancer. Our study showed that after education, physicians were ten times more likely to screen patients for lung cancer (Odds ratio 9.98, 95% CI 5.87-16.94, p<0.0001). **Conclusion:** We confirmed there was a suboptimal adherence to established LDCT lung cancer screening guidelines, mainly due to unfamiliarity with the screening criteria. By providing educational lectures, compliance improved significantly. We concluded that educating physicians about lung cancer screening guidelines can effectively increase LDCT screening tenfold, and therefore benefit patients at high risk for developing lung cancer.

Keywords: Quality Improvement, lung cancer screening

P2.11-04 LONGITUDINAL SURVEILLANCE OF CIRCULATING TUMOR CELL IN PATIENTS WHO PRESENTED WITH RESECTABLE PULMONARY LESION SUSPICIOUS MALIGNANCY

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Background: Lung cancer is a leading cause of cancer-related death. The major factor that affect patients' survival was recurrence and could only detect by image tools. The most crucial disadvantage of image modalities was only detected the space occupying lesions instead of minimal residual disease. ((More and more undetermined lung lesions were identified by lung cancer screening and majority were early stage non small cell lung cancer. We need a less invasive tool to help us detecting minimal residual disease in order to improve patients' survival. The aim of this study was tried to clarify the clinical significance of CTCs for patients with resectable lesion suspect malignancy **Method:** From January 2017 to December 2018, 51 consecutive patients were enrolled into this study. One patient who could not tolerable tumor resection due to unstable intraoperation saturation was excluded. All patients received tumor resections. CTCs and image survey were check at scheduled time table. Data from medical record were collected and analyzed with CTCs in order to analyze the its clinical significance **Result:** Median follow-up time of 12.1 (1.5 – 23.6) months, a total of 386 CTC tests were performed in this cohort when the cutoff data was in December 2019. The mean and median number of CTC testing of the whole cohort were both 7.0 cells/mL (range, 4.0-12.0; SD, 2.4). CTC counts declined with statistical significance in all patients. CTC count declined in first 3

days was 2.2637 (cells/ ml/ day) which was statistically significant in cancer group. (P = 0.0009) The daily decline of CTC counts in lung cancer without recurrence (n=30) was 2.5359 (cells/mL/day) within the first 3 days of surgery and 1.4 (cells/mL/day) in lung cancer with recurrence (n=11). For lung cancer without relapse, the daily decline of CTC counts is statistically significant after adjust. (P=0.0068). The CTC decline in stage I and Tis group (n=26) was 2.8526 cell/ ml/ day and remained statistically significant after adjust. (P = 0.0079) **Conclusion:** CTCs had high detection rate in all clinical scenarios that could be identified in resectable undetermined lung lesions. CTC counts drop the lowest point in post-operation day 1 in all scenarios and rebound in post-operation day 3 for those patients were confirmed with relapse. Greater CTC count declined in first 3 days were identified in patients who presented with benign lesion and non small lung cancer without relapse.

Keywords: circulating tumor cell, Non small cell lung cancer, relapse predition

P2.11-05 PERIPHERAL BLOOD-BASED T CELL RECEPTOR SIGNATURES AS POTENTIAL BIOMARKERS FOR EARLY DIAGNOSIS OF LUNG CANCER

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Background: As more and more solitary pulmonary nodules (SPNs) are detected by low dose CT (LDCT) screening following with high false positive rate, early diagnosis of lung cancer is challenging. Immuno-sequencing provides a feasible strategy for investigate the immune microenvironment of SPNs. However, whether T cell receptor signatures are potential peripheral biomarkers for early diagnosis of lung cancer is unclear. **Method:** Resected SPNs, which were detected by LDCT screening, and paired peripheral blood from 92 patients were collected, including 27 benign SPNs and 65 lung cancers consisting of 15 LUSC and 50 LUAD. T cell repertoire of tissue and PBMC was evaluated by T cell receptor β genes (TCRβ) sequencing. The GLIPH-based algorithm was referenced to clustered TCR clones according to the motif, and SPN status was predicted by using the clone data from peripheral blood. **Result:** The Shannon index, indicated diversity in PBMC in malignant patients is lower than that in health cohort (p=8.2e-05). Comparing LUSC and LUAD with Benign patients, lower Shannon index was detected in LUSC patients(p=0.036). With the increase of stage, the Shannon index was gradually decreased(p=0.042). By analysis of the TCR clone similarity of tissues, more similar was found in malignant patients than benign ones (p=2.5e-11), indicating that there are some clones enriched in tumor contributing to the similarity in malignant patients. And then, to get the enriched clones, we built an algorithm which is fishing the clones by enriched motif firstly and by clone incidence secondly. Finally, we got seven enriched clones for number-limited malignant tumors. Seven enriched clones were detected in 34 malignant tissues and 4 benign tissues. Meanwhile, enriched clones also found in PBMC of 25 patients, containing 20 malignant bloods and 5 benign ones, indicating that clones relating to tumor could be a biomarker for peripheral diagnosis for lung cancer. And then we did the validations by independent sets, the sensitivity was 11.9% in 84 lung cancer patients. What's more, the specificity was 95.8% in 260 healthy cohorts, and 100% in 16 benign nodules. **Conclusion:** Our preliminary data demonstrate that the distinct immune microenvironment in different SPNs may be associated with particular pathological features. Meanwhile, our approach implied that blood TCR sequencing can provide a high specificity diagnosis of SPNs, accordingly avoiding false positive test and treatment. As the number of patients increases, a more extensive enriched-clone system that covers more population by using our strategy will be constructed.

Keywords: T cell receptor signature, liquid biopsy, early detection of lung cancer

P2.11-06 SERUM PROTEOMIC SIGNATURE AS A POTENTIAL BIOMARKER FOR SURVIVAL IN PATIENTS WITH NSCLC RECEIVING IMMUNOTHERAPY

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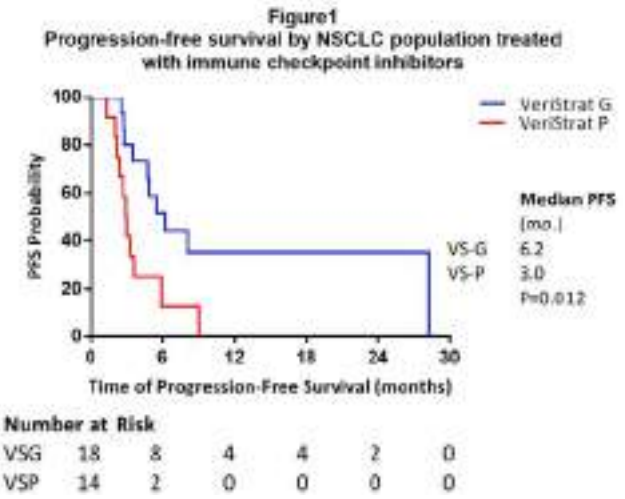
Background: The VeriStrat Test is a serum assay which uses a mass spectrometry (MS)-based proteomic signature derived from machine learning. It is currently used as a prognostic marker for patients with NSCLC receiving chemotherapy. However, little is known about its role for NSCLC patients receiving immune checkpoint inhibitors (ICIs). **Method:** This is a retrospective study that includes 47 patients with advanced stage NSCLC without an activating *EGFR* mutation, who underwent the VeriStrat Test from 2016 to 2018. Spectra from blood samples were evaluated to assign patients into the VeriStrat 'Good' (VS-G) or VeriStrat 'Poor' (VS-P) risk group. The clinical outcomes of 32 patients who received programmed cell death 1(PD-1) inhibitors nivolumab or pembrolizumab were analyzed by the VeriStrat status. **Result:** The VS-G group demonstrated significantly higher progression-free survival (PFS) and overall survival (OS) compared to the VS-P group among overall NSCLC patients regardless of treatment (median PFS of 7.1 vs. 4.2 months, p=0.013, and median OS, not reached vs. 17.2 months, p=0.012). Among NSCLC patients treated with ICIs, VS-G classification was associated with significantly increased PFS in comparison to VS-P classification (median PFS of 6.2 vs. 3.0 months, p=0.012), while the differences in OS trended towards significance (median OS, not reached vs. 16.5 months, p=0.076). Multivariate analyses showed that the VeriStrat status had a borderline significance (p=0.051) in predicting PFS in NSCLC patients treated with ICIs.



Conclusion: MS-based serum proteomic signature has a potential as a biomarker for survival outcome in NSCLC patients receiving immunotherapy.

Keywords: Serum proteomic test, Non-small cell lung cancer (NSCLC), immune checkpoint inhibitor

P2.11-07 BENEFITS AND HARMS OF CONTEMPORARY LUNG CANCER SCREENING: AN INFOGRAPHIC TO SUPPORT PUBLIC AND PATIENT EDUCATION

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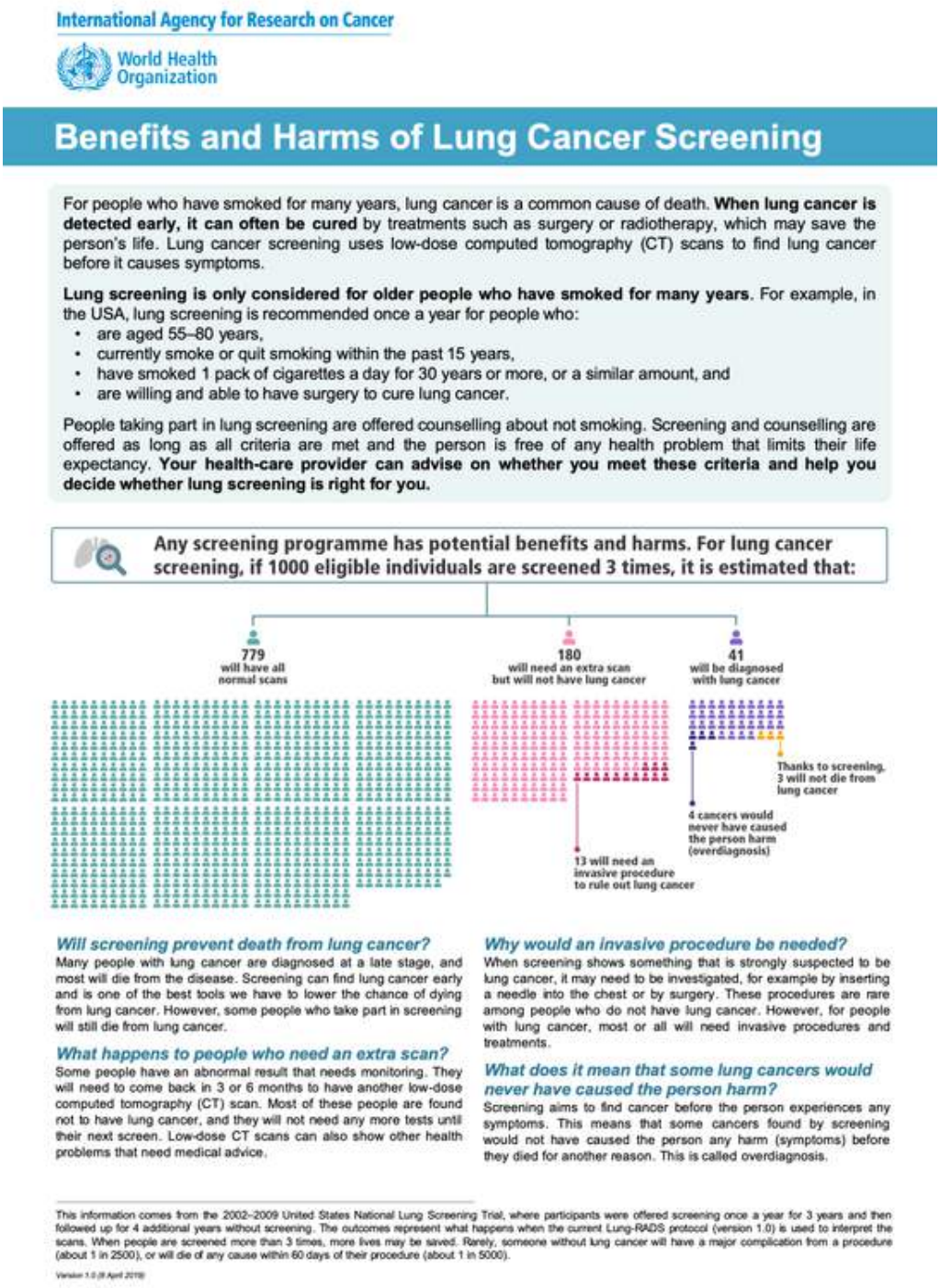
Background: Quantifying and communicating the benefits and harms of low-dose CT (LDCT) lung cancer screening is a complex challenge. Multiple tools have been developed based on the US National Lung Screening Trial (NLST). However, some of these have

produced debate and confusion in the public-facing media due to the outdatedness of the NLST protocol and the complexity of the information presented. **Method:** We developed a new infographic to represent the benefits and harms of contemporary lung screening. We applied the current US nodule management protocol (Lung-RADS v1.0) to the NLST retrospectively. Across the 3 NLST screens and 4 years of follow-up, we used individual-level data to quantify the number of people per 1000 who would have had (a) all normal results (Lung-RADS categories 1 and 2) without lung cancer; (b) any abnormal results (Lung-RADS 3 and 4A/B/X) without lung cancer; (c) invasive diagnostic procedures without lung cancer; and (d) lung cancer diagnosed. We estimated overdiagnosis using the published NLST estimate (18.5%) and reduced the mortality benefit from screening using the reduction in sensitivity from Lung-RADS (13.3%). **Result:** Applying Lung-RADS to NLST, we found that 779 per 1000 people would have had all normal results, 180 any abnormal results without lung cancer, and 41 lung cancer. Among the 180, 13 would have had an invasive procedure, 0.4 (1 in 2500) a major complication, and 0.2 (1 in 5000) death from any cause within 60 days of the procedure. Finally, among 41 lung cancers, 4 represent overdiagnosis and 3 prevented lung cancer deaths. We compiled these results into an infographic (Figure).



Conclusion: Compared with the NLST protocol, modern nodule management reduces harms from screening. Our infographic tool may facilitate communication about lung screening to providers, patients, and the public. It should be updated as additional trial data become available.

Keywords: low-dose CT screening, risk communication

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P2.11-08 CT SCREENING OF NEVER SMOKERS

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Background: We wanted to update our previous reports of the impact of SHTS on lung cancer and cardiovascular disease in never smokers and the usefulness of low-dose CT (LDCT) screening using the I-ELCAP protocol. **Method:** Never smokers, defined as having smoked less than 100 cigarettes in their lifetime, were enrolled in our LDCT screening program. All signed IRB-HIPAA compliant consents. Patient demographics, medical history, and validated SHTS-exposure questionnaire were obtained at baseline. The SHTS-exposure score was computed for all participants together with LDCT Ordinal score for coronary artery calcifications (CAC), emphysema, lung cancer diagnosis and treatment were documented. At two of the institutions, we also performed pulmonary function tests, and measured the main pulmonary artery(MPA) and ascending aorta(AA) measurements, determined the automated aortic calcium score and extent of atherosclerotic plaque present in the coronary arteries using CT angiograms. Frequency of abnormal pulmonary function (FEV1/FVC ratio<0.7) and MPA/AA ratio≥1.0 were evaluated. We examined the relationship between SHTS exposure and these disease conditions. **Result:** Among 14,018 never smokers, 6733 (48.1%) were women, 7276 (51.9%) men. Among them, 5236 (37.4%) had at least one noncalcified nodules (NCNs). Of the 14,018, 855 (6.1%) had at least one NCN 6.0 mm but less than 15.0 mm for which follow-up LDCT is recommended and 113 (0.8%) had NCN 15.0 mm or larger (Table 1). Lung cancer was diagnosed in 55 (0.4%); 53(96.4%) resulting from findings on baseline LDCT and 2(3.6%) from the subsequent annual repeat LDCTs. Of the 55, 47 (85.5%) were clinical stage I; 49 had surgical resection, 4 treated with radiation therapy, and 2 with chemotherapy. Diagnosis was adenocarcinoma in 44, squamous-cell in 7, small-cell in 1 and other in 3. Post-surgically, 45 (81.8%) of the 47 were pathologic Stage IA (T1a-1cN0M0). Of the 14,018 never smokers, the CAC score was 0 for 10,956 (78.2%), 1-3 for 1941 (13.9%), and 4-12 for 1211(8.0%). Emphysema was present in 310 (2.2%) participants. The prevalence of lung cancer (p=0.04) was significantly associated with SHTS exposure, as was CAC (p<0.0001) and emphysema (p=0.03). In the subset of participants where additional measurements are available, abnormal pulmonary function tests (p=0.04), automated aortic calcium score (p=0.009), MPA/AA ratio≥1.0 (p=0.009) and presence and extent of coronary artery plaque (p<0.0001). **Conclusion:** These results suggest that LDCT screening is of benefit for never smokers exposed to SHTS for identification of early lung cancer, cardiovascular disease and emphysema.

Keywords: secondhand tobacco smoke exposure, Lung cancer, cardiovascular disease

P2.11-09 AUSTRALIA-WIDE CROSS-SECTIONAL SURVEY OF GENERAL PRACTITIONERS' KNOWLEDGE AND PRACTICE OF LUNG CANCER SCREENING

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Background: High quality randomised controlled trials have demonstrated that low dose computed tomography (LDCT) screening reduce lung cancer deaths in high risk individuals yet current Australian guidelines do not recommend nor fund screening. 1-3 Little is known about current screening practices in Australia. **Method:** A survey was distributed to a nationally representative sample of 4 000 Australian general practitioners (GPs) registered with the commercial database of the Australasian Medical Publishing Company. The questionnaire included, respondent demographics, self-reported screening practices, knowledge of screening recommendations, recent screening education and potential factors influencing GPs' screening practice. Two logistic regression models identified factors associated with self-reported chest X-ray (CXR) or LDCT screening within the last 12 months. **Result:** A total of 323 General Practitioners attempted the survey (participation rate 8.1%); 21 were excluded as they did not report recent screening practice. Participants were mostly females (153/302, 50.6%), from collective/group practices (239/302, 79.1%) and metropolitan-based practices (222/302, 73.5%). Despite the majority of responders understanding that screening is not recommended by Australian professional societies (215/302, 71.2%) a substantial proportion of participants requested a CXR or LDCT screening (140/302, 46.4% and 63/302, 20.8% respectively). A variety of shared factors (GP reassurance, perceived cost-effectiveness of screening, believing screening is funded) and unique practice, educational and cognitive factors were associated with self-reported LDCT and CXR screening, with the strongest association being recent education about screening from radiology practices (aOR for LDCT screening 10.443, p<0.001, Table 1).

Table 1: Multivariate logistic model for factors associated with LDCT screening

Variable	Adj Odds Ratio	95% CI	P value
LDCT SCREENING			
Practice location			0.01
- Metropolitan	Reference		
- Rural or remote	2.517	1.012-6.186	
Screening funded by MBS/Medicare			0.008
- No	Reference		
- Yes	2.502	1.012-6.186	
- Don't know	0.576	0.260-1.276	
Screening education from radiology providers	10.443	4.258-25.612	<0.001
Agreeing with the following statements (Per point on a 5-point disagree-to-agree Likert scale)			
"Screening can provide me with reassurance my patient does not have lung cancer"	1.548	1.002-2.392	0.04
"Screening can lower the chance that my patient will die from lung cancer"	1.818	1.083-3.048	0.02
"Lung cancer screening would cost our society too much money"	0.622	0.423-0.915	0.02
CHEST X-RAY SCREENING			
Practice type			0.009
- Collective/Group practice	Reference		
- Solo practice	2.47	1.005-6.09	
- -Corporate practice	4.764	1.229-18.46	
Screening funded by MBS/Medicare			0.02
- No	Reference		
- Yes	2.839	1.315-6.128	
- Don't know	1.056	0.612-1.823	
Agreeing with the following statements (Per point on a 5-point disagree-to-agree Likert scale)			
"Screening can provide me with reassurance my patient does not have lung cancer"	1.357	1.016-1.811	0.04
"It is too hard for my patients to access a radiology practice with CT scans"	1.534	1.016-2.165	0.01
"I am more likely to recommend screening if my patient has respiratory symptoms like a cough or breathlessness"	1.451	1.085-1.946	0.01
"Lung cancer screening would cost our society too much money"	0.724	0.546-0.960	0.02
MBS: Medical Benefits Scheme. Alpha intercept estimates: LDCT model 0.3895 CXR model 1.8726			

Conclusion: In Australia, lung cancer screening is occurring outside a coordinated programme and there is discordance between reported screening practice and national recommendations due to a variety of factors. This highlights an urgent need for clearer guidance and direction from national and professional bodies.

Keywords: low dose CT, Screening, Early lung cancer

P2.11-10 DISCOVERY OF POTENTIAL BIOMARKERS THAT DISCRIMINATE EARLY STAGE NSCLC FROM CONTROLS BY NON-TARGETED METABOLOMICS PROFILING

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Background: Detection of NSCLC at the early stage is a potential means to reduce mortality and morbidity of lung cancer. Development of an accurate, non-invasive, economical, and safe test to detect early stage NSCLC remains a challenge. We explored metabolomics profiling of plasma to discriminate early stage NSCLC cases from Cancer-Free Controls (CFC). **Method:** Frozen plasma samples collected from 2004 to 2014 from 250 patients with clinical early stage NSCLC (drawn prior to surgical resection) and 250 CFCs were obtained from a provincial biorepository. Samples were thawed, extracted, and analyzed in duplicate by blinded laboratory

personnel using non-targeted Ultra High Performance Liquid Chromatography/Quadrupole Time-Of-Flight Mass Spectrometry (UHPLC-QTOF-MS). Individual metabolic entities were identified and quantified using Mass Profiler Professional Software (Agilent Technologies, CA, USA). Analysis was restricted to known human metabolites identified by the Metlin and Human Metabolome databases. Candidate metabolites quantified in less than 20% of samples were dropped; missing values were replaced with one-half of the smallest measurement for each metabolite. Final candidate metabolites were screened for differential abundance (DA) between NSCLC cases and CFCs using: (1) False discovery rate (FDR)-adjusted p-values less than 1% after controlling for age, sex and smoking status in linear regression; (2) <1% change in DA due to covariates; (3) up-regulation in NSCLC. **Result:** Of the 250 NSCLC Cases, 185 (74%) had adenocarcinoma, 65 (26%) had Squamous Cell Carcinoma; 204 (81.6%) had pathological Stage I/II disease (AJCC 7th ed) and 46 (18.4%) had stage III/IV disease. Median age was 70 (range 46-88) in NSCLC cases and 56 (20-89) in CFCs (p<0.001), and NSCLC cases had more males compared to CFCs (46.4% vs 31.2%, p <0.001). NSCLC patients had a higher proportion of current (27.2% vs 6%) or ex-smokers (64.8% vs 20.8%) compared to CFCs (p<0.001). A total of 1,209 known human metabolites were detected using UHPLC-QTOF-MS technique, of which 676 were present in a minimum of 80% of all samples and were used for modeling. Table 1 lists candidate metabolomics biomarkers strongly upregulated in NSCLC cases versus CFCs which were unaffected by covariates of age, sex, and smoking. A multiple logistic regression model using the top 3 metabolites correctly classified NSCLC case from CFC with an overall accuracy of 93.6% and an area under the curve of 0.975.

Table 1: Rank List of Top Potential Endogenous Metabolomics Biomarkers Which Distinguished NSCLC Cases from Controls.

Rank	Metabolite	Classification	ESI mode	Log_2 Fold Change	FDR-adjusted P-Value
1	N-Acetylornithine	Amino Acid Derivative	+	8.9273	<0.00001
2	13S-hydroxyoctadecadienoic acid	Fatty Acyl	+	8.9191	<0.00001
3	9,10-Epoxyoctadecenoic acid	Fatty Acyl	+	8.9191	<0.00001
4	Alpha-dimorphecolic acid	Fatty Acyl	+	8.9191	<0.00001
5	12,13-EpOME	Fatty Acyl	+	8.8911	<0.00001
6	Dodecanedioylcarnitine	Hydroxy Acid	+	10.0674	<0.00001
7	PI(16:0/18:1(11Z))	Glycerophospholipid	+	7.3867	<0.00001
8	PI(16:0/18:1(9Z))	Glycerophospholipid	+	7.3867	<0.00001
9	PI(16:1(9Z)/18:0)	Glycerophospholipid	+	7.3867	<0.00001
10	PI(18:0/16:1(9Z))	Glycerophospholipid	+	7.3867	<0.00001
11	PI(18:1(11Z)/16:0)	Glycerophospholipid	+	7.3867	<0.00001
12	PI(18:1(9Z)/16:0)	Glycerophospholipid	+	7.3867	<0.00001
13	PI(16:0/18:0)	Glycerophospholipid	+	6.8392	<0.00001
14	PI(18:0/16:0)	Glycerophospholipid	+	6.8392	<0.00001
15	17-Hydroxyprogesterone	Steroid	+	5.4172	<0.00001
16	Deoxycorticosterone	Steroid	+	5.2858	<0.00001
17	Nonanoylcarnitine	Hydroxy Acid	+	4.2974	<0.00001
18	1b,3a,12a-Trihydroxy-5b-cholanoic acid	Steroid	-	5.5153	<0.00001
19	Cholic acid	Steroid	-	5.5153	<0.00001
20	Ursocholic acid	Steroid	-	5.5153	<0.00001
21	Arachidonic acid	Fatty Acyl	-	4.7791	<0.00001
22	8,11,14,17-Eicosatetraenoic acid	Fatty Acyl	-	4.7791	<0.00001
23	Farnesol	Prenol Lipids	-	4.8348	<0.00001
24	Cinnamic acid	Cinnamic Acids	+	1.9656	0.0188

Legend: ESI = Electrospray Ionization Detection Mode; FDR = False Discovery Rate

Conclusion: Metabolomics profiling of plasma represents a potential means to distinguish NSCLC cases from CFCs. Further targeted metabolomics analyses of specific classes of metabolites in larger cohorts are warranted.

Keywords: early detection, metabolomics, Biomarker

P2.11-11 EXOSOMAL MIRNAS AS DIAGNOSIS BIOMARKERS FOR DISTINGUISHING BENIGN AND MALIGNANT NODULES IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the most common malignancy worldwide with the highest morbidity and mortality. The milestone National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer-specific mortality in high-risk individuals with screening low-dose computed tomography (LDCT). However, the high false positive rate of LDCT demands more accurate diagnostic technique. Liquid biopsy represent a valuable non-invasive approach when tumors are not suitable for biopsy or resection. Till now, it is rare to see the studies on plasma exosome-derived miRNAs as early diagnosis biomarkers to distinguish benign and malignant nodules based on miRNA sequencing. **Method:** Forty-eight patients including twenty-eight lung adenocarcinoma and twenty benign nodules with various pathological characteristics (granuloma, atypical neoplasia, fibrosis, tuberculosis, and other benign types) were enrolled as a training cohort. A testing cohort consisted of 46 patients with benign and malignant nodules. Exosomes were precipitated from the plasma of patients, and RNA sequencing were performed to identify the differential expressed miRNAs. The statistical model was trained and tested to discriminate benign nodules from malignant ones. **Result:** The typical exosome markers CD9 and CD63 were successfully confirmed by western blotting of extracted exosomes. Seven differential expressed miRNAs (let-7b-3p, let-7d-3p, miR-150-5p, miR-30e-5p, miR-125b-5p, miR-361-5p, and miR-378c) with median expression > 50 were selected by LASSO-penalized regression to classify the samples into correct groups. LOO-CV (leave one out cross validation) was used to stabilize the model parameter with minimal error rate (16.7%). ROC curves with area under curve (AUC) of the model are achieved to 0.952, while sensitivity and specificity of distinguishing between benign and malignant nodules were 93% and 85%, respectively. In addition, the AUC in a part of testing cohort (1 benign and 11 tumor) was up to 1.000. The rest samples of testing cohort were being detected using RNA sequencing. **Conclusion:** This study using plasma exosome-derived miRNA sequencing identified seven miRNAs to train and test a model to distinguish benign and malignant nodules, which provides insights into the feasibility of exosomal miRNA as a novel early diagnosis approach for lung cancer.

Keywords: Non-Small Cell Lung Cancer, miRNAs biomarkers, exosome

P2.11-12 SPUTUM LIQUID BIOPSY PROVIDES A NON-INVASIVE MODALITY TO ASSESS DRIVER MUTATIONS AND TUMOR HETEROGENEITY IN NSCLC

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Background: The incidence of lung cancer has significantly increased over the last century and remains the most common cause of cancer death worldwide. Our better understanding of the tumor microenvironment and of how tumors interacts with the host systemically, combined with the recent advent of the liquid biopsy, may allow non-invasive, assessment of tumor heterogeneity and evolution. Sputum has been used for the investigation of biomarkers in lung cancer since it carries airway epithelial cells, and molecular alterations identified in sputum are most likely to reflect tumor-associated changes. Our aim is to evaluate whether the molecular alterations identified in the sputum is representative of the mutations found in the tumor. **Method:** Sputum samples were prospectively collected from 30 patients with lung adenocarcinoma at AC Camargo Cancer Center, from January 2017 till November 2018. Samples were collected at the time of diagnosis for further evaluation of actionable mutations in 14 genes, including *EGFR, KRAS, BRAF* and *NRAS*. Driver mutations were detected in 16 (53%) patients in tissue biopsy (six in *KRAS* and 10 in *EGFR*), and 2 cases also had *EGFR* T790M detected in circulating tumor DNA (ctDNA) isolated from plasma after disease progression post EGFR-TKI. **Result:** Mutations were detected in 9 out of 16 sputum samples with previously known driver mutations: 3/7 with *KRAS* mutation (codon 12 and 61) and 6/9 with *EGFR* with (four exon 19 deletions, five L858R point mutations and one exon 18 G719A). Two patients with mutant *KRAS* detected in their sputum, did not exhibit *KRAS* mutations in tissue biopsy of primary tumor. One of them had a *KRAS* mutation detected only in a metachronous brain metastasis. *EGFR* T790M mutation was detected in sputum in 1 out of two samples previously positive for T790M in plasma ctDNA. All seven sputum samples negative for mutations were derived from peripheral lesions or cases with low tumor burden. **Conclusion:** As a preliminary result, analysis of driver mutations in sputum had a good correlation with tissue biopsy (60%), especially in patients with centrally located tumors and high tumor burden, and seems to reflect tumor heterogeneity.

Keyword: liquid biopsy, sputum, non-invasive approach, driver mutation, lung adenocarcinoma

POSTERS

P2.11-13 WHAT IS THE IMPACT OF LOCALISED DATA WHEN TRAINING DEEP NEURAL NETWORKS FOR LUNG CANCER PREDICTION?

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Background: Deep neural networks (DNN) have been shown to offer a viable alternative for risk cancer prediction of indeterminate pulmonary nodules (IPNs). While the type of data used for training is known to impact performance, this issue has not been extensively studied. We present, for the first time, a study of the effect of including training data that matches the clinical pathway of the independent validation dataset, a nodule clinic of incidental findings. **Method:** Two identical DNNs were trained on the task of diagnosis prediction of pulmonary nodules from CT images. The first one (*DNNnlst*) used purely screening data from the US National Lung Screening Trial (922 cancer and 14733 benign nodules), while the second one (*DNNnlst+incidental*) included data of incidentally detected nodules from European hospitals (1064 cancer and 7207 benign nodules). Both models were evaluated in an independent validation set of nodules coming from a referral center in the UK (Royal Brompton and Harefield Hospital, London) consisting of baseline scans of 406 cancer and 325 benign nodules. The models were compared in terms of AUC, as well as their ability to reclassify cancer patients with intermediate risk nodules. The Intermediate risk sub-population was defined by selecting patients with nodules in the size range of 8 to 15mm, and who were followed-up within a year with CT, referred to PET-CT, or referred to biopsy. Within this sub-population, a cancer prevalence of 30% was assumed. The operating points of the cancer prediction models were chosen by setting a cancer risk of 70%, corresponding to high-risk nodules in the guidelines of the British Thoracic Society. **Result:** The *DNNnlst* and *DNNnlst+incidental* models achieved an AUC of 84.33 (95%CI: 81.49, 87.15) and 87.43 (95%CI: 84.79, 89.82) respectively on the entire validation set, showing an improvement in the discrimination capabilities ($p < 0.01$). For reference, using the nodule's maximum axial diameter as a predictor led to an AUC of 79.07 (95%CI: 75.73, 82.73). Additionally, considering only the intermediate risk population of the data, all of which would require workup according to guidelines, the *DNNnlst+incidental* model correctly classified as high risk 34.34% more cases than the *DNNnlst model (sensitivity* 59.39% (95%CI: 47.68, 75.17) vs. 44.21% (95%CI: 20.98, 64.42)), an improvement significant at $p < 0.05$. **Conclusion:** Although a DNN trained only on the US lung cancer screening data could have clinical utility in an incidental setting, exposing it to further incidental data can not only increase its discriminability, as expected, but also make it a potentially more effective tool for speeding up the diagnosis of cancer patients with intermediate risk nodules and reducing unnecessary workups.

Keywords: AI, early detection, Lung cancer

P2.11-14 EVOLUTIONARY ACTION SCORE OF TP53 PREDICTS THE PROGNOSIS OF PATIENTS WITH STAGE I LUNG ADENOCARCINOMA

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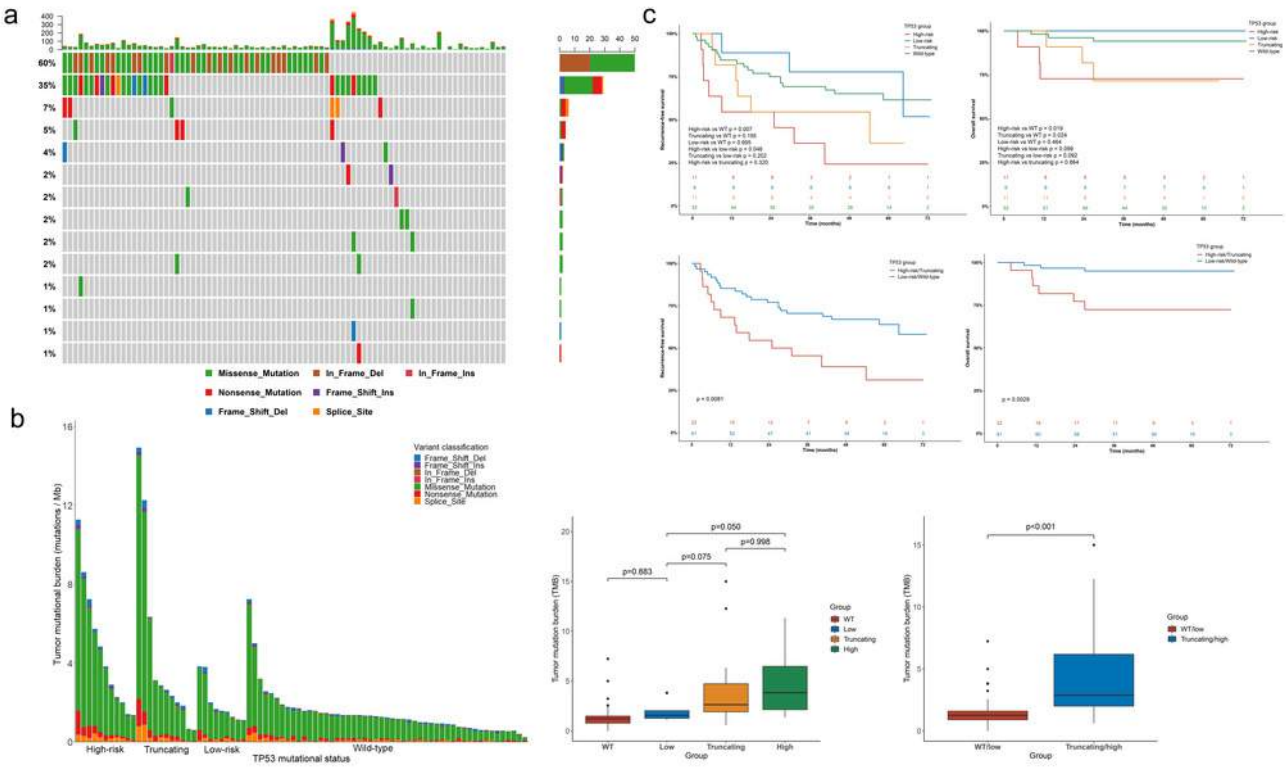
Background: Several studies have reported that *TP53* mutations were associated with poor prognoses for patients with non-small-cell lung cancer. *TP53* was reported to have a mutation rate of 46% in lung adenocarcinoma patients. Whether these mutations are of the same prognostic value is questionable. Here we use an algorithm named Evolutionary Action of *TP53* (EAp53) which stratifies *TP53* missense mutations into high-risk and low-risk groups based on the scores calculated to see whether different types of *TP53* mutations are of prognostic value for patients with stage I lung adenocarcinoma. **Method:** Whole-exome sequencing was performed on 83 patients who underwent surgery and with a pathologically confirmed adenocarcinoma between January 2011 and August 2013 at Fudan University Shanghai Cancer Center. No patient underwent neoadjuvant therapy. Missense *TP53* mutations were classified to low-risk and high-risk groups according to their EAp53 score, which assesses the genotype-phenotype perturbation of point mutations. Patients were divided into 4 groups based on *TP53* mutational status: wild-type *TP53*, truncating mutations, including frame-shift mutations, nonsense mutations, small indels, and splice-site mutations; high-risk missense mutations, defined as missense mutations with an EAp53 score >75.00; low-risk missense mutations, defined as missense mutations with an EAp53 score ≤75.00. **Result:** Mutations of major driver genes, tumor suppressor genes and genes of interest for lung adenocarcinoma, including *EGFR* (60%), *TP53* (35%), *RB1* (7%), *RBM10* (5%), *NF1* (4%), *CDKN2A* (2%), *ERBB2* (2%), *KRAS* (2%), *PIK3CA* (2%), *SMARCA4* (2%), *APC* (1%), *BRAF* (1%), *KEAP1* (1%) and *STK11* (1%) were identified in our cohort of 83 stage I lung adenocarcinoma patients (fig 1a). *TP53* mutations were identified in 29 patients (35%), with 11 high-risk, 9 low-risk, and 11 truncating mutations. Compared with patients with wild-type *TP53*, patients with *TP53* mutations had a significantly lower tumor mutational burden ($p < 0.001$, fig 1b). Furthermore, there was a significant difference between the wild-type/low-risk group and the truncating/high-risk group ($p < 0.001$, fig 1b). Compared with the low-risk group, the high-risk group had significantly worse recurrence-free survival ($p = 0.046$), while there was no significant difference between the low-risk group and the wild-type group ($p = 0.695$, figure 1c). Moreover, when we combined the groups into a high-risk/truncating group and a low-risk/wild-type group, the high-risk/truncating group had a significantly worse recurrence-free survival ($p = 0.0081$, figure 3c) and overall survival ($p = 0.0029$, figure 1c).



Conclusion: *TP53* mutational type is of prognostic value for patients with stage I lung adenocarcinoma.

Keywords: prognosis of lung adenocarcinoma, Evolutionary Action score, TP53

P2.11-15 DETECTION OF CIRCULATING GENETICALLY ABNORMAL CELLS IMPROVES THE DIAGNOSTIC ACCURACY IN LUNG CANCER PRESENTING WITH GGNS

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Background: Popularization of low-dose computed tomography (LDCT) screening enables more finding of pulmonary ground glass nodules (GGNs). It remains a challenge for distinguishing between malignant and benign nodules in patients with size ≤30mm GGNs depending on CT. Moreover, serum tumor markers showed poor prediction value. There is an urgent need to develop a noninvasive and highly accurate biomarker for detection. Recent studies have suggested that circulating genetically abnormal cells (CACs) can be identified by fluorescence in situ hybridization (FISH) from peripheral blood of early-stage lung cancer in Caucasian. This study aimed to use CACs to improve the diagnostic accuracy of early-stage lung cancer with GGNs in Chinese population. **Method:** Peripheral blood was collected from 107 patients with GGNs and 55 healthy donors. All GGNs identified by CT were between 5-30mm in diameter and confirmed with histopathological diagnosis after surgical resection. The level of serum-based biomarkers (CEA, NSE, TPSA, SCC, PROGRP, CA19-9 and CYFRA21-1) were measured. CACs were enriched by density gradient separation, and visualized by 3p22.1, 3q29, 10q22.3, CEP10 FISH. CACs were identified by finding gains in two or more probes. **Result:** Of these 107 GGNs, 96 were malignant (45 pure GGNs and 51 mixed GGNs) and 11 were Benign. All malignant GGNs were stage I lung adenocarcinomas. CACs were detected in 68 of 96 lung cancers, while serum-based biomarkers were just positive in 39 of those. The sensitivity, specificity of CACs test were 70.8%, 77.3% respectively for this cohort (96 malignant GGNs, 11 benign GGNs and 55 healthy donors). The area under the receiver operating characteristic (ROC) curve was 0.760 from this data set. There was no significant difference in CACs test sensitivity between GGNs size of <20mm and ≥20mm (71.3% vs 68.8%, p=0.84). Comparing to serum-based biomarkers, the sensitivity of CACs test was significantly improved. Combining the CACs test results with serum-based biomarkers, the overall sensitivity increased to 77.1% without lowering specificity.

	Sensitivity on malignant GGNs (N=96)	Sensitivity on malignant pure GGNs (N=45)	Sensitivity on malignant mixed GGNs (N=51)
CACs	70.8%	68.9%	72.5%
serum-based biomarkers	40.6%	40.0%	41.2%
Sig.	P<0.05	P<0.05	P<0.05

Conclusion: Our study showed that using CACs as a noninvasive malignant biomarker could improve the diagnostic accuracy in early-stage lung cancer presenting with GGNs.

Keywords: Lung cancer, ground glass nodules, Circulating genetically abnormal cells

P2.11-16 VARIABILITY IN READING LOW-DOSE CHEST CT: INDIVIDUAL READERS VS. CENTRAL REVIEW IN A NATIONWIDE LUNG CANCER SCREENING PROJECT

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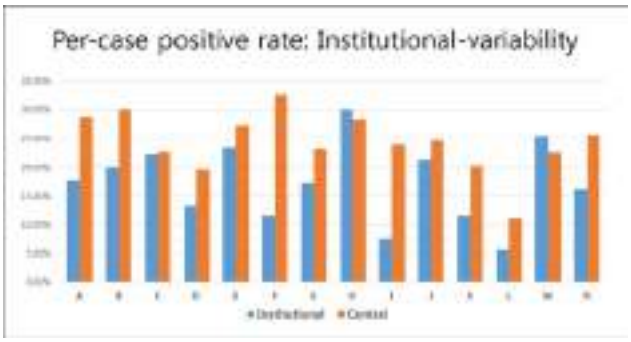
Background: Variability in interpretation among readers or institutions is an important issue in the nationwide lung cancer screening. The potential of computer-aided detection and volumetry

in reducing interobserver variability has rarely been investigated in the actual screening situation. This study aimed to evaluate the variability among experts in a nationwide lung cancer screening project. **Method:** We evaluated 1647 consecutive baseline screening CT scans obtained during one month period of December 2017 from a nationwide lung cancer screening project in Korea (K-LUCAS) in which 14 institutions participated. One of 20 chest radiologists in each institution assessed CT scans using a thin-client system equipped with semi-automated nodule segmentation and computer-aided detection software based on Lung-RADS (institutional reading). One chest radiologist retrospectively reviewed all these CT scans while minimizing modification of segmentation results and rejection of tiny nodules (central review). Reading results between institutional reading and central review were compared. Per-case and per-nodule positive rates of central review using Lung-RADS and NELSON criteria were also compared. **Result:** Per-case positive rate was significantly higher in central review (24.9% [410/1647; 11.1-32.7% across institutions] vs. 19.3% [319/1647; 5.6-30.0% across institutions]; *P*<.001), while per-nodule positive rate was significantly higher in institutional reading (10.2% [511/4497; 5.2-21.9%] vs. 19.9% [382/1920; 9.5-60.6%]; *P*<.001). The number of detected nodules was significantly larger in central review (3.04 vs. 1.17 nodule/case; *P*<.001), while the size of detected nodules was significantly smaller in central review (4.0 vs. 5.1 mm; *P*<.001). Variability in positive rates among institutions was significantly lower in central review (coefficient of variability, 21.9% vs. 40.2%; *P*=.044). Manual measurements after rejecting result of semi-automated segmentation occurred in 1.6% (80/5008) of nodules at central review and in 17.8% (342/1920) nodules at institutional reading. Positive rate with Lung-RADS was significantly higher compared with that of NELSON criteria (24.9% vs. 3.9%; *P*<.001), however, including indeterminate scan by NELSON criteria which requires additional scanning, positive rate was higher in NELSON criteria (24.9% vs. 33.4%; *P*<.001).



Conclusion: Even in a situation where computerized tools are adopted, considerable variability was observed in interpretation of lung cancer screening CT even among expert chest radiologists. The variability was mainly caused by discarding tiny nodules and modifying or rejecting segmentations results, and reduced by central review. The NELSON criteria did not reduce the number of additional scanning in nodule management compared with Lung-RADS. The value of reducing variability by applying stricter rules should be further investigated.

Keywords: lung cancer screening, Low dose chest CT, Variability

P2.11-17 ANALYSIS OF LUNG ADENOCARCINOMA EGFR MUTATION BY LAMP METHOD COMPARISON WITH PCR METHOD AND IDENTIFICATION OF A NOVEL EXON19 DELETION MUTATION

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Background: Detection of EGFR mutation has been widely used for the lung cancer treatment. The accuracy of detecting EGFR mutations is, therefore, very important. We here adopted a method of Loop-mediated isothermal amplification (LAMP) used for the detection of bacteria, which amplifies DNA with high specificity and efficiency under isothermal conditions. So that we evaluated the usefulness of LAMP for detecting various EGFR mutations using cancer tissues in comparison to conventional PCR technique. **Method:** We enrolled 59 surgically resected lung adenocarcinoma patients. We used Therascreen EGFR PCR Kit as a conventional PCR. Then, we tried to detect EGFR mutations for those specimens using LAMP method, and compared the result of LAMP to that of Therascreen. **Result:** 26 cases had no mutation in the analysis using Therascreen and LAMP method. In 32 cases which showed positive mutations according to Therascreen, and LAMP method, however, we found a single case showing no mutations by LAMP method, and exon 19 deletion by Threascreen. The direct sequence analysis revealed no mutations in the case as shown with LAMP method. Here, we repeated several experiments using LAMP method for the purpose of comfirmation of EGFR status of the case. These additional tests revealed Exon 19 deletion using the LAMP method, moreover, another direct sequencing discovered a novel EGFR mutation. Sensitivity for LAMP method was calculated as 97.0%, specificity as 100%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 96.3 % and accuracy was 98.3%. **Conclusion:** The accuracy of detecting EGFR mutation in LAMP method was nealy equivalent to that in Therascreen. Moreover, we detected a novel EGFR exon 19 deletion mutation with the direct sequence.

Keywords: LAMP, EGFR mutation, novel mutation

P2.11-18 CIRCULATING SERUM KLK5 AND L1CAM LEVELS POTENTIALLY PREDICT CLINICAL OUTCOME TO ANLOTINIB THERAPY IN NSCLC PATIENTS

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Background: Anlotinib is an oral multi-targeted tyrosine kinase inhibitor (TKI), which has been demonstrated to be effective upon non-small cell lung cancer (NSCLC) in clinical trials at 3rd line. However, the underlying anlotinib-responsive patients remain elusive. In the present study, we aimed to screen out the potential biomarkers for anlotinib-responsive stratification via transcriptome analysis. **Method:** Anlotinib-resistant NCI-H1975 cells were established *in vitro*. Toxicologic effects undergoing anlotinib stress were observed upon NCI-H1975 cells and anlotinib-resistant NCI-H1975 cells, respectively. Transcriptome profiling was performed to screen anlotinib resistance-associated genes between NCI-H1975 cells and anlotinib-resistant NCI-H1975 cells. The correlations between mRNA levels of the anlotinib resistance-associated genes and clinical outcomes of NSCLC patients were analyzed via Kaplan-Meier survival analysis in TCGA cohort. Potential biomarkers for anlotinib-responsive stratification were examined in a 28 patients' cohort of anlotinib clinical trial (NCT02388919). **Result:** Anlotinib-induced cytotoxic effects nearly disappeared in anlotinib-resistant NCI-H1975 cells, which are majority attributed to the modulated gene expression of multiple biological processes. Among these biological processes, angiogenesis plays an important role in anlotinib resistance. Up-regulation of angiogenesis-related *KLK5* and *L1CAM* are mostly associated with poor clinical outcome in NSCLC patients. Knockdown of *KLK5* and *L1CAM* contribute to increase anlotinib-induced cytotoxicity upon NCI-H1975 cells and anlotinib-resistant NCI-H1975 cells. High serum levels of KLK5 and L1CAM are also associated with poor anlotinib response in NSCLC patients at 3rd line. **Conclusion:** This study suggested that serum levels of KLK5 and L1CAM potentially serve as biomarkers for anlotinib-responsive stratification in NSCLC patients at 3rd line.

P2.11-19 EFFECTS OF INCORPORATING A LUNG CANCER SCREENING EDUCATIONAL INTERVENTION INTO TOBACCO CESSATION COUNSELING

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Background: Lung cancer screening (LCS) with low-dose computed tomography (LDCT) reduces lung cancer mortality in high-risk patients, but most of those eligible are not referred for screening, and most eligible smokers are not aware about LCS. Tobacco cessation counseling may be an opportune time to educate smokers about LCS, but it is unclear whether providing such information is effective in improving LCS utilization and what effects it may have on success of

tobacco cessation. **Method:** We randomized 1281 smokers age 55-80 who underwent tobacco cessation services between January 2016 and February 2018 in a large integrated health care system to view a web-based educational video about LCS (n=1026) or to receive usual care (n=255). We analyzed results according to both intention-to-treat as well as a pre-planned subset analysis of participants who completed the video. A survey on perceptions of LCS was included at the completion of the video and this was analyzed as well. We then compared the utilization of chest CT scan (any chest CT or specifically LDCT for LCS) in both groups of participants during a specified 90 day follow-up period and modeled the incidence rate ratios (IRR) for participants who completed the video and all invited to view the video compared with controls. **Result:** In the intervention arm, 191 (14.9%) patients watched part of the video, and 136 (10.6%) of participants completed watching the video. The video was well received by those completing it. Overall, 47(4.6%) of participants in the intervention group underwent chest CT and 31 (3.0%) underwent LDCT compared with 12 (4.7%, p=0.082) and 7 (2.8%, p=0.30) in the control group during a 90 day follow-up. Among participants who completed watching the video, 18 (13.2%, p=0.033 compared with control) underwent chest CT and 10 (7.4%) underwent LDCT during follow-up (p= 0.003 compared with control). IRR for participants completing the video was 2.01 (95% CI 1.06-3.82, p=0.03) for LDCT compared with control, and 2.15 (95% CI 1.30-3.55, p=0.003) for chest CT compared with control. **Conclusion:** These data suggest that a lung cancer screening educational intervention may be effective in improving utilization of LDCT in eligible smokers at the time of tobacco cessation counseling. Our study was limited by relatively low response rate to viewing the educational video. We plan to study the optimal way to deliver LCS education in the setting of tobacco cessation. Further research on the effect of lung cancer screening education on the effectiveness of tobacco cessation interventions is also needed.

Keyword: Lung cancer screening, Low-dose computed tomography, tobacco cessation

P2.11-20 RISK FACTORS OF LUNG CANCER DEVELOPMENT IN IPF PATIENTS

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Background: Idiopathic pulmonary fibrosis (IPF) is known as a risk factor for lung cancer (LC) by several previous studies, and that the presence of LC shortens survival in patients with IPF. However, the risk factors for the development of LC after the diagnosis of IPF have not been fully evaluated. We investigated the predictive factors for LC by longitudinal cohort analysis. **Method:** This was a retrospective study of a single center interstitial lung disease cohort. Study patients were consecutively enrolled to the cohort between March 2006 and December 2018 at Bucheon St. Mary's Hospital, The Catholic University of Korea. This cohort study consists of 102 patients with IPF, and the incidence of LC and the outcomes were investigated. **Result:** During the mean follow-up periods of 62.7 months, 27 patients (26%) developed LC. The most frequent cell type was Squamous cell carcinoma, and the proportion of male was higher in IPF-LC group (92.6% vs 70.7%, p=0.021). In univariate cox regression analysis, low forced vital capacity (FVC) <75% (p<0.001), and low diffusion capacity of the lungs for carbon monoxide (DLco) <55% (p<0.001) was associated with LC development. In Cox proportional hazards model, low FVC (hazard ratio [HR]: 5.65; 95% confidence interval [CI]: 1.78-17.84, p=0.003) and low DLco (HR: 27.5; 95% CI: 1.97-386.6, p=0.014) were independent predictive factors for LC in stepwise multivariate analysis. **Conclusion:** Low FVC and Low DLco, which are pulmonary function parameters reflecting their severity of IPF, are suggested as independent risk factors for LC development in IPF patients.

Keywords: Lung cancer, idiopathic pulmonary fibrosis, pulmonary function

P2.11-21 USEFULNESS OF DIFFUSION-WEIGHTED WHOLE-BODY IMAGING WITH BACKGROUND SUPPRESSION IN THE POSTOPERATIVE FOLLOW-UP PERIOD

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Background: Diffusion-weighted whole-body imaging with background suppression (DWIBS), a magnetic resonance diffusion-weighted imaging method of the whole body, has recently been adopted as a method for detecting malignant lesions, but there have been few reports discussing the usefulness of this technique with respect to the detection of recurrent postoperative lesions. Herein, we describe the usefulness of DWIBS for identifying recurrence, following surgery for primary lung cancer. **Method:** We performed a retrospective investigation of the accuracy of detection of recurrent lesions using DWIBS in 76 patients (46 men, 30 women) between November 2016 and October 2018, who were being followed up after primary lung cancer surgery. Diagnosis of recurrence was made after comprehensive imaging findings, clinical findings, and histopathological findings. While performing DWIBS, photographs were taken using a SIEMENS MAGNETOM Skyra 3.0T device and no contrast agent was used. The b factors were set to 0 and 1000, and high signal and low apparent diffusion coefficient (ADC) values in the diffusion weighted image (b = 1000) were evaluated visually. **Result:** The mean period from surgery to DWIBS was 1243 days (range: 116-3557 days) and the median period was 999 days. Of the 76 cases considered, recurrence was observed in 32 cases, of which DWIBS detected the lesion in 24 cases (75%). Of the 44 non-recurrent cases, 18 exhibited a strong signal in DWIBS. Of these 18 cases, 12 were false positives and 6 were primary lesions. Accuracy was 73.6%, sensitivity was 78.9%, and specificity was 68.4%, respectively. The breakdown of the location of lesions identified through DWIBS that were indicative of recurrence was as follows: Lymph nodes: 15 and bones: 8; with others located in the lungs, liver, and pancreas. In addition, the breakdown of the location of lesions identified in the chest through DWIBS that were not indicative of recurrence was as follows: Pulmonary recurrence: 6, hilar lymph node recurrence: 1, and mediastinal lymph node recurrence: 1. The reasons for performing DWIBS were elevated tumor marker values in 33 cases and whole-body testing for recurrence via computed tomography (CT) in 24 cases. **Conclusion:** We believe that DWIBS is a useful technique when performing whole-body malignancy screenings after surgery for primary lung cancer. As this technique is less sensitive in identifying small recurrent lesions in the chest, it may be necessary to make a comprehensive diagnosis based on other findings as well, such as contrast-enhanced CT and PET results.

Keywords: DWIBS, Diffusion-Weighted Whole-Body Imaging with Background Suppression, Diagnosis of recurrence

P2.11-22 COMPARISON OF THE SENSITIVITY OF USPSTF AND PLCOM2012 LUNG CANCER SCREENING CRITERIA IN A RACIALLY DIVERSE POPULATION

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Background: Objective: To compare the sensitivity to detect lung cancer of two lung cancer screening selection criteria, the USPSTF (≥30 pack-years smoked, quit-time ≤15 years, age 55-80) and the PLCOm2012 model 6-year risk ≥1.5%, in a racially diverse population including a high proportion of Blacks. **Method:** Lung cancer cases diagnosed at a Chicago academic hospital in 2010–2017 were retrospectively analyzed for whether they met lung cancer screening eligibility using the USPSTF and PLCOm2012 criteria. Contingency table analysis with McNemar's odds ratios, confidence intervals and p-values evaluated comparisons. **Result:** The race/ethnic distribution of the 823 lung cancer cases was 245 (29.8%) Whites, 435 (52.9%) Blacks, 75 (9.1%) Hispanics, 39 (4.7%) Asians, and 29 (3.5%) others. Overall, data on criteria risk factors were available for 770 (93.6%) individuals: 68.3% were positive by PLCOm2012 criteria and 49.9% were positive by the USPSTF (Table 1, McNemar's odds ratio (ORM)=11.9, 95%CI 6.8-22.9, p<0.0001). Limited to Blacks, the

USPSTF criteria identified 50.8% and the PLCOm2012 identified 74.9%. Only 3 individuals were USPSTF+ve/PLCOm2012-ve and 104 individuals were PLCOm2012+ve/USPSTF-ve (Table 2, ORM=34.7, 95%CI 11.5-170.8, p<0.0001). **Conclusion:** Overall and especially in Blacks, compared to the USPSTF criteria, the PLCOm2012 criteria was significantly more sensitive at identifying lung cancer patients.

Table 1. Lung cancer cases (N=770) stratified by USPSTF and PLCOm2012 selection criteria status, all races/ethnicities. Cells contain number, (row percent), [column percent].

	PLCOm2012 risk < 1.5%	PLCOm2012 risk ≥1.5%	Total
USPSTF criteria -ve	231 (59.8%) [94.7%]	155 (40.2%) [29.5%]	386 (100.0%) [50.1%]
USPSTF criteria +ve	13 (3.4%) [5.3%]	371 (96.6%) [70.5%]	384 (100.0%) [49.9%]
Total	244 (31.7%) [100.0%]	526 (68.3%) [100.0%]	770 (100.0%) [100.0%]

Table 2. Lung cancer cases (N=419) stratified by USPSTF and PLCOm2012 selection criteria status, Black race only. Cells contain number, (row percent), [column percent].

	PLCOm2012 risk < 1.5%	PLCOm2012 risk ≥1.5%	Total
USPSTF criteria -ve	102 (49.5%) [97.1%]	104 (50.5%) [33.1%]	206 (100.0%) [49.2%]
USPSTF criteria +ve	3 (1.4%) [2.9%]	210 (98.6%) [66.9%]	213 (100.0%) [50.8%]
Total	105 (25.1%) [100.0%]	314 (74.9%) [100.0%]	419 (100.0%) [100.0%]

Keywords: lung cancer screening, Risk stratification, Health disparities

P2.11-23 PERFORMANCE OF LUNG CANCER RISK PREDICTION MODELS IN I-ELCAP SMOKERS

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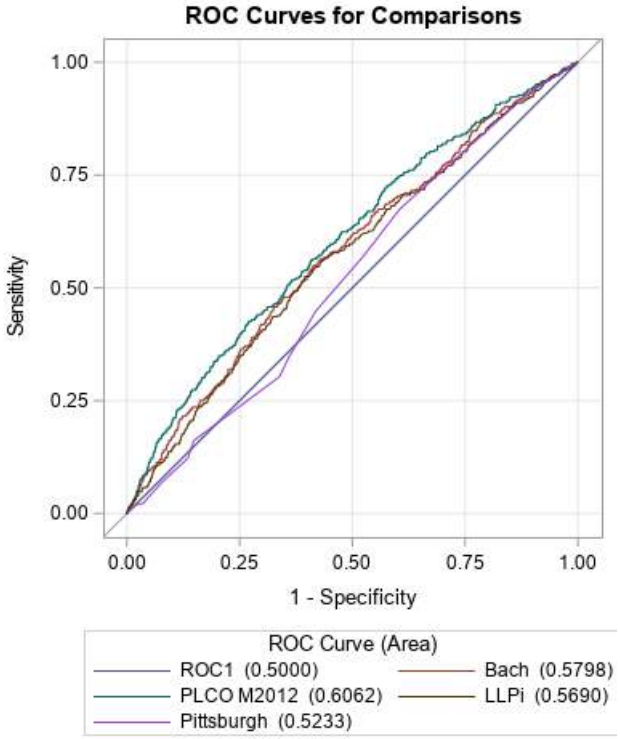
Background: To determine the performance of lung cancer risk prediction models in predicting lung cancer in smokers enrolled in the International Early Lung Cancer Program (I-ELCAP). **Method:** 62,071 asymptomatic ever-smokers enrolled into the international multi-institutions I-ELCAP for low-dose CT screening between 1993-2018. Demographics, smoking history, comorbidities, exposures and family history of lung cancer were collected at time of baseline CT scan. All participants received a baseline screening scan and subsequently annual repeat CT scans, and they were prospectively followed for the diagnosis of lung cancer. Diagnosis and treatment of lung cancer were verified and documented in the ELCAP Management System. To compare the predicted risk of lung cancer, we applied four lung cancer risk models: the Bach Model, the Liverpool Lung Project Incidence (LLPi) Risk model, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012 (PLCOM2012), and the Pittsburgh Predictor Model to the I-ELCAP cohort. Model calibration and discrimination were assessed using expected-to-observed (E/O) ratio and the area under the curve (AUC) statistics. E/O ratio >1 indicates that the model predicts more lung cancer cases than observed. **Result:** PLCOM2012 model was the most predictive of lung cancer for ever-smokers in I-ELCAP with the AUC 0.61 being the highest, followed by Bach model (AUC 0.58), LLPi model (AUC 0.57) and Pittsburgh Predictor (AUC 0.52). E/O ratios suggested that the PLCOM2012 model, Bach model, LLPi model and Pittsburgh Predictor model tends to overestimate the number of lung cancers. The LLPi model overestimated as many as 4 times more lung cancer cases.



Conclusion: Using data from I-ELCAP, the four existing lung cancer risk prediction models have AUCs ranged between 0.52-0.61, PLCOM2012 model was the top performer out of the four models.

Keywords: risk models, Lung cancer, Screening

P2.11-24 THE FIRST COMPREHENSIVE PRIMARY CARE PROVIDER TRAINING FOR LUNG CANCER CARE IN THE U.S. - AN INNOVATIVE ONLINE COURSE

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Background: Lung cancer (LC) is the leading cause of cancer death in the U.S., and primary care provider (PCP) education is essential for reducing the country's overall LC burden. Despite recent LC treatment advances, several studies show that LC patients receive treatments at lower rates than other cancer patients, regardless of stage of diagnosis. Despite decades of research into tobacco use treatment, many PCPs still lack the expertise to assist patients in their quit attempts. PCP understanding and adoption of the U.S. Preventive Services Task Force (USPSTF) recommendation for LC screening with low-dose CT (LDCT) remain low, making PCP education crucial for impacting the leading cause of cancer death. **Method:** The LuCa National Training Network provides training, materials, and technical assistance for professionals who educate PCPs and other health care professionals on LC. In developing an online training course on lung cancer care for PCPs, LuCa moved beyond the traditional, using innovative technology to engage PCPs and influence practice behaviors. The free course, *Lung Cancer and the Primary Care Provider,* delivers comprehensive, interactive education on best practices related to lung cancer prevention, early detection, treatment, and survivorship. The course includes a library of practice tools available for download. This presentation will provide an overview of the online course, lesson content, features, interactivity, and results to date. **Result:** *Lung Cancer and the Primary Care Provider* launched in April 2019 and is the only comprehensive online course on LC care for PCPs in the U.S. Learners complete pre- and post-tests and evaluations immediately following the course and three months later regarding practice changes. Up-to-date participation and evaluation trends, demographic comparisons, knowledge changes, lessons learned, and participant feedback will be shared. This presentation will review the practice areas on which the course had the strongest influence, based on PCP self-reported data.

Conclusion: PCPs play a pivotal role in determining the care pathways for their patients who are at risk for, or diagnosed with, lung cancer. They are an ideal audience for pertinent lung cancer-focused educational interventions. Creative online learning has tremendous potential to improve patient care and achieve broad reach to this critical provider audience. Adoption of new screening and prevention modalities takes time, but high quality training with simple downloadable practice tools can accelerate adoption of these best practices. Provider education must be engaging, evidence-based, on-demand, and cutting-edge in order to capture focus with competing demands, and affect knowledge and confidence on complex lung cancer topics.

Keywords: Cancer screening, Provider education, Online

P2.11-25 PRE- AND POST-SURGERY METABOLOMIC PROFILES IN EARLY-STAGE NSCLC PATIENTS

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Background: Finding biomarkers to detect cancer at its early stage is of importance. Since metabolic reprogramming is a hallmark of cancer, oncometabolite is thus a promising target.Progress in cancer metabolomics opens the door for large scale screening of cancer-specific metabolites that could be future applied for subclinical stage detection and novel therapeutic targets. **Method:** Seventy paired pre- and postoperative plasma samples of early-stage NSCLC patients who had completed curative surgery during 2015-2018 with ≥ 3 months disease free were retrieved. Demographic and Clinical data were collected. All samples were subjected to targeted metabolomics analysis using AbsoluteIDQ® p180 Kit on ESI 5500 LC-MS/MS System equipped with 1260 Series HPLC, according to the manufacturer's instruction.Multivariate analysis including PCA and OPLS-DA were used to identify the difference between pre- vs post-operative sample set. T-test was used to confirmed if the metabolites significantly different among groups at the univariate level ($p < 0.05$). **Result:** Of the 70 patients, 31 (44.3%) were male and 39 (55.7%) were female. Median age was 63 years old (23 - 85). Majority of them were never-smokers (64.3%). Adenocarcinoma was the most common histology (91.4%). EGFR mutation was tested in 34 (48.6%) patients, of which, 22(64.7%) of them were positive. Metabolomic analysis revealed tryptophan as the most statistically significant change, together with other amino acids, carnitines, biogenic amines, and lipids (Table1). Besides glutamate, all metabolites increased postoperatively. Metabolites with VIP scores (Variable Importance in Projection) ≥ 1.5, including tryptophan, lysophosphatidylcholine-acyl C16:0, lysophosphatidylcholine-acyl C18:0, and carnitine, were assembled together for a predictive model which will be presented at the congress. Table 1: Metabolites with significant difference between pre- and post-surgery in early-stage NSCLC patients

Metabolite (ng/ml)	Pre operation (N=70)		Post operative (N=70)		Fold change	p-value	VIP score
	Mean	SD	Mean	SD			
Amino acid							
Glutamate	17,449.31	7,808.80	10,192.53	5,294.28	-0.374	<0.001	1.21
Glutamine	87,406.56	22,839.10	104,994.00	26,276.52	0.324	<0.001	0.77
Arginine	10,869.44	5,082.21	16,101.94	8,220.61	0.481	<0.001	0.79
Asparagine	5,023.79	1,294.80	7,630.93	2,343.85	0.663	<0.001	1.34
Tryptophan	6,921.41	1,579.37	13,189.77	4,105.45	0.992	<0.001	1.70
Acrylcarnitine							
carnitine (C0)	4,680.23	1,292.54	7,263.51	2,136.29	0.657	<0.001	1.50
Biogenic amine							
Creatinine	7,262.43	2,410.21	10,529.83	4,070.33	0.536	<0.001	1.14
Kynurenine	363.42	126.06	571.91	232.05	0.723	<0.001	0.82
Sphingolipid							
SM C16:1	8,837.49	2,290.28	10,875.53	2,970.15	0.290	<0.001	1.33
SM C20:2	178.18	60.77	205.47	66.55	0.304	0.005	0.43
Phosphatidylcholine							
lysoPC a C16:0	26,863.83	6,420.81	45,877.36	13,732.55	0.774	<0.001	1.67
lysoPC a C16:1	740.24	287.44	1,256.99	588.67	0.842	<0.001	1.33
lysoPC a C17:0	303.24	90.78	521.36	200.39	0.853	<0.001	1.45
lysoPC a C18:0	8,449.64	2,593.82	14,854.50	5,047.03	0.885	<0.001	1.60
lysoPC a C18:2	6,818.04	2,466.61	11,990.73	4,760.87	0.965	<0.001	1.37

Conclusion: We identified a distinct cluster of significant metabolic biomarkers associated with early-stage NSCLC. Tryptophan is the most significant one that associated with cancer metabolome. These would be potential biomarker profile for early-stage NSCLC detection.Larger cohort is needed to be validated.

Keyword: metabolomics, non-small cell lung cancer, metabolic biomarkers, tryptophan

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P2.11-26 SURVIVAL OF PATIENTS WITH MULTIPLE PRIMARIES AND SINGLE LUNG CANCER - A COMPARATIVE ANALYSIS

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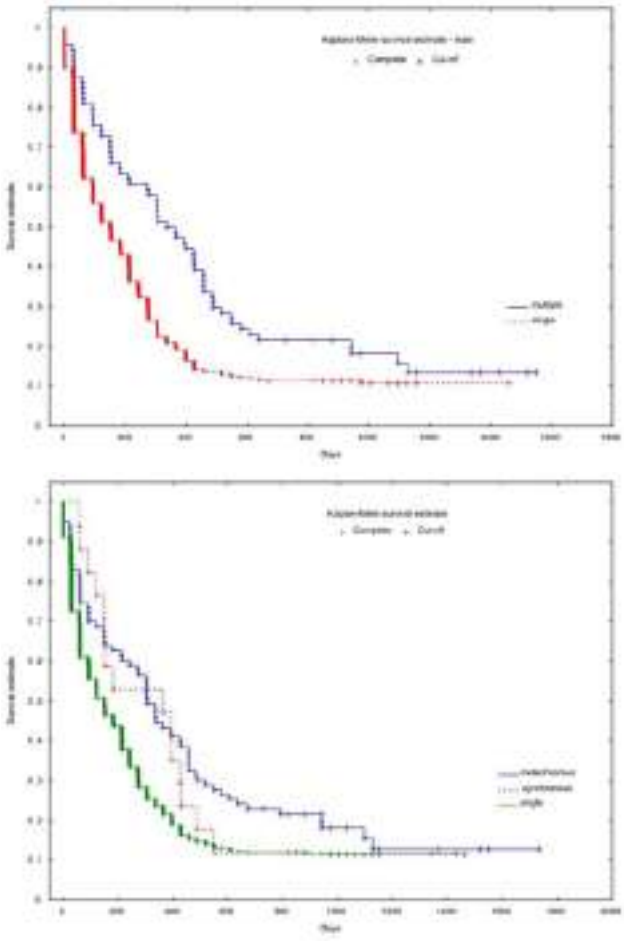
Background: From the mid-1980s, lung cancer is the most commonly diagnosed malignant tumor. Longer survival is associated with an increased likelihood of new, subsequent neoplasms. The incidence of multiple primary neoplasms in the oncology population ranges from 0.73 to 11.7%. The aim of the study was to assess the survival of patients with single lung cancer in relation to patients with multiple primary neoplasms. **Method:** The study was conducted based on the retrospective analysis of data collected from patients hospitalized at the Center for Pulmonary Diseases in Olsztyn (Poland). Data on multiple malignancies (140 patients) were collected from January 2013 to December 2017. Data on single primaries (601 patients) were collected from January 2016 to December 2017. Total survival was calculated beginning from the date of the first cancer diagnosis to the day of death or last observation. The statistical analysis was conducted using Statistica version 12. **Result:** Based on the collected data, it was revealed that the survival of patients with a single lung cancer (0.17 years; SD 0.81) is significantly shorter than those who had multiple primaries (7.15 years; SD 7.42) (p <0.05). The average survival time of cancer patients with metachronous tumors (8,29 years; SD: 7.58) is significantly longer than patients with synchronous tumors (1.30 years; SD: 1.17) (p <0.05) and single ones (0.71 SD: 0.82) (p<0.05). It was also revealed that patients who smoked in a group of single cancer lived shorter than those with multiple malignancies (p<0.05). The average number of packyears for patients with multiple tumors was 33.95 (SD: 24.95), and with single primaries 39.90 (SD: 21.26).



Conclusion: Survival time for patients with single lung cancer is worse than for patients with multiple tumors, both in relation to the first and subsequent tumors. Smoking reduces survival time of patients with both multiple and single primaries.

Keywords: multiple primary malignanices, Lung cancer, Survival

P2.11-27 EARLY DETECTION OF LUNG CANCER: OPTIMAL STRATEGIES

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Background: Significance of blood cell subpopulations in terms of early detection of lung cancer (LC) was investigated. **Method:** In trial (1987-2019) consecutive cases after surgery, monitored 115 LC patients (LCP) (m=100, f=15; lobectomies=115) with pathologic stage IA (tumor size=1.86±0.30 cm; squamous=51, adenocarcinoma=59, large cell=5; T1N0M0=115; G1=39, G2=42, G3=34, 5-year survival=100%) and control group (CG) (n=402): 120 healthy donors (HD) (m=69, f=51) and 282 patients with lung non-malignant pathology (NMP) (m=188, f=94; pneumonectomies=5, lobectomies=179, segmentectomies=98; non-malignant tumors=100; abscess=112; tuberculoma=70) were reviewed. Variables selected for study were input levels of blood cell circuit, sex, age, TNMG. Differences between groups were evaluated using discriminant analysis, clustering, nonlinear estimation, structural equation modeling, Monte Carlo, bootstrap simulation and neural networks computing. **Result:** It was revealed that early detection of LC from CG (n=517) significantly depended on: leucocytes (abs, total), segmented neutrophils (%, abs, total), lymphocytes (%), monocytes (%, abs, total) (P=0.048-0.000). Neural networks computing, genetic algorithm selection and bootstrap simulation revealed relationships of early detection of LC and lymphocytes (rank=1), segmented neutrophils (rank=2), monocytes (3), eosinophils (4), leucocytes (5), stick neutrophils (6). Correct recognition of early LCP from CG was 100% by neural networks computing (error=0.000; area under ROC curve=1.0). **Conclusion:** Early detection of LC from HD and NMP significantly depended on blood cell subpopulations.

P2.11-28 LATE-BREAKING ABSTRACT - CLINICAL POTENTIAL OF SPUTUM HYALURONAN MEASUREMENT IN THE DIAGNOSIS AND PROGNOSIS OF PATIENTS WITH NSCLC

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Background: Lung cancer is the most frequently diagnosed and also the most lethal due to late diagnosis. Many efforts are being made to mitigate this problem. In this scenario, sputum is a potentially attractive source of biomarkers present in the extracellular matrix such as hyaluronan (HA). The aim of this study is to validate HA levels in sputum's patients with non-small cell lung cancer (NSCLC) at the time of diagnosis and after first-line treatment evaluation response and correlate the values response rate in patients submitted to definitive treatment with chemotherapy and/or radiotherapy, progression and recurrence. We also evaluated the HA concentrations in chronic obstructive pulmonary Disease (COPD) and healthy volunteers and its impact on the screening and diagnosis of lung cancer patients. **Method:** HA was examined in sputum samples of 64 NSCLC, 14 COPD patients and 15 healthy controls. All the patients and healthy controls selected underwent a sputum induction.The levels of HA were measured in ng/ug of protein by a noncompetitive ELISA-like fluorometric assay. **Result:** A significant different concentration pattern of HA in the sputum was found among NSCLC (median: 33.25 ng/mg), COPD (median:16.6ng/ug) and healthy individuals (median: 12.2 ng/ug), (p<0.001, Fig. 1A), as well as NSCLC before first-line treatment (median:33.25ng/mg) and after 6 months treatment regimens with good response (median:6.2ng/ug), (p<0.001, Fig 2). **Conclusion:** Based on the results obtained so far, we rely on the clinical potential of sputum as a screening tool in the early detection of lung cancer.

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Fig. 1A

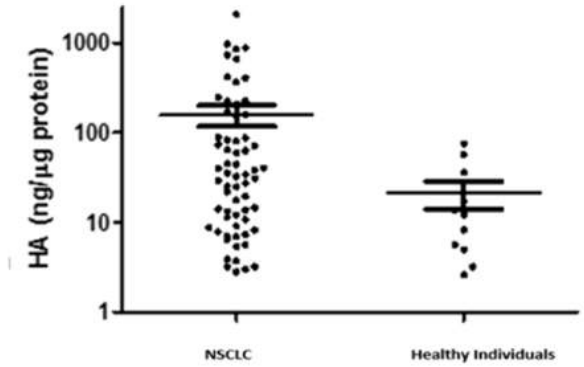
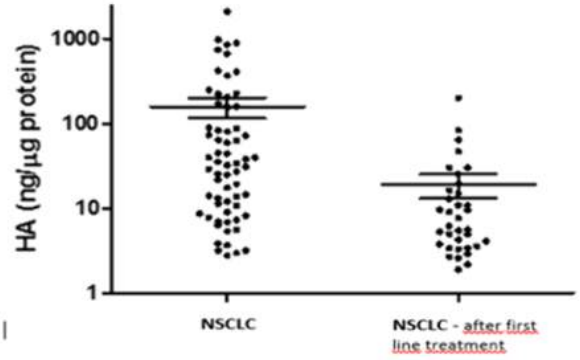


Fig. 2



Keywords: hyaluronan, sputum, lung carcinoma

P2.11-29 DIAGNOSIS AND SURVEILLANCE OF SOLITARY PULMONARY NODULES WITH CTDNA METHYLATION SEQUENCING: PROTOCOL FOR A PROSPECTIVE MULTICENTER STUDY

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Background: LDCT screening can identify early-stage lung cancers yet introduces excessive false positives, which calls for better non-invasive diagnostic tools. We previously established a diagnostic model of early stage lung cancer based on high-throughput DNA methylation sequencing of ctDNA (Theranostics 2019; 9(7)). The aim of the present study is to assess the role of ctDNA methylation markers in differential diagnosis and surveillance of pulmonary nodules. **Method:** A prospective cohort of 10,560 patients from 20 centers in China with non-calcified nodules range from 0.5 to 3 cm in diameter indicated by LDCT or CT will be included and followed up for 2 to 3 years. Each patient will undergo LDCT/CT follow-up and their information as well as blood sample will be collected at baseline, 3, 6, 12, 24 and 36 months. Blood samples will be subjected to ctDNA methylation test. Sensitivity, specificity, positive predictive value and negative predictive value are used to measure the diagnostic value of ctDNA methylation test in differentiating benign and malignant pulmonary nodules. **Result:** This study is registered in clinicaltrials.gov (NCT03651986, BELL study) and has launched since Oct 2018. Upon submission, 975 cases had been enrolled from 13 centers who had begun recruiment. Completion of data collection is anticipated by March 2023. **Conclusion:** To the best of our knowledge, this is the first and largest study worldwide to test the efficacy of ctDNA methylation markers in differential diagnosis and surveillance of pulmonary nodules.

Keywords: solitary pulmonary nodules, ctDNA, methylation

P2.11-30 EFFECTS OF THE SIZE OF NODULES, RECONSTRUCTION SLICE THICKNESS AND CONVOLUTION KERNEL ON RADIOMICS MODEL IN CLASSIFYING PULMONARY NODULES

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Background: In recent years, the number of chest CT and LDCT scans for annual lung cancer screening has been increasing, the detection rate of the intermediate pulmonary nodules (IPNs) has increased, especially small pulmonary nodules (PNs). A non-invasive method be needed to early diagnosis the benign and malignant of IPNs, then it would be possible to reduce the false positives, missed diagnosis rate, and avoid overdiagnosis and over-treatment. The ability of radiomics to classify PNs by radiologists has been widely described, however, the detection performance of each radiomics varies greatly and the reproducibility was poor that are identified from these studies. Variability of acquisition parameters like contrast enhancement, slice thicknesses can affect the diagnostic performance of radiomic biomarkers. But there are few reports on the effect of PN size, reconstruction slice thickness and convolution kernels on the performance of radiomics in classifing PNs. **Method:** We retrospectively collected 696 patients with 316 benign and 380 malignant PNs who underwent preoperative chest CT in the institution from March 1, 2015 to March 31, 2018. First, we analyzed the CT image of all the patients, and then we divided these images according to the nodule size and reconstruction kernel to test the diagnostic performance of the radiomic. 696 PNs were classified into three groups by nodule diameter: T1a (diameter $\leq$ 1.0 cm), T1b (1.0 cm < diameter $\leq$ 2.0 cm) and T1c (2.0 cm < diameter $\leq$ 3.0 cm). All CT images divided three groups according convolution kernels: Setting 1 (1mm/1.25 mm sharp), Setting2 (5 mm sharp), Setting 3 (5 mm smooth). Totally 1160 radiomic features were extracted from PNs segmentation on CT image delineated by an experienced radiologist. Sixteen radiomic models for predicting the malignancy of PNs in different size, reconstruction slice thickness and convolution kernels were built, respectively, based on the extracted radiomic features. Random selection of cases (70% Training and 30% testing) was employed to estimate the area under the receiver operating characteristic curve, accuracy, sensitivity and specificity to indicate the performance of the prediction models. **Result:** The performance (AUC, accuracy, sensitivity and specificity) on prediction PN malignancy in different size PN with all convolution kernels were 0.817, 0.766, 0.807, 0.717 of all size-modal; 0.679, 0.756, 0.629, 0.796 of T1a-model; 0.700,0.690,0.757,0.594 of T1b-model and 0.703, 0.684, 0.673, 0.731 of T1c-model, respectively. AUC of all size PN with setting 1,2,3 group were 0.793, 0.800, 0.793, respectively. AUC was the highest in T1a with setting 2 model which equal 0.841, and the lowest in T1c with setting 4 which equal 0.625. **Conclusion:** Reconstruction slice thickness and convolution kernel have significant influence on the diagnosis performance of radiomics in classifying of less than 1cm PNs in CT images, and using 1 mm shin sharp reconstruction algorithm can obtain the best diagnosis performance in less than 1cm PNs. Big samples of PNs could alleviate the effect of reconstruction slice thickness and convolution kernel on radiomics in classifying of less than 3cm PNs in CT images and improve the diagnostic performance of radiomics of larger than 1cm PNs

Keywords: pulmonary nodule, kernel, Radiomics

P2.11-31 DNA METHYLATION MARKERS FOR PREDICTION OF RECURRENCE IN STAGE I NON-SMALL CELL LUNG CANCERS

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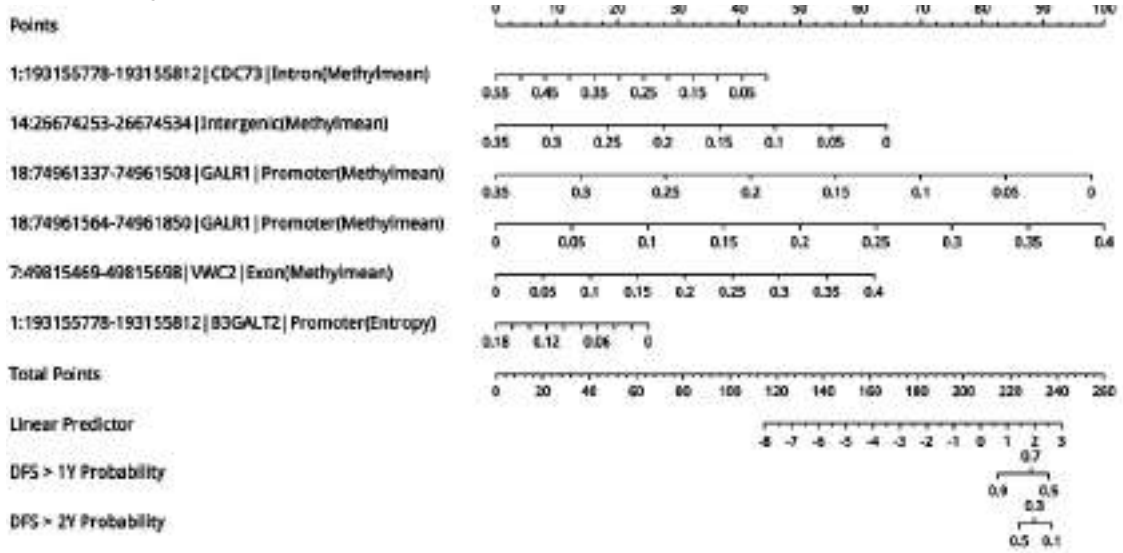
Background: Surgery with curative intent is the standard of care for patients with stage I non-small cell lung cancer (NSCLC). However, many patients die of recurrent disease despite of lesion resection. The value of DNA methylation for predicting the recurrence of early-stage, resected NSCLC remains to be determined. The aim of this

study was to find DNA methylation markers for recurrence prediction. **Method:** 39 paired tumor tissues and adjacent normal tissues from stage Ia NSCLCs were sequenced using bisulfite sequencing panel which covers 80,672 CpG sites and spans 1.05 mega base of human genome. The average sequencing depth was 1000X. Methylation blocks (MBs) were defined as the genomic region between the neighboring CpG sites and 8312 MBs were generated using the linkage disequilibrium and statistical modeling. Methylmean indicates the mean methylation value of MB, and methyentropy denotes the randomness of DNA methylation pattern of MB. **Result:** A total of 726 tumor-specific MBs shared by 1098 Methylentropy and 1316 Methylmean variates were obtained from matched tumor tissues and adjacent normal tissues using t-test (P<0.05). Then the multivariable analysis, conducted via the Cox regression model, generated 15 significant disease-free survival (DFS)-related MBs which shared by 56 methylentropy and 46 methylmean variates. A final model was selected using a backward step-down process and 6 significant DFS-related MBs were selected (1 methylentropy and 5 methylmean variates). A nomogram model that incorporated the 6 MBs was established to predict the DFS, and it performed well (C index=0.729, Figure 1).



Conclusion: We established an effective nomogram that may well distinguish the potential subgroup of patients with different DFS based on DNA methylation. Further perspective study should be conducted to validate this nomogram model in larger cohorts.

Keywords: DFS, NSCLC, DNA methylation

P2.11-32 PROJECT ACTS (ADHERENCE TO CT SCREENING): DEVELOPING PATIENT ENGAGEMENT TOOLS TO SUPPORT LUNG CANCER SCREENING ADHERENCE

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Background: The National Lung Screening Trial and the NELSON trial have established that low-dose computed tomography (LDCT) is beneficial for early detection of lung cancer among high-risk individuals. In 2014 the USPSTF began recommending LDCT scans for people at high risk for developing lung cancer. Part of the recommendation includes annual screening as well as follow-up for abnormal scans per Lung-RADS recommendations. However, rates of adherence to annual screening have been less than desirable with some screening programs anecdotally reporting rates as low as 20% and 50%. Concerns have also been raised regarding adherence to recommended interval scans following suspicious LDCT results. To address this need, Project ACTS aims to create a toolkit to facilitate lung cancer screening (LCS) adherence rates by addressing barriers and enhancing facilitators to participating in lung cancer **Method:** To explore barriers and facilitators of screening program adherence, this study employed a sequential qualitative and quantitative assessment to identify components of a successful screening adherence paradigm. Semi-structured interviews and surveys were conducted with 15 Lung Cancer Screening (LCS) Program Directors and staff and 8 LCS Program Participants. Interviews were transcribed and analyzed using direct content analysis. **Result:** Using the socio-ecological model of health promotion as a conceptual framework for analysis, the team mapped interview and survey findings to identify facilitators and barriers to adherence. Significant findings included: (1) the importance of personalized delivery of scanning results, embedding the opportunity to ask questions; (2) positive interactions with the CT techs; (3) the importance of a consistent program contact for engagement and continuity of care; (4) preference for increased screening accessibility with more locations and the option of weekend or later hours; and (5) the benefits of an active reminder system that utilizes multiple communication approaches. In addition, LCS program staff indicated interest in receiving training in shared decision-making and patient engagement strategies. **Conclusion:** Our formative research highlights the complex and multi-factorial nature of screening adherence and identifies facilitators and barriers that may impact optimal adherence. The next step in this research will involve development, usability testing, and pilot studies of the proposed patient engagement toolkit.

Keywords: lung cancer screening, early detection, screening adherence

P2.11-33 ORGANIZATIONAL READINESS FOR IMPLEMENTATION OF LUNG CANCER SCREENING IN A VETERANS AFFAIRS HEALTHCARE SYSTEM

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Background: Implementation of high quality lung cancer screening is complex and requires close coordination between radiology and primary care teams. Organizational readiness for change (ORC) is an important factor in successful implementation of complex healthcare programs such as lung cancer screening. Using the Consolidated Framework for Implementation Research (CFIR), we tested the hypothesis that ORC would differ between radiology and primary care prior to deployment of a centralized lung cancer screening program. **Method:** We conducted a cross-sectional observational study. We invited all radiology and primary care providers (hospital and community-based) and affiliated staff at a single large VA Healthcare System in the US by email to participate in a web-based survey. We measured demographic information and adapted 9 validated items on ORC (domains of change commitment and change efficacy) and 10 items on change valence (value of a planned organizational change) using a 7-point Likert-type scale. Respondents' ORC and change valence scores were calculated by averaging individual item responses for each scale. The primary outcome, ORC, was evaluated as a continuous variable with higher scores representing more readiness. We compared mean ORC scores between radiology and primary care using independent 2-sample t-tests. **Result:** The overall response rate was 54% (76/128 [59.4%] radiology, 206/398 [51.8%] primary care). After 12 respondents were excluded for incomplete data (5 from radiology and 7 from primary care), the analytical sample was 270 respondents. Respondents were on average 47 years old [SD 11.24], 72% female, and 17% self-identified as having a leadership role. Individuals affiliated with radiology reported higher ORC than those affiliated with primary care (5.50 [SD 1.42] versus 5.07 [SD 1.22], p=0.03). Individuals self-identifying as having leadership roles in implementation of lung cancer screening reported higher ORC than those without leadership roles (5.56 [SD 1.38] vs 5.11 [SD 1.28], p=0.05). Those with leadership roles reported higher change valence than those without (5.91 [SD 1.20] vs. 5.36 [SD 1.88], p=0.006). We found no difference in reported change valence between radiology and primary care. **Conclusion:** Radiology providers and staff have higher perceived ORC to implement a centralized lung cancer screening program compared to primary care. Providers and staff with implementation leadership roles reported higher ORC than those without leadership roles. Understanding these differences in readiness will inform future work as we focus on strategies to engage primary care providers and staff during implementation of lung cancer screening. We will deploy these strategies at Veterans Health Administration facilities across the US with the support of the VA-Partnership to increase Access to Lung cancer Screening (VA-PALS) and the VA Office of Rural Health.

Keywords: lung cancer screening, organizational readiness, veterans

P2.11-34 APPLICATION OF NEXT-GENERATION SEQUENCING FOR SCREENING OF SPUTUM SAMPLES

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Background: Since the efficiency of CT mass-screening was reported in NEJM in 2013, many countries have been actively adopting CT screening for detection of lung cancers, especially peripheral-type lung adenocarcinoma. On the other hand, another mass-screening method, "sputum cytology", has a very low cancer detection rate and its use has been decreasing worldwide. Nevertheless, sputum is one of the easiest types of sample to collect from patients, and sputum samples are thought to contain not only cancer cells, but also cancer cell-free DNA.The present study examined genomic abnormalities in DNA contained in sputum, and investigated the efficiency of next-generation sequencing (NGS) for detection of lung cancer or identifying patients at high risk. **Method:** Using the Saccomanno method, we collected sputum samples from 15 patients (5 with squamous cell carcinoma, 5 with adenocarcinoma, and 5 with non-neoplastic conditions). A 1500 µl volume of each sample was centrifuged, and the sediment was resuspended in 180 µl of supernatant. After incubation with protease K at 56ºC for 90 min, DNA was extracted using MagLead 6GC (Precision System Science Co., Ltd., Japan). All DNA samples were subjected to NGS using Ion AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific, USA). **Result:** The median age of the patients overall was 71 years (range, 56–94 years), and that of patients with squamous cell carcinomas, adenocarcinomas and non-neoplastic conditions was 66 years (64-78), 71 years (67-73) and 86 years (56-94), respectively. HRAS and p53 mutations were found only in cancer patients (HRAS 2/10, p53 4/10). There were no significant differences in mutation pattern between squamous cell carcinoma and adenocarcinoma patients. Although mutations of ALK, PIK3CA, PTEN, KRAS, FLT3, and RB1 were frequently found in samples from cancer patients (ALK 5/10, PIK3CA 5/10, PTEN 7/10, KRAS 7/10, FLT3 4/10, and RB1 8/10), such mutations were also present in non-neoplastic conditions. Mutations at the same locus in ALK, PIK3CA, PTEN and RB1 were also found in non-neoplastic conditions (ALK 1/5, PIK3CA 1/5, PTEN 2/5, and RB1 1/5). Seventeen out of 48 gene mutations were found only in non-neoplastic conditions. **Conclusion:** Detectable mutation patterns differed between cancer and non-neoplastic conditions, but were similar between squamous cell carcinoma and adenocarcinoma. Validation tests will be performed on DNA extracted from more than 400 sputum samples.

Keywords: mass-screening method, sputum cytology, Next-generation sequencing

P2.11-35 LUNG CANCER SCREENING KNOWLEDGE, PERCEPTIONS AND DECISION-MAKING AMONG AFRICAN AMERICANS

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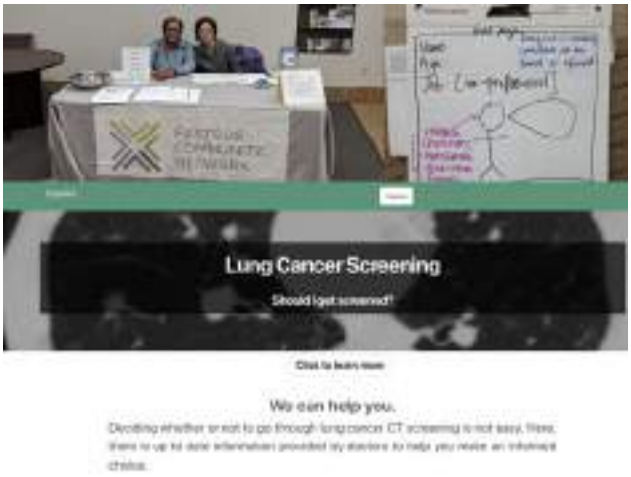
Background: Significant lung cancer disparities exist in the USA, where African American men have the highest incidence rate. However, most available web-based lung cancer screening decision aids have been designed without substantive feedback from African Americans, and few have been validated in this population. Therefore, we sought to evaluate and redesign an existing decision aid with input from African Americans in Detroit. **Method:** Using insights obtained from participatory design workshops in this population, we implemented content changes to shouldiscreen.

com and evaluated this modified version with a before-after study. Surveys took place between April and July 2018. Data were collected from 78 participants who were current/former smokers, had no history of lung cancer, and aged between 45 and 77. Participants were contacted six months after to assess if they took steps to receive lung cancer screening.



Result: Knowledge about risk factors and screening between before and after viewing the decision aid was 6.4 and 8 out of 15 points, respectively (25% increase). Notably, half of the participants felt uncomfortable answering surveys electronically and requested paper versions. There was a 31% improvement in knowledge score among those who took the electronic survey (6.7 to 8.8), and 18% for paper (6.1 to 7.2). Acceptability was high: 93% of all participants said the tool helped them consider screening. Concordance between individual preference and eligibility for screening increased from 22% to 34% (n = 74). The primary source of discordance was from those who should not be screened but prefer to be screened, although the largest improvement came from those who were unsure. There was significant loss to follow-up at six months: only 14 out of 78 participants were successfully contacted. Of these, three were eligible for screening according to USPSTF criteria. Five followed up with their physicians, and the three who were eligible were strongly encouraged to be screened. Two went through with lung cancer screening and one had quit smoking. **Conclusion:** Use of the tool led to improvements in lung cancer screening knowledge and concordance with current recommendations. Additional design modifications and modes of information delivery of current decision aids should be considered to increase their efficacy in helping populations with lower educational attainment and computer literacy. Partnering with community organizations and community leaders to demonstrate the use of the tool and explain the benefits of screening is paramount to help encourage those who might benefit most from it.

Keywords: lung cancer screening, patient centered decision aid, informed decision making

P2.11-36 THE ROLE OF FDG-PET SCANS IN PRE-INVASIVE ENDOBRONCHIAL LESIONS

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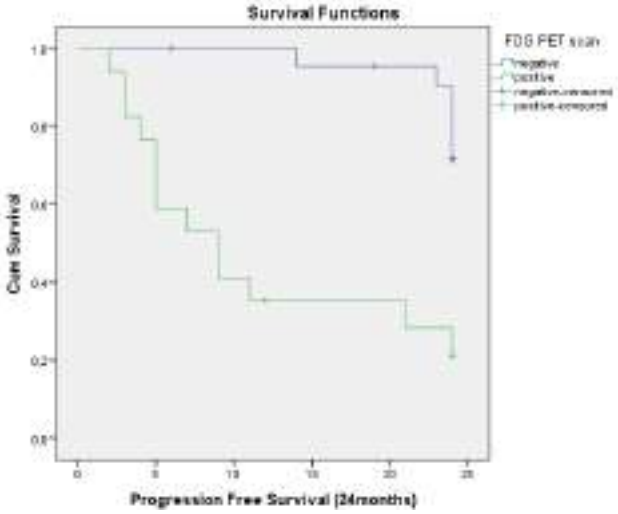
Background: Pre-invasive endobronchial squamous lesions, especially high-grade lesions, may serve as risk markers for developing lung cancer. However, it remains difficult to determine whether individual lesions will progress to lung cancer. 18 fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET) is currently used as a golden standard for staging patients with lung cancer and to monitor treatment response. The role of FDG-PET-scans in patients with pre-invasive lesions has not yet been established. In our study we report the outcome of surveillance of 40 subjects with pre-invasive endobronchial lesions and investigate the use of 18F-FDG-PET-scans as part of a surveillance program. **Method:** We retrospectively selected patients with pre-invasive endobronchial lesions who underwent pre-treatment FDG-PET scans at the VU Medical Center Amsterdam between 1995 and 2016. Patients with signs of invasive carcinoma at baseline, as confirmed by histology, were excluded. Autofluorescence bronchoscopy (AFB) was used for tissue sampling. The minimum follow up period was three months and the group underwent close surveillance with repeated AFB. Outcomes included progression-free survival (PFS) and overall survival (OS). **Result:** Among 40 included patients, 17 patients had a positive FDG-PET-scan at baseline of which 13 (76,5%) patients developed lung cancer during follow up. Twenty-three patients had a negative FDG-PET of which 6 (26,1%) developed lung cancer during follow-up. The FDG-PET-positive group had a median progression free survival of 5,0 months and the FDG-PET-negative group 33,0 months (p<0,0001, Figure 2). There was no significant difference in overall survival between both groups.



Conclusion: Our present work demonstrates that subjects with pre-invasive endobronchial lesions and a positive FDG-PET scan are at high risk to develop lung cancer. We reported a significantly longer progression free survival in patients with pre-invasive lesions with a negative FDG-PET scan. This suggests that FDG-PET scan can be used to select patients that require more radical cancer treatment.

Keywords: pre-invasive lesions, pet-scan, Lung cancer

P2.11-37 LOW-DOSE CT LUNG SCREENING: ANALYSIS OF RISK FACTORS RELATED TO LUNG CANCER

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Background: LDCT has been increasingly accepted as an efficient screening method for lung cancer detection and mortality reduction in high-risk populations. Screening data based lung cacer risk factors analysis is supposed to benefit identifying high-risk population of lung cancer.The aims of this study are to provide data support for identifying high-risk groups of lung cancer and to improve the effectiveness of LDCT lung cancer screening. **Method:** Subjects consisted of 5366 asymptomatic and voluntary participants (includes 2762 males and 2604 females) aged 40-87 years old, who received LDCT in Cancer Hospital, Chinese Academy of Medical Sciences between Jan 1st, 2014 and Dec 31st, 2017. Participants finished questionnaires relevant to risk factors and were provided Low-dose CT scans. The LDCT Radiological results were interpreted according to the I-ELCAP lung Screening Protocol. Multivariate logistic regression examined associations of risk factors within Age, Sex, Smoking status, Second-hand smoking status, COPD, Asthma, Family history of lung cancer, History of tuberculosis, Occupational exposure and Diabetes. **Result:** 389 of the 5366 participants had a positive(including lung cancer) screen with LDCT, 26 participants were pathologically confirmed lung cancer. Multivariate logistic regression showed that age and smoking (previous smoking and current smoking) were risk factors related to lung cancer and positive nodules. There was no risk factor in distinguishing between lung cancer and positive nodules(excluded lung cancer). Stratified by age, Multivariate logistic regression did not identify any risk factor related to lung cancer and positive nodules in 40-49 years old group, while 3 risk factors were identified in ≥50 years old group (age, smoking, and history of tuberculosis).

Table 1. Multivariate logistic regression of risk factor associated with lung cancer and positive nodules (389Cases of LDCT positive nodules versus 4977Cases of LDCT negative)

Variable	*OR*	*95% CI*	*p-value*
Age	1.04	1.02-1.05	**<0.001**
Sex			
Female	Ref.		
Male	1.02	0.78-1.34	0.873
Smoking status			
No	Ref.		
Former	1.87	1.33-2.63	**<0.001**
Current	1.72	1.27-2.32	**<0.001**
Second-hand smoking status			
No	Ref.		
Yes	0.90	0.69-1.18	0.445
Diabetes			
No	Ref.		
Yes	0.63	0.39-1.02	0.062
Unknown	1.19	0.73-1.93	0.492
Family history of lung cancer			
No	Ref.		
Yes	0.92	0.68-1.25	0.600
History of COPD			
No	Ref.		
Yes	1.63	0.93-2.86	0.086
Unknown	1.17	0.70-1.93	0.553
History of Asthma			
No	Ref.		
Yes	0.88	0.45-1.73	0.712
Unknown	0.48	0.24-0.95	0.036
History of tuberculosis			
No	Ref.		
Yes	4.26	1.12-16.14	0.033
Unknown	0	0-1000	0.968
Occupational exposure			
No	Ref.		
Yes	1.42	0.87-2.31	0.157

Table 2. Multivariate logistic regression of risk factors related to lung cancer and positive nodule(s) in ≥50years old (255 Cases of LDCT positive nodules versus 2564 Cases of LDCT negative)

Variable	*OR*	*95% CI*	*p-value*
Age	1.04	1.02-1.06	**<0.001**
Sex			
Female	Ref.		
Male	1.09	0.78-1.52	0.632
Smoking status			
No	Ref.		
Former	2.11	1.41-3.17	**<0.001**
Current	1.86	1.28-2.70	**0.001**
Second-hand smoking status			
No	Ref.		
Yes	0.83	0.60-1.15	0.261
Diabetes			
No	Ref.		
Yes	0.65	0.39-1.10	0.107
Unknown	1.21	0.66-2.19	0.538
Family history of lung cancer			
No	Ref.		
Yes	1.21	0.85-1.73	0.284
History of COPD			
No	Ref.		
Yes	1.56	0.79-3.09	0.107
Unknown	1.20	0.61-2.36	0.538
History of Asthma			
No	Ref.		
Yes	0.77	0.33-1.83	0.562
Unknown	0.49	0.21-1.17	0.107
History of tuberculosis			
No	Ref.		
Yes	10.29	1.96-54.06	**0.006**
Unknown	0	0-1000	0.977
Occupational exposure			
No	Ref.		
Yes	1.58	0.89-2.80	0.122

Conclusion: • Age, smoking are risk factors related to lung cancer and positive nodules. • ≥50 years old with a history of smoking or tuberculosis may be a high risk group for lung cancer in China.

Keywords: Lung cancer, Risk Factors, LDCT screening

POSTERS

P2.11-38 CREATING A SUCCESSFUL MULTIDISCIPLINARY CONFERENCE FOR REVIEW OF SUSPICIOUS LUNG NODULES

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Background: National Jewish Health established a weekly Multidisciplinary Conference for review of suspicious lung nodules in December 2016. The conference provides a forum to guide prompt work-up and provide management recommendations to providers. Experience with the conference and lessons learned are described. **Method:** A Lung Nodule Registry with a tracking system for the management of incidental lung nodules was implemented in 2011. Nodule follow-up recommendations are based on Fleischner Society guidelines, with an additional category, Track Dx, created within the tracking system for radiologists to flag reports with highly suspicious lung nodules. A local Lung Cancer Screening Registry was created in 2015 based on LungRADS. Radiologists provide a Tracker phrase or a LungRADS classification at the bottom of their reports. The Lung Nodule Registry and the Lung Cancer Screening Registry are data-mined weekly to create a report of patients who have received a Screen 4A, 4B, 4X or Track Dx recommendation in their imaging reports. These entries populate a list of cases for the upcoming Nodule Conference and ordering providers for the patients are invited to attend. Ideally the ordering provider attends the conference to review the patient history and engage in the discussion of recommended next steps. The radiologist prepares cases for review. The conference occurs immediately following Thoracic Tumor Board and is attended by thoracic radiology, pulmonology, thoracic surgery, oncology and interventional pulmonary. After the conference the lung nodule navigator and radiologist send an email summarizing the recommendations to the ordering provider. Cases are entered into a REDCap database for long term follow-up to ascertain outcomes. **Result:** From December 2016 – March 2019, 681 suspicious nodule cases were identified and reviewed at Nodule Conference. Of these, 155 were screening CTs classified as 4A, 4B or 4X. 371 were Track Dx cases. 133 additional cases were reviewed at the request of the ordering providers. Successful components and lessons learned from the conference are: Timely review of cases on a weekly basis is important to promote prompt work-up and evaluation. It is beneficial to schedule the Nodule Conference immediately after the regular Thoracic Tumor Board since the key people are already gathered. While LungRADS 3 cases are considered "positive," there is usually little debate about the recommendation for a 6 month follow-up CT. We initially included the LungRADS 3 cases in our Nodule Conference but soon discovered this was unnecessary and subsequently included only the LungRADS 4 cases. The radiologist covering the conference adds an addendum to the original radiology report outlining the recommendations from Nodule Conference so this is documented in the EHR. The radiologists add the LungRADS 4 and Track Dx notations to the radiology reports for PET-CT and outside exam interpretations so these can be data-mined and tracked. **Conclusion:** The conference has been well received by the ordering providers. The conference has resulted in a cultural change in our clinical staff with increased provider awareness of the need for timely nodule management and multiple requests for assistance with nodule cases.

Keyword: nodule management, suspicious nodules, multidisciplinary committee review

P2.11-39 MULTIMODAL MONITORING OF PATIENT-DERIVED EARLY-STAGE LUNG ADENOCARCINOMA WITH THE CHICKEN CHORIOALLANTOIC MEMBRANE SYSTEM

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Background: Positron-emission-tomography (PET), imaging uptake of [18F] fluorodeoxyglucose (FDG), is a powerful tool for lung cancer staging, but lacks sensitivity in early lesions. We have recently discovered that early-stage lung adenocarcinoma (LUAD) depends on another system for glucose uptake, the sodium- glucose transporter 2 (SGLT2), not detected by FDG PET. The tracer methyl 4-[18F] fluorodeoxyglucose (Me4FDG) is specific for SGLTs. Because the establishment of patient-derived xenografts (PDXs) from early-stageLUAD is characterized by low efficiency and long experimental times, we have developed an alternative model to study tumor metabolism in LUAD, based on the implantation of tumor tissue on the chorioallantoic membrane (CAM) of chicken eggs (in ovo system). **Method:** PDXs of LUAD were established in ovo by implanting tumor fragments or dissociated cells in matrigel onto the CAM of fertilized chicken eggs. Xenografts were grown for up to 10 days. After day 7, the eggs were imaged with FDG and Me4FDG PET to characterize glucose uptake, then rescanned with both tracers after treatment with SGLT2 inhibitor dapagliflozin to prove SGLT2 specificity of Met4FDG. Multiparametric magnetic resonance imaging (MRI) was performed to assess tumor growth, morphology (T1w, T2w, diffusion-weighted imaging) and vasculature (angiography; GadospinP). At day 10, the xenografts were harvested for histology and immunohistochemistry or reimplanted onto a new CAM for continuous passaging. **Result:** FDG- and Me4FDG-PET adenocarcinomas confirmed the presence of both glucose transporters, GLUT1 and SGLT2. MRI angiography revealed that both tumor plaques and tumor fragments were connected to the embryonic vasculature. Following dapagliflozin treatment, Met4FDG uptake was successfully blocked in the PD tumor fragments. **Conclusion:** The CAM xenograft model is useful for studying the heterogeneity of glucose uptake in ovo by imaging the activity of different transporters with FDG and Me4FDG. The novel PET tracer Met4FDG allows to validate SGLT2 expression as well as its blockage by SGLT2 inhibitors gliflozins.

Keywords: early-stage lung adenocarcinoma, preclinical imaging, patient-derived xenografts

P2.11-40 INTEGRATION OF INDIVIDUALIZED TOBACCO CESSATION COUNSELING IN A LUNG CANCER SCREENING PROGRAM

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Background: Many patients in a lung screening program are unable to quit despite the knowledge that smoking is harmful. Continued smoking leads to increased risk of poorer outcomes in all patients. Our lung cancer screening program has a high rate of patients smoking at the time of the Low Dose Computed Tomography (LDCT) (70.2% smoking; 309/440). Screening with LDCT has been considered a teachable moment and a possible time for intervention with smoking cessation resources. Providing counseling at the point of service may be a convenient and effective method to deliver smoking cessation resources to a population in need. **Method:** Individualized counseling was provided for all patients in our lung cancer screening program as a standard part of their care using an opt-out framework. All patients were surveyed for use, and cessation support consisted of individual counseling by a nurse practitioner and tailored to the patient. The counselor met the patient at the time of the LDCT in the radiology department for a structured tobacco cessation intervention which typically lasted 10-15 minutes. Data regarding use was entered in the electronic medical record and an IRB approved database. Exhaled breath carbon monoxide testing was used in some cases to validate cessation or reduction. The intervention consisted of counseling and referral to a quitline, a group counseling session, and/or recommendations for over-the-counter pharmacotherapy. **Result:** A total of 263 patients had undergone LDCT, had been smoking at the time of the LDCT, and have follow up data available. A combination of retrospective chart review, scripted telephone survey, and/or in-person follow up was used to collect data regarding tobacco use. Of those who were smoking and received a LDCT, 12.9% (34/263) of patients had quit smoking while after receiving personalized counseling. Of the 229 patients still smoking, the quantity that they were smoking was available for 156 of these patients. Of those with data available, 50.0% (78/156) who were still smoking had decreased the amount that they were using. **Conclusion:** Patients who undergo screening with LDCT are receptive to individualized in person counseling when provided at the point of service. This model of opt-out cessation counseling was well received and yielded a 12.9% cessation rate, with one session of counseling and referral to an outside resource. Due to the logistics of the intervention in the radiology department, the counselors did not directly provide pharmacotherapy to the patients in this intervention, but made recommendations. Cessation rates

would likely increase when pharmacotherapy and further counseling is used. Even in those who do not quit, half of patients decrease the amount used on a daily basis.

Keywords: smoking cessation, Screening, Tobacco

P2.11-41 IMPROVING ANNUAL ADHERENCE IN A COMMUNITY BASED LUNG CANCER SCREENING PROGRAM

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Background: Lung cancer is the third most common type of cancer diagnosed in the United States, but it is the leading cause of cancer deaths (U.S. Cancer Statistics Working Group, 2018). Lung cancer is most often diagnosed at late stages which have low survival rates. The National Lung Screening Trial (NLST) was an NCI funded trial which determined that screening with annual low dose CT as compared to chest radiograph would reduce mortality by 20% in high risk populations (Team, 2011). Since the implementation of our screening program in 2012 we witnessed a steady increase in our initial screening LDCT scans. However the rate of overall adherence was surprising low at 40.1% despite programmatic efforts to contact patients for annual LDCT scans. The NLST included an impressive level of adherence of 95% in the LDCT group and 93% in the radiography group (Cattaneo II, Meisenberg, Geronimo, Bhandari, Maxted, & Brady-Copertino, 2018). We designed a quality improvement project seeking to increase our annual adherence rate. **Method:** At the start of 2018 we created a reminder letter directed towards the patients' referring providers. Using the existing tracking system which was put into place to ensure the necessity of follow up scans are communicated to the patients and completed, we generated reminder letters to the referring providers as well as the patients for anyone that had a scan in 2017. **Result:** Based on our added communications with the referring community providers, we increased our overall adherence rate to 58.2%. Looking at smoking status, current smokers increased their adherence by 15.3%, former smokers increased by 16.1%, recent smokers increased by 23.1%. Looking at patients that indicated they had prior lung disease, we increased their adherence by 15.5%. Those who indicated no prior lung disease, we increased their adherence by 17.8%. Patients who identified a family history of lung cancer we increased their adherence by 18.1%. Those who indicated no family history of lung cancer, we increased their adherence by 17.1%. Patients in their 50s, we increased their adherence by 23.3%. Patients in their 60s, we increased their adherence by 17.5% Patients in their 70s we increased their adherence by 7.8%. Males increased their adherence by 20.1% and females by 14.7%. From 2012-2017, we diagnosed 5 lung cancer and 7 non lung cancers. In 2018 we diagnosed 7 lung cancers and 1 non lung cancer. **Conclusion:** We have found communicating with referring community providers as well as patients increase adherence in a community based lung cancer screening program. This led to increased diagnosing of early stage lung cancers in high risk populations.

Keywords: adherence, community screening program, community providers

P2.11-42 A PROSPECTIVE MULTICENTER STUDY TO ASSESS COMBINED 6 TUMOR MARKERS FOR EARLY STAGE LUNG CANCER IN PATIENTS WITH LUNG NODULE

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Background: Lung cancer (LC) is one of the most prevalent and fatal cancer worldwide. The prognosis of LC is closely related to the stage. Low-dose computed tomography (LDCT) is recommended for LC screening in high risk population. More and more lung nodules were detected, but only less than 4% patients were LC. Also, the access to LDCT scan for the high risk population was very low. We conducted a prospective, multicenter study to assess the diagnostic accuracy of combined 6 tumor markers (TMs, CEA, CYFRA21-1, CA15-3, SCC, NSE and ProGRP) for aid in diagnosis in lung nodule patients. **Method:** Patients, ≥18years old, who were newly diagnosed with lung nodules, 830 mm, by CT scan were prospectively recruited. Blood samples were obtained by peripheral venipuncture in all patients before the final diagnosis had been established. The patients were divided into two groups according to the pathology result or clinical diagnosis: LC group and benign lung nodule group. The 6 serum TMs were tested for all patients. When these six TMs were assessed in combination, the presence of ≥1 abnormal TM values were considered as abnormal. Sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were calculated and the area under the receiver operating characteristic curve (AUC) was analyzed. **Result:** A total 492 predominant lung nodules patients were included in the study analysis, with median age of 59 (IQR: 53-66) years old. 59.6% of the patients were female and 67.5% were non-smokers. Median lung nodule size was 15.75 mm (IQR: 11.75-21.00). 374 (76.02%) patients were diagnosed with LC, of which 94% patients were at I-II stage. SN, SP, PPV, and NPV of the combined 6 markers for LC diagnosis were 39.57% (95%CI, 34.62%, 44.53%), 75.42% (95%CI, 67.66%, 83.19%), 83.62% (95%CI: 78.16%, 89.07%) and 28.25% (95%CI, 23.28%, 33.23%), respectively. AUC showed the combined 6 markers had better diagnostic performance than each individual marker. **Conclusion:** Combined 6 TMs increased the diagnostic performance for LC, comparing to the use of individual marker. Given its higher specificity, the presence of ≥1 abnormal TM values could support LC diagnosis in patients with predominant lung nodule detected by CT scan.

Keywords: Lung cancer, tumour marker, lung nodule

P2.11-43 MANAGEMENT OF PULMONARY NODULES DETECTED ON CT: MULTICENTER COLLABORATIVE STUDY IN NAGASAKI PREFECTURE

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Background: Pulmonary nodules are frequently detected on low-dose CT screening of the chest. Most of them are benign and lung cancer is only a part, so handling of pulmonary nodules is a major issue. Although the guidelines of the Japanese Society of CT Screening have been published, the examination of their usefulness is not sufficient. Therefore, the pulmonary nodules detected on CT were handled according to the guideline (version 2), and the clinical significance and the usefulness of the guideline were examined. **Method:** Pulmonary nodules with 5mm or larger in size on initial chest CT were followed up prospectively at five facilities in Nagasaki Prefecture. CT Images and clinical data were collected in one center, and analysis was performed on the same workstation (Aquarius Net Station ver. 1.5). In the central review, measurement at the workstation and evaluation of visual characteristics of the nodules were performed by two or more experienced radiologists, and the results were returned to the participating facilities to be reflected in the handling and follow-up of the nodules. **Result:** 131 cases were registered in total, 39 cases were excluded and the remaining 92 cases were analyzed (57 women, 35 men, average age 65.6 (39-87) years old). 39 cases were solid nodule, 17 cases were part solid ground-glass nodule (GGN) and 36 cases were pure GGN. 20 cases were surgically resected, and histological findings were obtained for 17 nodules: 14 adenocarciomas (two solid nodules, 7 part solid GGNs and 5 pure GGNs), two squamous cell carcinomas (two solid nodules), one lung metastasis (solid nodule). Fifteen cases shrank or disappeared overtime (7 solid nodules, 4 part solid GGNs and 4 pure GGNs). Twenty-four month follow-up was completed in 57 cases (27 solid nodules, 3 part solid GGNs and 27 pure GGNs). **Conclusion:** Although handling of pulmonary nodules detected on chest CT was conventionally left to the discretion of the institution /in-charge doctor, using this guideline made the policy of clearer and became possible to evaluate the natural history of pulmonary nodules correctly. There were no cases that became inoperable due to the appearance of distant metastasis during follow-up, and this guideline was considered appropriate.

Keywords: pulmonary nodule, CT screening

P2.11-44 A PRELIMINARY STUDY INVESTIGATING THE IMPACT OF PLATELET ON CIRCULATING TUMOR CELL ENUMERATION

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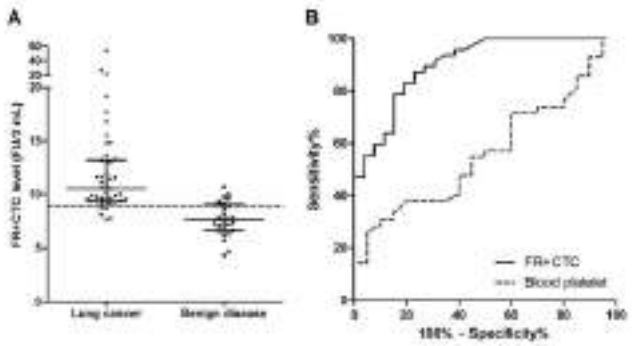
Background: Circulating tumor cell (CTC) is generally considered as the source of cancer metastasis. Blood platelet has been reported to interact with CTCs and enhance its survival. However, the "masking effect" of blood platelet may lead to the false-negative results in CTC test. In this preliminary study, we aimed to investigate the impact of platelet on CTC enumeration. **Method:** A total of 73 treatment-naïve participants with indeterminate pulmonary nodules according to computed tomography scan were recruited. Three milliliters of baseline peripheral blood samples were collected from each participant for CTC enumeration. Negative enrichment and ligand-targeted polymerase chain reaction methods were used to examine the expression level of folate receptor-positive CTC (FR+CTC). All participants subsequently undergo surgery or biopsy to obtain tumor specimens for pathological assessment. ROC analysis was used to determine the diagnostic performance of FR+CTC. For the recruited lung cancer patients, the association between FR+CTC levels and platelet count was also analyzed.



Result: 47 patients with pathologically confirmed lung cancer and 26 patients with benign lung diseases (considered as the control group) were included in this analysis. In agreement with previous studies, lung cancer patients showed a significantly higher FR+CTC level compared to the control group (10.6 versus 7.7 FU/3 mL, P<0.0001). With 9.1 FU/3 mL as the cut-off threshold, the sensitivity and specificity of FR+CTC were 87.23% and 76.92%, respectively (Area under curve=0.9006, 95% confidence interval: 0.8291-0.9720). Among the 42 patients with platelet count in the lung cancer group, 36 (85.7%) were positive for CTC and 6 (14.3%) were negative for CTC. The levels of platelet count in CTC-positive group were lower than those in CTC-negative group, but the difference was not statistically significant (217.8±73.6 versus 253.5±41.4 ×109 /L, P=0.1833). Correlation was also not statistically significant between the FR+CTC level and platelet count (Spearman R=-0.2113, P=0.0993). **Conclusion:** CTC enumeration in this study was not affected by the surface epitope masking effect of blood platelet, suggesting that FR+CTC detection has better applicability than the positive enrichment and immunocytochemical method. Further systematic study is required to validate the hypothesis.

Keywords: circulating tumor cell, Enumeration, Platelet

P2.11-45 ECONOMICAL SCREENING FOR LUNG CANCER IN A DEVELOPING COUNTRY - 5 YEARS EXPERIENCE

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Background: In India where the tobacco use in the form of smoking like cigarettes,Beedi and cigars is highly prevalent and to screen for lung cancer earlier is essential and should be economical considering the less healthcare funds.Hence this study. **Method:** Patients attending the General Medicine department for the past five years from 2014 to 2018 with the history of smoking of any type,of duration of more than ten years and cough for more than ten days duration were enlisted for this screening for lung cancer. Passive smokers like wives of the husbands who smoke were also considered for screening.The duration of smoking ranges from 12 years to 25 years and the mean duration was 18 years. The duration of cough ranges from 11 days to 20 days and the mean duration was 15 days.The tests are easily available and affordable.Totally 100 patients were screened.Ninety males and ten females were included in the study. The age ranges from 35 years to 60 years and the mean age was 52 years.The investigations conducted were X- ray chest PA view as a first line of screening. If shadows were found suspicious of possible malignancy in the imaging,the blood investigations ESR,Hb and LDH total were estimated for every patient listed for study. The increase in ESR more than 50 mm per hour,Hb ,less than 10 Gms and the total LDH more than 500 units per litre (normal being upto 350 units per litre) were the screening criteria.When all the three criteria of blood fulfilled or two,then CT Scan chest was ordered.Out of 100 patients screened,24 males and 2 females underwent CT Scan.CT Scan showing possible malignant lesions were subjected to CT guided biopsy of the lesion and reported about the malignancy and types. **Result:** Out of 100 patients,24 males and 2 females undergone CT Scan Chest. Biopsy has been taken in all the above patients by CT guidance.15 males and 1 female were reported as malignancy. The statistical significance cannot be applied because of the non availability of control patients.The details of the types and grading will be presented.All were referred for further management to Oncology centres. **Conclusion:** When suspecting lung cancer in a smoker or passive smoker,following the already described investigations which are economical before going for CT Scan and guided biopsy,will be economical for developing countries like India because of the less availability of funds.This study highlights the economical method of screening for Lung Cancer especially in developing countries.

Keywords: economical screening of lung cancer, x-ray chest, CT-guided biopsy

P2.12 SMALL CELL LUNG CANCER/NET
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.12-01 SMALL CELL LUNG CANCER (SCLC) TREATMENT AND SURVIVAL IN THE UK: A REAL-ONCOLOGY ANALYSIS FROM THE I-O OPTIMISE INITIATIVE

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Background: Outcomes for patients with extensive disease (ED) SCLC are poor. Treatment options have remained mostly unchanged for several decades. As part of I-O Optimise, a multinational research platform providing insights into the real-world management of lung cancers, clinical characteristics and outcomes of patients with ED-SCLC at Leeds Cancer Centre, UK, are presented. **Method:** This retrospective cohort study used longitudinal data collected from electronic medical records of adult patients diagnosed with ED-SCLC between January 2007 and August 2017 (follow-up to December 2018). ED was defined as stage IV disease at diagnosis or, where staging was missing, by clinical review using the Veterans Administration Lung Cancer Study Group (VALSG) system. Patients with a concomitant malignant primary tumour or missing data for age or sex were excluded. Distinct lines of therapy (LoTs) were identified using a clinically verified algorithm based on name and date of systemic anti-cancer therapy (SACT) prescribed. Overall survival (OS) was determined using Kaplan–Meier methods. **Result:** Of 5834 patients diagnosed with lung cancer during the study period, 695 (11.9%) had SCLC. Of 655 patients remaining after study exclusions, 425 (64.9%) had ED-SCLC. Where complete years of data were available (2007–2016), there was a decrease in the proportion of ED-SCLC diagnoses (from 76.3% to 60.0%). Among patients with ED-SCLC, median age was 69 years (range: 62–75) and 50.4% were male; 31.3% had a World Health Organization performance score (PS) of 0–1, 23.8% had PS2, 21.9% had PS3, and 7.3% had PS4. In total, 272 patients (64.0%) received SACT. Annual rates of treatment were similar between 2007 and 2016. Proportions treated were highest in patients with PS0–1 (87.2%) and lowest in those with PS4 (9.7%).

Almost all treated patients (96.7%, n=263) received platinum-based SACT as first LoT; 47 patients (17.3% of treated patients) received a second LoT. Median OS (Q1–Q3) for patients with ED-SCLC receiving SACT was 7.2 months (4.3–10.5) versus 0.7 months (0.3–1.6) for those not receiving SACT. Median OS was similar for treated patients with PS0–1 and PS2 (7.4 and 7.2 months, respectively). **Conclusion:** In line with other real-world studies, outcomes for patients presenting with ED-SCLC are poor, especially if untreated. Levels of treatment have not improved over the past decade. Availability of new immune checkpoint inhibitors may provide improved survival for some patients, but additional approaches are urgently needed.

Keywords: Immunotherapy, I-O Optimise, real-world evidence

P2.12-02 INTERTUMORAL HETEROGENEITY IN SMALL CELL LUNG CARCINOMA ACCORDING TO THE PRIMARY TUMOR VERSUS LYMPH NODE METASTASES DELINEATED BY RNA SEQUENCING

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Background: The pathological diagnosis of small cell lung cancer (SCLC) was determined mainly based on the simple morphological pattern for decades with no significant therapeutic advancements. Exploring the gene expression profile of matched primary and lymph node (LN) metastatic SCLC tumors might provide unique insights into new potential therapeutic approaches. **Method:** A total of 32 histologically confirmed SCLC patients underwent surgical resection with available tumor tissue specimen were included in our study. We performed targeted RNA sequencing, to analyze tumor heterogeneity in terms of differences in gene expression and relevant pathways according to primary tumor and LN metastases. **Result:** We found 6% (n=154) RNA genes with significant differences and only 13.1% (n=336) of all genes in the entire panel had a strong correlation between the primary tumor and LN metastases. Transcription factors had higher percentage of correlation compared to genes in importance in extracellular and cell adhesion receptors and signaling. According to the top 25 RNA genes in our gene panel with significant difference in RNA gene expression the majority of these RNA genes were downregulated (n=20) in LN metastases, having a wide range of functions including proliferation, growth and survival. In contrast, the upregulated top RNA genes (n=5) have a major role in cell adhesion, lymphoid tissue development and inflammatory response. **Conclusion:** Our findings highlight the RNA gene discordance between primary tumors and corresponding LN metastases indicating a non-homogeneous nature of the tumor mass at different anatomical locations with potential therapeutic applications.

Keyword: small cell lung cancer, lymph node metastasis, tumor heterogeneity

P2.12-03 BUILDING AND VALIDATING A LYMPHOCYTE NADIR BASED MODEL TO PREDICT SURVIVAL IN PATIENTS WITH LIMITED STAGE-SMALL CELL LUNG CANCER

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Background: Increasing evidence indicates host immunity participate in cancer progression and metastases. It has been reported that the lymphocyte nadir is an independent prognostic marker for survival in various cancers. We have previously reported a survival significance of baseline lymphocyte in limited stage small cell lung cancer (LS-SCLC). Here we hypothesize that treatment induced lymphopenia, like the lymphocyte nadir during the course of treatment, in combination of clinical factors can predict survival better than conventional models in patients with LS-SCLC. **Method:** This is a retrospective study of 616 patients from a single Institution. Consecutive patients with LS- SCLC treated with thoracic radiation (with or without concurrent chemotherapy) from 2013 to 2017 were included. Additional eligibility included availability of complete-blood-count data from baseline and at least two time points during the course of radiotherapy. These 616 patients were randomly divided into a training dataset (n=308) and a validation dataset (n=308). The primary endpoint was overall OS. Univariate proportional hazard (PH) cox model was used to assess potential clinicopathological predictors on OS. The multivariable Cox PH model was constructed by the forward selection. According to the final Cox model built using significant variables from training dataset, we calculated the risk score for every patient and validate the predictive valuable of the risk score on OS in the validation set. **Result:** Under univariate analysis, younger age (HR 1.02 per 1 yr, 95%CI 1.006-1.043, p=0.008), female gender (HR 1.40, 95%CI 0.95-2.07, p=0.09), earlier stage (stage I-II vs stage III, HR 2.2, 95%CI 1.11-4.33, p=0.02), concurrent chemotherapy (concurrent vs. not, HR 0.61, 95%CI 0.42-0.88, p=0.01) and a higher lymphocyte nadir (HR 0.48, 95% CI 0.20-1.14, per 103 lymphocytes/ μL, p=0.097) was significantly associated with increased OS in the training dataset. Using lymphocyte nadir in combination of significant clinical factors from univariate analysis, we developed a multivariable Cox PH model (lymphocyte nadir: HR 0.39, 95% CI 0.16-0.99, per 103 lymphocytes/ μL, p=0.048) with concordance (C)-index of 0.63. In the validation dataset, the multivariable model revealed that lymphocyte nadir had a borderline significance on OS (HR 0.45, 95% CI 0.19-1.06, per 103 lymphocytes/ μL, p=0.067) with a comparable c-index of 0.60. Moreover, the risk score calculated using the coefficients from the final Cox model built using the training dataset remained to be a significant predictor for OS (HR 2.04, 95% CI 1.36-3.07, per 1 risk score increase, p<0.0001) in validation dataset. **Conclusion:** This may be the first study validated a survival predictive model based on lymphocyte nadir in a large sample of patients with LS-SCLC. Should it should be validated in an external dataset, this model might provide some prediction for each patient and provide an opportunity to individualize treatment based on the individual's survival probability.

Keywords: LS-SCLC, lymphocyte nadir, overall survival

P2.12-04 CLEPSIDRA: A PHASE II TRIAL COMBINING IADADEMSTAT WITH PLATINUM-ETOPOSIDE IN PLATINUM-SENSITIVE RELAPSED SCLC PATIENTS

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Background: Small cell lung cancer (SCLC), an aggressive neuroendocrine malignancy, shows a dismal prognosis with the current pharmacopeia. Notch is a tumor suppressor repressed in SCLC. Iadademstat is the leading selective LSD1 inhibitor and has been shown to re-activate the NOTCH pathway in SCLC, resulting in the repression of ASCL1, a well-known non-druggable SCLC tumor driver, and to produce robust, and in some cases complete and durable, tumor regression in some chemoresistant PDX models. In a previous Phase I study in acute leukemia, iadademstat was safe and well tolerated, supporting it is a meaningful candidate for combination therapy with other agents. This is the first combo trial in SCLC with a LSD1 inhibitor and the current SoC. **Method:** CLEPSIDRA (EudraCT nº 2018-000469-35) is a Phase II study of iadademstat as a second line treatment in combination with platinum plus etoposide re-challenge chemotherapy in patients with relapsed extensive stage SCLC, that includes biopsy biomarkers expression as inclusion criteria to increase likeliness of response to iadademstat treatment. CLEPSIDRA is an open label single-arm multicenter study to assess for the first time the safety, tolerability, dose finding and efficacy of iadademstat in combination with chemotherapy in SCLC patients. It is planned to enroll up to 36 patients. The study is composed of a dose/regime finding part aimed to establish the recommended dose and regime of the combination, and a second part to assess clinical activity by RECIST criteria. **Result:** The design of the trial and the preliminary results in safety, tolerability and clinical activity as per August 2019 cut-off will be presented and discussed. Preliminary results of the first three subjects with RECIST data available as per April showed a 72% RECIST reduction (from 80 at screening to 43 on cycle 2 and 23 after 4 cycles of treatment) in one subject and stable disease at cycle 2 in the other two subjects. **Conclusion:** Combination of multiple oncological drugs requires careful selection of doses and regimes as their toxicity is often accentuated by the addition of a

new component. Neutropenia induced by the etoposide-platinum has to be managed when dosing iadademstat. Current data suggest that these toxicities may be managed in an acceptable manner. The initial clinical responses observed also suggest that the combination of iadademstat with SoC may be clinically effective in second line relapsed SCLC patients.

Keywords: SCLC, LSD1 inhibitor, epigenetic

P2.12-05 A PHASE II TRIAL OF PEMBROLIZUMAB WITH CHEMOTHERAPY IN METASTATIC OR UNRESECTABLE HIGH GRADE NEUROENDOCRINE CARCINOMA

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Background: Combination chemotherapy is the mainstay of treatment for patients with high-grade gastroenteropancreatic neuroendocrine carcinoma (GEPNECs) and neuroendocrine carcinomas (NECs) of the lung. Pembrolizumab, a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb), has high specificity for binding to the programmed cell death 1 (PD-1) receptor thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). In combination with chemotherapy, pembrolizumab blocks the protective mechanism of cancer cells and allows the immune system to destroy them. Combination chemotherapy and pembrolizumab was recently FDA approved and ongoing trials are utilizing this or similar combinations with data demonstrating a promising safety profile. The purpose of this study is to test the efficacy, safety, and tolerability of combination chemotherapy with pembrolizumab in patients with high-grade neuroendocrine carcinomas of the gastroenteropancreatic system or lung who are chemotherapy naïve. **Method:** This is an open label, phase II, single institution, multi-site trial using pembrolizumab in combination with either cisplatin or carboplatin and etoposide in patients with high grade neuroendocrine carcinomas of the gastroenteropancreatic system or lung who are chemotherapy naïve. Patients with a histologic diagnosis of a GEPNECs with a Ki-67 of 55% or higher or a large cell NEC of the lung will be eligible for inclusion in this study. Subjects must be deemed unresectable and have not undergone prior chemotherapy for metastatic disease. Patients must also have at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1, and a predicted life expectancy > 3 months. Approximately 36 GEPNEC patients will be enrolled with an exploratory LCNEC of the lung cohort of approximately 6 patients. Patients will receive pembrolizumab 200mg IV in combination with cisplatin 80 mg/m2 or carboplatin AUC 6 on day 1 and etoposide 100mg/m2 on days 1-3 of a 21-day cycle. Tumor response will be assessed by computerized tomography scan every 6 weeks calculated with the first CT within 7 days of initiation of treatment. RECIST 1.1 will be used for treatment decisions until there is evidence of progressive disease (PD). Those patients who have responsive or stable disease after 4-6 cycles of platinum-based chemotherapy will move to maintenance pembrolizumab every 3 weeks. The primary endpoint will be progression free survival (PFS) per RECIST 1.1. ClinicalTrials.gov Identifier: NCT03901378 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Pembrolizumab, Anti–PD-1 Immunotherapy, High Grade Neuroendocrine Carcinoma

P2.12-06 FACTORS OF IMPORTANCE FOR SURVIVAL AFTER PLATINUM RE-CHALLENGE IN PLATINUM-SENSITIVE SMALL-CELL LUNG CANCER PATIENTS

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Background: Small-cell lung cancer (SCLC) patients showing sensitivity to platinum-based chemotherapy (PDCT) are usually offered the same combination at the time of tumor progression, if this occurs >3 months after the completion of the first-line treatment. However, no decision tools are available to predict what patients might benefit most from this approach. The aim of the present study was to investigate if certain clinical factors could be of prognostic relevance for re-challenge of PDCT in previously platinum-sensitive patients **Method:** This retrospective study was based on patients diagnosed with SCLC in Sweden between January 2008 and February 2016. The study included patients who had received ≥ 1 cycle of PDCT in the 1st and 2nd line setting, respectively, and had "sensitive relapse", which was defined as PFS ≥180 days after the start of first-line PDCT. The following baseline characteristics were collected; Age, Gender, Stage of the disease, presence of Brain metastasis, treatment with Consolidating thoracic radiotherapy or Prophylactic brain irradiation (PCI) after completion of 1st line PDCT and "Sensitivity days", which was defined as the interval between the initiation of 1st and 2nd line PDCT, respectively. In addition, Performance status (PS) and Laboratory values (Hb, Na, C-reactive protein, Albumin, LDH) before starting 2nd line PDCT were compiled. The uni- and multi-variate analyses were performed using the cox proportional hazards regression model to assess the relationship between clinical characteristics and prognosis. Overall survival was defined as the interval between the initiation of 2nd line until death due to any cause. **Result:** The patient cohort consisted of 101 subjects. The distribution of baseline characteristics was as follows: male/female 46/55, median age (IQR) 68y (61-72), Stage II/III/IV 3/41/57, Brain metastases present/absent 39/62, Thoracic radiotherapy Y/N 30/71, PCI Y/N 52/49, median Sensitivity days (IQR) 399 days (307-511), PS 0/1/2/3 23/38/36/4. The statistically significant independent prognostic factors for overall survival on the multivariate model were PS, LDH values (HR, 95% CI for unit increase 2.10, 1.13-3.91), PCI (HR, 95% CI for presence vs absence 0.27, 0.13-0.56) and "Sensitivity days" (HR, 95% CI for unit increase 0.15, 0.07-0.32). **Conclusion:** The results of this retrospective data analysis suggest that besides PS, other clinical factors that showed robust prognostic relevance for re-challenge with PDCT in platinum-sensitive SCLC are baseline LDH values, the time elapsed between the start of 1st-line PDCT until the start of 2nd-line PDCT, which we have defined as "Sensitivity days", and the administration of PCI after completion of 1st-line chemotherapy. These elements might potentially be taken into consideration for patient selection in this setting.

Keywords: clinical prognostic factors, platinum-sensitive, platinum re-challenge

P2.12-07 PHASE I STUDY OF AMRUBICIN AND CISPLATIN WITH CONCURRENT THORACIC RADIOTHERAPY (TRT) IN LIMITED-DISEASE SMALL CELL LUNG CANCER (LD-SCLC)

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Background: Amrubicin and cisplatin is one of active regimens for patients with extensive-disease small cell lung cancer (ED-SCLC). Combined modality of combination chemotherapy and concurrent thoracic radiotherapy has been recognized as standard treatment for LD-SCLC. This study aimed to determine the maximum tolerated dose (MTD), and dose limiting toxicity (DLT) of amrubicin and cisplatin with concurrent TRT in LD-SCLC. **Method:** Patients fulfilling the following eligibility criteria were enrolled: chemotherapy-naïve, PS0-1, age =<75, LD-SCLC, and adequate organ function. Patients received escalating doses of amrubicin on days 1, 2, and 3, under a fixed 60 mg/m2 of cisplatin on day 1. Four cycles of chemotherapy were repeated every 4 weeks. TRT of once-daily 2Gy/day commenced on day 2 of the first cycle of chemotherapy. The initial doses of amrubicin was 20 mg/m2 (level 1), and the dose was escalated to 25 (level 2) and 30 (level 3) mg/m2. **Result:** Eight patients were enrolled at three dose levels. male/female=3/5; PS 0/1=4/4; median age (range) =68.5 (60-73). Two of two in level 3 experienced DLTs. The presentation of DLTs was grade4 neutropenia and leukopenia lasting more than four days. The MTD determined level 3, and level 2 was recommended for this combined modality. Evaluation of responses were 7 partial response and 1 progressive disease (response rate 87.5%) and the median overall survival time was 24.7 months, and suggested the regimen seemed to be modest activity. **Conclusion:** In combined modality of this chemotherapy with TRT for LD-SCLC, MTD was amrubicin 30 mg/m2 and cisplatin 60 mg/m2, and DLTs were neutropenia and leukemia.

Keywords: amrubicin, cisplatin, radiotherapy

P2.12-08 SURPRISINGLY PROMISING TUMOR CONTROL RATE OF S1 COMBINATION WITH ANLOTINIB WITH REFRACTORY RELAPSED SCLC WHO FAILED ≥ 2 LINES CHEMOTHERAPY

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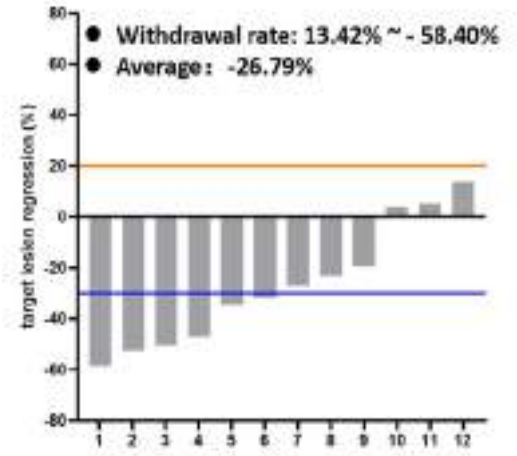
Background: Patients with refractory relapsed small cell lung cancer (SCLC) who failed more than 2 lines chemotherapy have limited options. Objective Response Rate (ORR) of Immunotherapy (CheckMate-032 and Keynote-158) was only 20%. Anlotinib is a novel TKI on multi-kinase (VEGFR, c-Kit, PDGFR, FGFR) angionesis inhibitor, had ORR of only 4.9% in ALTER1202 for the third-line and further-line treatment of SCLC. S-1, a combination of three pharmacological compounds, namely tegafur (prodrug of 5-fluorouracil), gimeracil, and oteracil potassium, is a new oral fluoropyrimidine derivative designed to enhance anticancer activity and reduce gastrointestinal toxicity, has been used for treatment of SCLC with ORR of 4% (MOLECULAR AND CLINICAL ONCOLOGY 1: 263-266, 2013). In patients without any option of systemic therapy, our clinic started combined use of these drugs. This study aimed to report the preliminary results of combined S1 and anlotinib therapy in these refractory released SCLC. **Method:** This study retrospectively analyzed refractory relapsed in SCLC who failed to more than 2 lines' chemotherapy. Eligible patient must have received Anlotinib (12 mg PO QD from day 1 to 14, every 3 weeks) and S1(60mg PO Bid from day 1 to 14, every 3 weeks) combined therapy. The primary endpoints were ORR and disease control rate (DCR). The secondary endpoints were PFS, OS, and safety and tolerability. **Result:** A total of 12 patients were recruited from Nov 2018 in this study. There were 2 females and 10 males. The median age was 64 years (37-75 years). 6 patients had failed 2 lines of refractory diseases and 6 cases failed 3 lines's chemotherapy. Until 31 March 31, 2019, 2, 3, 3, 2, and 2 cases had accomplished 6, 5, 4, 3, and 2 cycles, respectively. The ORR and DCR were 50% and 100%, respectively (Figure 1). The median PFS and OS were not reached at the time of data analysis. The most common Treatment-related adverse events (TRAEs) were hypertension, anorexia, fatigue, blurred vision, and hand-foot syndrome. Grade ≥3 TRAEs occurred in 5 (41.7%) of patients. Anlotinib was reduced to 8mg in 2 patients and 10mg in 3 patients due to grade 3 TRAEs.



Conclusion: The study demonstrates that S1 combination with anlotinib seemed to be an effective treatment option for patients with surprisingly promising response rate in refractory relapsed SCLC. Prospective clinical trial (SALTER Trial, ClinicalTrials.gov ID: NCT03823118) is ongoing to confirm the promising results.

Keywords: S1, Anlotinib, Objective Response Rate (ORR)

P2.12-09 PHASE 2 STUDY OF TALAZOPARIB PLUS LOW-DOSE TEMOZOLOMIDE IN PATIENTS WITH RELAPSED/ REFRACTORY EXTENSIVE-STAGE SMALL CELL LUNG CANCER

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Background: Talazoparib exhibits cytotoxic effects by inhibiting poly (ADP-ribose) polymerase (PARP) proteins 1 and 2 in addition to "trapping" PARP on DNA. Temozolomide (TMZ) has been shown to increase antitumor response when combined with a PARP inhibitor in small cell lung cancer (SCLC) models (Wainberg AACR 2016). Combining PARP inhibition with TMZ as second-line therapy for ES-SCLC may improve disease-related outcomes. **Method:** This is a phase 2, open-label, single-arm study of the safety and efficacy of talazoparib plus TMZ in patients with extensive-stage SCLC. The primary endpoint is objective response rate (ORR) based on RECIST 1.1 criteria. Secondary endpoints include progression-free survival, overall survival, duration of response, and time to response. Exploratory endpoints include biomarker studies such as DNA damage response gene analysis and patient reported outcomes (PRO). Participants are required to have relapsed (progressed within 6 months) or refractory (progressed during or within 4 weeks of completing 1stline platinum-based regimen) ES-SCLC. Those with a best response of progressive disease to first-line therapy per RECIST 1.1 or more than one line of cytotoxic therapy are excluded. Prior immunotherapy is allowed. Participants receive talazoparib 0.75 mg po daily on 28-day cycles with TMZ 37.5 mg/m2 po on days 1-5. 15 participants will be enrolled in the first part of a Simon two-stage design; if 3 or more responses are seen, an additional 13 participants will be enrolled. The null hypothesis will be rejected if 8 or more objective responses are observed compared to a historical control of 15% ORR in second-line topotecan (Horita Sci Rep 2015). **Result:** As of 8 March 2019, 3 participants were evaluable for treatment response. Median age was 51 (range 46-80). One participant had a confirmed partial response (PR) with 50% reduction in target lesions, one had stable disease with 16% reduction in target lesions, and one had progressive disease (PD). Biomarker and PRO analysis correlated with the radiographic response. In the participant with PR, Guardant circulating tumor DNA testing showed PIK3CA amplification and TP53 mutations at baseline that were not detectable at week 5 of treatment, whereas the other subjects has persistent ctDNA. Patient-reported outcomes similarly noted improvement in the participant with PR within 2 weeks while the one with PD showed no improvement throughout treatment course. Adverse events were hematologic, including one grade 4 thrombocytopenia that resolved within 2 weeks. **Conclusion:** Combination talazoparib and TMZ used as second-line therapy in ES-SCLC is tolerable and has shown promising preliminary results. The trial will continue to enroll. Updated response and biomarker data will be presented.

Keywords: Extensive-Stage Small Cell Lung Cancer, clinical trial, biomarkers

P2.12-10 THE CIRCULAR RNA CESRP1 SENSITIZES SMALL CELL LUNG CANCER TO CHEMOTHERAPY

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Background: Circular RNAs (circRNAs), a novel class of non-coding RNAs, have been drawn lots of attention in the pathogenesis of human cancers. However, the biological roles and clinical significance of Circular RNA (circRNAs) in chemosensitivity are not fully understood. In this study, we aim to investigate the biological function, mechanism and clinical significance of hsa-circ-0084927, which we termed ESRP1 gene derived circRNA (cESRP1), in small cell lung cancer (SCLC). **Method:** Differentially expressed circRNAs between chemoresistant cell line and chemosensitive cell line were identified by circRNA microarray and confirmed by qRT-PCR. The functional roles of cESRP1 were demonstrated by a series of in-vitro and in-vivo experiments. The miRNA RNA pull-down, RNA immunoprecipitation, serial deletion analysis and luciferase analyses were used to investigate the potential mechanisms of cESRP1.

Result: The results showed that cESRP1 expression was significantly downregulated in chemoresistant cell lines in comparison with parental chemosensitive cell lines. cESRP1 controlled multiple drugs sensitivity through miR-93-5p in SCLC. In exploring the underlying interaction between cESRP1 and miR-93-5p, we identified that cytoplasmic cESRP1 directly binds to miR-93-5p and inhibits the transcriptional repression of miR-93-5p, thereby up-regulating miR-93-5p downstream target-Smad7/p21 expression and forming a negative feedback loop to regulates TGF-β signaling pathway-induced epithelial-mesenchymal transition. Furthermore, interfering cESRP1 expression or inhibiting TGF-β signaling pathway by inhibitors altered tumor chemotherapy response in mice xenografts including PDX model. In addition, we found cESRP1 was low expressed in SCLC tissues and associated with the patient's survival prognosis. **Conclusion:** Together, our findings reveal the indispensable role of cESRP1 in negative regulation of Smad7/P21-dependent TGF signaling pathway involvement in EMT-induced chemotherapy resistance, providing insights toward a better understanding of the mechanism of resistance to chemotherapy drugs and peripheral recurrence of SCLC.

Keywords: chemoresistance, small cell lung cancer (SCLC), Circular RNA cESRP1

P2.12-11 QUALITY OF LIFE IN ALTER1202 TRIAL OF ANLOTINIB AS THIRD-OR FURTHER LINE THERAPY FOR ADVANCED SMALL CELL LUNG CANCER (SCLC): A POST-HOC ANALYSIS

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Background: Anlotinib significantly improved progress-free survival of advanced small cell lung cancer (SCLC) patients in ALTER1202 trial. In this post-hoc analysis, we assessed the effect of anlotinib on health-related quality of life in ALTER1202 trial. **Method:** In the randomised, phase 2, multicentre ALTER1202 trial, patients with advanced SCLC that received at least two previous lines of chemotherapy were enrolled from 11 centers in China. Eligible patients were randomly assign (2:1) to receive anlotinib or placebo. Health-related quality of life was assessed by EQ-5D scores. Patients filled out questionnaires at screening period and the end of each treatment cycle. **Result:** Between March 30, 2017 and June 8, 2018, a total of 120 patients were enrolled. There were 119 patients with completed questionnaires at screening period, and 106 patients completed questionnaires at the end of the first treatment cycle (76 in anlotinib group, 30 in placebo group). EQ-5D scores had no significant difference between baseline and the end of the first treatment cycle in patients with anlotinib (0.85 versus 0.85, P=0.706). The median EQ-5D VASscores were 80.0 versus 85.0 in anlotinib and placebo group respectively (P=0.323) at screening period, and 90.0 versus 82.5 at the end of the first treatment cycle (P=0.273). The change of EQ-5D VAS scores from baseline to the end of the first treatment cycle was statistically significant (P=0.001) in patients with anlotinib compared to patients with placebo. **Conclusion:** This post-hoc analysis showed that anlotinib maintained health-related quality of life in advanced SCLC patients.

Keywords: Health-related quality of life, Anlotinib, advanced small cell lung cancer

P2.12-12 NOMOGRAMS TO PREDICT SURVIVAL IN PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER TREATED WITH DEFINITIVE CHEMORADIOTHERAPY

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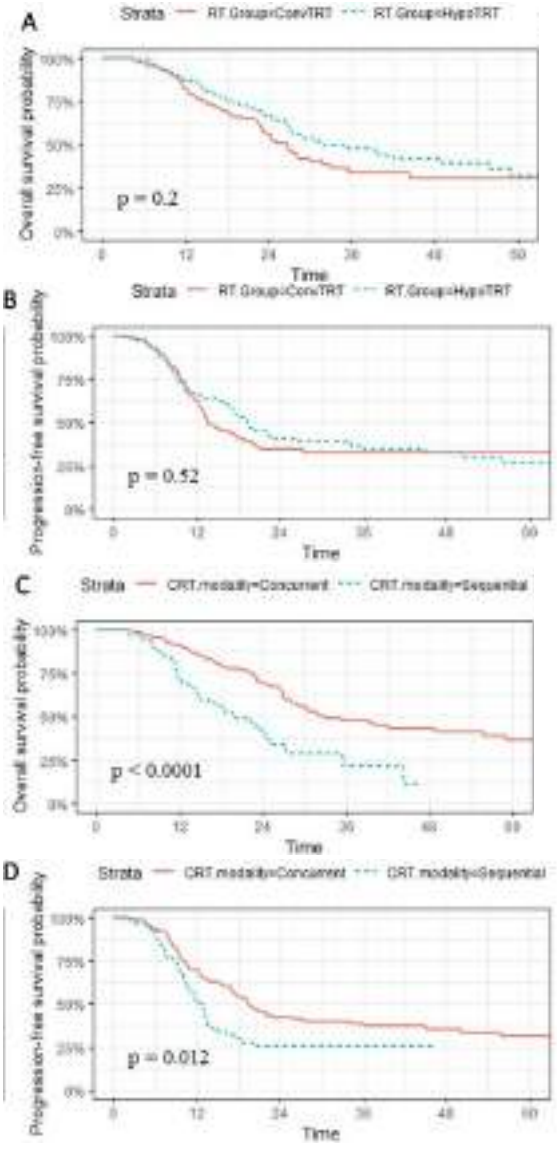
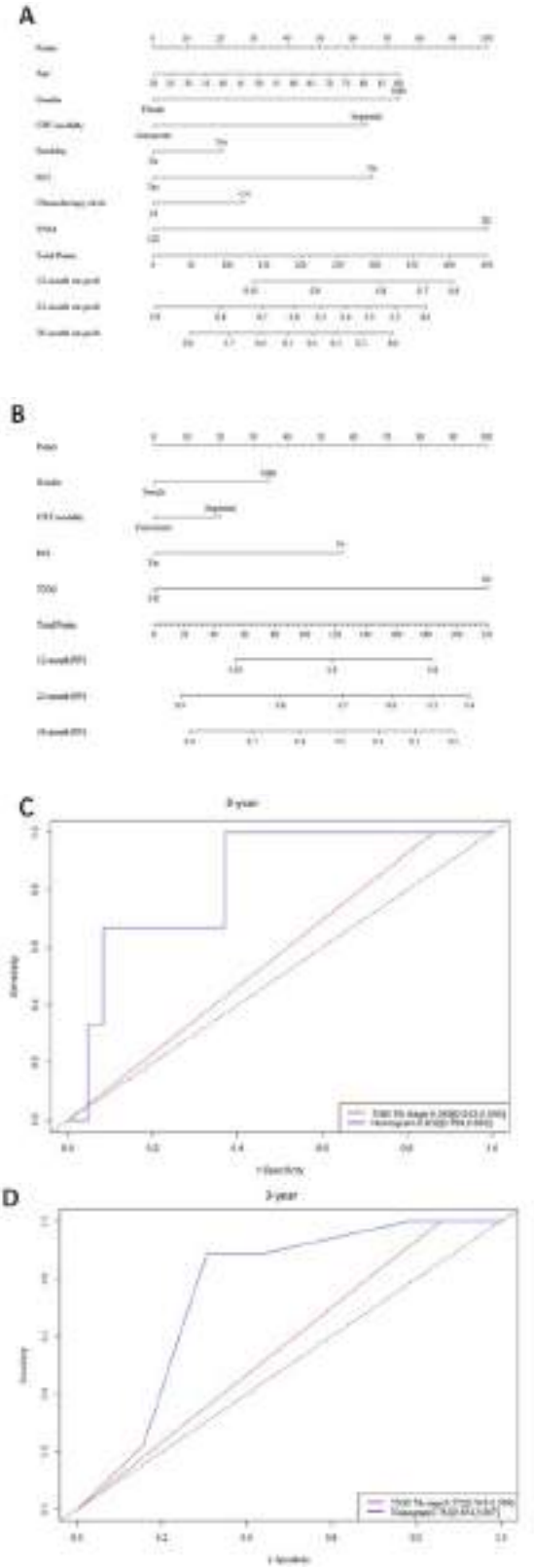
Background: To build nomograms to predict progression-free survival (PFS) as well as overall survival (OS) in patients with limited stage small cell lung cancer (LS-SCLC) treated with definitive chemoradiation. **Method:** A total of 170 patients treated with chemotherapy and hypo- (HypoTRT) (n = 69) or conventionally (ConvTRT) (n = 101) fractionated radiotherapy between 2010 and 2013 were included. Primary endpoints were progression-free survival (PFS) and overall survival (OS). The prognostic effects of variables were analyzed using Kaplan–Meier method and Cox regression model. Nomograms were established for estimating 1-, 2- and 3-year OS and PFS based on Cox regression model. The utility of the proposed model was evaluated using the time-dependent ROC and area under ROC (AUC). **Result:** The survival analysis showed no difference between HypoTRT and ConvTRT combined with chemotherapy. However, regard with the chemoradiotherapy (CRT) modality, the median PFS and OS were 19.4 and 33.0 months in the concurrent group, which was significantly better than those in the sequential group (PFS 12.2 months, p=0.012, OS 20.1 months, p<0.001). According to the multivariate analysis, the final nomograms for OS and PFS were developed. Two nomograms shared common variables including gender, CRT modality, prophylactic cranial irradiation (PCI) and TNM stage, while age at diagnosis, smoking status and chemotherapy circle were only incorporated in the OS nomogram. Nomograms showed better performance than TNM algorithm (3-year AUC for OS: TNM, 0.569; nomogram, 0.832; 3-year AUC for PFS: TNM, 0.572; nomogram, 0.761).





Nomograms for OS (A) and PFS (B) in LS-SCLC patients. ROC curve of the in prediction of prognosis at 3 year point for OS (C) and PFS (D).

Conclusion: Our nomograms are reliable and powerful tools for distinguishing and predicting the survival of LS-SCLC treated with definitive chemoradiation, thus helping to better select medical examinations and optimize treatment options in collaboration with medical oncologists.

Keywords: Limited-stage small cell lung cancer, chemoradiotherapy, Nomogram

P2.12-13 LURBINECTEDIN (L) COMBINED WITH PACLITAXEL (P) OR IRINOTECAN (I) IN RELAPSED SCLC. RESULTS FROM TWO PHASE LB TRIALS

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Background: L is a new agent that exerts antitumor activity through inhibition of trans-activated transcription and modulation of tumor microenvironment. Preclinical evidence of synergism was observed for L in combination with P and I. **Method:** Activity of combinations with LP and LI in small cell lung cancer (SCLC) was reviewed in two phase Ib trials. Patients were enrolled following a 3+3 dose escalation design. SCLC patients with ECOG performance status (PS) 0-1 and pretreated with at least one platinum-based chemotherapy are presented. Extensive pharmacokinetic (PK) sampling for L and P or I was performed. **Result:** 19 pts were treated: 7 with LP and 12 with LI. Baseline characteristics (LP/LI) were: males, 57%/45%; median age, 55/57 years; ECOG PS score 1, 57%/92%; chemotherapy-free interval (CTFI) >90 days, 43%/67%; median (range) prior lines, 1 (1-3)/2 (1-3); liver metastases, 29%/33%.

	Lurbinectedin-Paclitaxel (L: 2.2 mg/m^2 – 5 mg FD + P: 60-80 mg/m^2) * (n=7)	**Lurbinectedin-Irinotecan (L: 1-2.4 mg/m^2 + I: 75 mg/m^2) ** (n=12)**
ORR (CR+PR) CR PR	71% (n=5) 14% (n=1) 57% (n=4)	25% (n=3) 0% 25% (n=3)
ORR in CTFI >90d	67%	38%
CB (CR+PR+SD≥4m)	71%	67%
Median DOR	2.3 m 95% CI (2.0-NR)	4.6 m 95% CI (3.0-6.8)
Median PFS	4.8 m 95% CI (1.8-12.5)	5.6 m 95% CI (1.4-8.3)

* Combination with P given for up to 6 cycles, followed by single-agent L 2.2 mg/m^2. ** One patient received L 3 mg/m^2 + I 15 mg/m^2. CB, clinical benefit; CR, complete response; CTFI, chemotherapy-free interval; d, days; DOR, duration of response; FD, flat dose; I, irinotecan; L, lurbinectedin; m, months; NR, not reached; ORR, overall response rate; P, paclitaxel; PFS, progression-free survival; PR, partial response; SD, stable disease.

Adverse events (AEs): grade (G) 4 neutropenia LP/LI 43%/27% of patients; no episodes of febrile neutropenia in LI, one (G3) in LP; no G4 anemia or G4 thrombocytopenia in either study. Non-hematological toxicity was mild and mainly consisted of G3 fatigue (18%) and G3 nausea (7%) in LI; no G3/4 toxicities were found in LP. No toxic deaths and no discontinuations were due to AEs. PK: mean clearance of L (12 L/h in combo with P, and 9.5 L/h in combo with I), of P (31.5 L/h) and of I (32.2 L/h) are comparable with reported data (11.2 L/h, 31.4/h and 25 L/h, respectively). **Conclusion:** LP and LI combinations showed promising activity after first-line therapy in SCLC. This activity seems consistent with that observed in other trials with L given alone or in combination. Both combinations showed acceptable safety profile. So far, no evidence of major PK drug-drug interactions has been observed. Further development of these combinations is warranted.

Keywords: SCLC, Lurbinectedin, Combination

P2.12-14 A PILOT STUDY OF SERIAL PLASMA METABOLOMICS IN SMALL CELL LUNG CANCER PATIENTS

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Background: Small cell lung cancer (SCLC) is among the deadliest cancers. SCLC is characterized by high proliferation and high turnover metabolism. There are few results of metabolomics analysis correlated with outcomes of SCLC patients. **Method:** This study included 27 patients after excluding eight who were treated with immunotherapy or placebo. Median age of the patients was 65 years (range, 43 to 82), and 23 male patients were included. Three (11%) never-smoker patients were included. Twelve patients were limited disease (LD) and 15 were extensive disease (ED) including three patients with brain metastases. All patients were treated with etoposide and platinum (EP, 20 cisplatin and 7 carboplatin), and nine among 12 patients with LD were treated concurrently with radiotherapy since 3rd cycle of EP chemotherapy. We planned to collect blood samples at diagnosis (T1), after two cycles of chemotherapy (T2) and at the first progression (T3). We analyzed 27 T1 samples, 14 T2 samples, and 18 T3 samples. Metabolomics analysis included 183 metabolites (21 amino acids, 19 biogenic amines, 40 acylcarnitines, 14 lysoglycerophosphocholines, 74 glycerophospholipids, and 14 sphingolipids, 1 hexose) using Absolute*IDQ*® p180 kit (Biocrates Life Sciences AG, Innsbruck, Austria). **Result:** Baseline levels of five acylcarnitines and one glycerophospholipid were associated with progression free survival whereas, the amino acid proline and acylcarnitine (C10:1) were associated to overall survival. In comparison to LD, amino acid, asparagine was elevated while two acylcarnitines (C10:2 and C12:1) were lower in patients with ED. After two cycles of chemotherapy without progression, plasma concentration of 37 lipids (5 LysoPC, 24 glycerophospholipids, 3 sphingolipids and 5 acylcarnitines) were increased. Five mono and poly unsaturated glycerophosphospholipids (PC aa and PC ae) with C42 and C44 fatty acid chains were significantly (adj $p < 0.05$) lower. Of these, chemotherapy and induction of remission induced change in glycerophospholipid PC ae C42:5 was related to overall survival ($p < 0.05$). The 7 glycerophospholipids with C42 and C44 fatty acids were elevated when patients relapsed post chemotherapy. Five glycerophospholipid metabolites were significantly lower in response to chemotherapeutic exposure. The metabolites tended to increase towards baseline levels upon relapse. **Conclusion:** With this preliminary exploratory study, we identified association of metabolites and initial status and outcomes of SCLC. We observed significant modulation in glycerophospholipids upon chemotherapy and relapse which may serve as indicators of therapeutic response and resistance. Further exploration and validation is being underway in larger SCLC population.

Keywords: small cell lung cancer, glycerophospholipids

P2.12-15 THE ROLE OF SURGERY IN PATIENTS WITH SMALL CELL LUNG CANCER: A PERIOD PROPENSITY SCORE MATCHING ANALYSIS OF THE SEER DATABASE, 2010-2015

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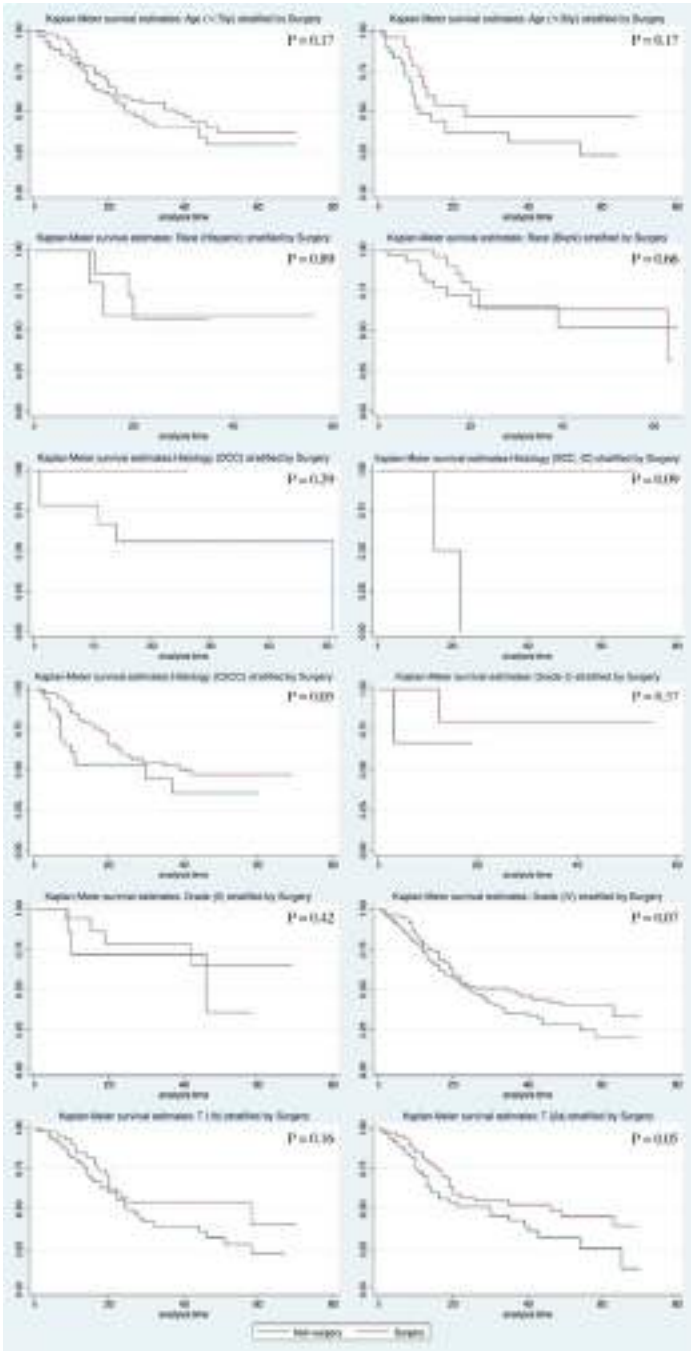
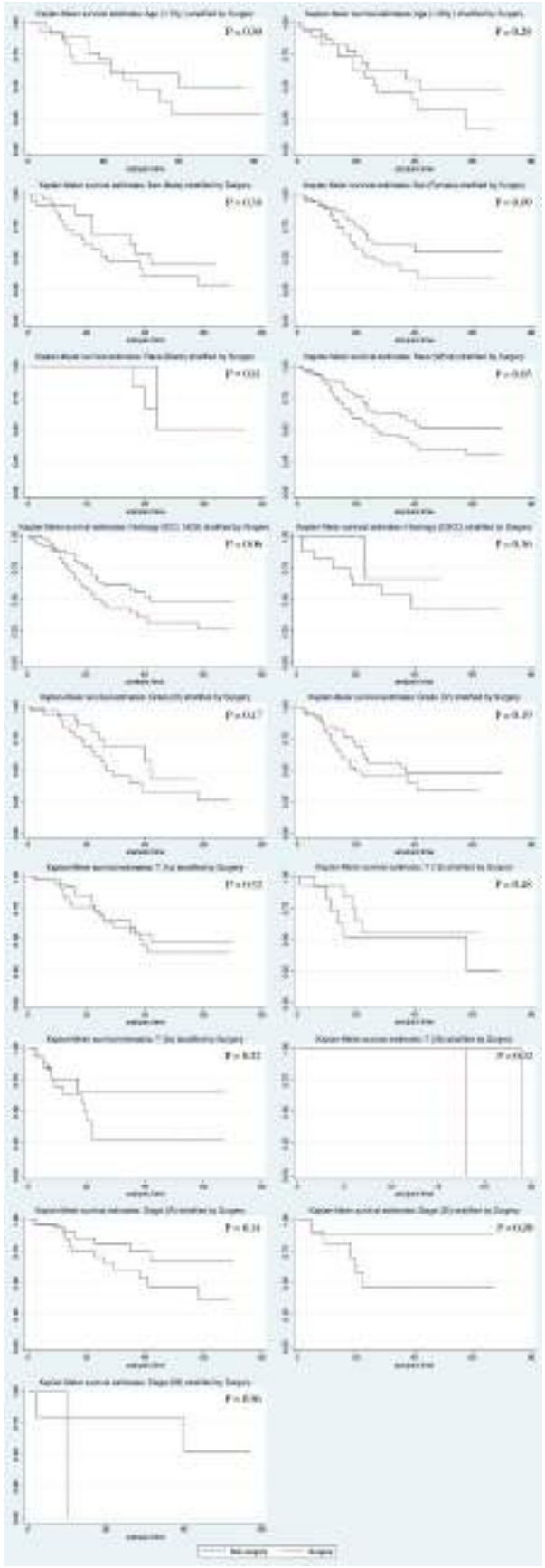
Background: Surgery for non-small cell lung cancer has been widely accepted for years. However, the role of surgery for small cell lung cancer (SCLC) remains controversial. We therefore performed this period propensity score matching analysis using the SEER database the Surveillance, Epidemiology, and End Results (SEER) Registry database to explore the role of surgery on survival in patients with SCLC. **Method:** Patients with SCLC from 2010 to 2015 were identified from the SEER. Individual data for each case were retrieved regarding general clinical characteristics, surgery of primary site, cause-specific death classification and survival time. Differences of cause-specific survival (CSS) between subgroups were estimated by log-rank test. Cox regression analysis was used to evaluate the effects of multiple variables on CSS. Difference of cause-specific death incidence was examined using chi-square (Chi2) test. **Result:** 1707 records met the criteria and were retrieved for analysis. There were significant differences of CSS in Clinical pathological features of N (P=0.01), Stage (P=0.00), and Surgery (P=0.00) when compared non-surgery with surgery, and in N (P=0.000), Stage (P=0.006), Surgery (P=0.049) compared sublobectomy with lobectomy or bilobectomy (bi-/lobectomy). More patients who did not receive surgery (P=0.00) or received sublobectomy (P=0.03) were at risk of death compared with receiving surgery and bi-/lobectomy respectively (Fig 1 and 2).





Conclusion: To conclude, surgery should be taken into account when initial treatment strategy is made in SCLC patients with clinical stage I-IIA (T1-2,N0,M0) even age older than 50 years, in spite of sex, histology and grad. It seems that some SCLC patients with stage IIB (N1) can also benefit from bi-/lobectomy, although further investigation is needed. Simultaneously, bi-/lobectomy is preferred than sublobectomy when a surgery is performed. However, the role of pneumonectomy for SCLC is unclear in this study.

Keywords: small cell lung cancer, surgery, Survival

P2.12-16 CHANGES OF PERIPHERAL BLOOD SPD-L1 IN PATIENTS WITH SMALL CELL LUNG CANCER DURING CHEMOTHERAPY AND ITS CLINICAL SIGNIFICANCE

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Background: As a new immunotherapeutic target, the inhibitors of programmed death 1 (PD-1) and programmed death ligand-1 (PD-L1) pathway have been used to treat a variety of tumors including small cell lung cancer (SCLC). However, the biomarkers now used to predict the efficacy of SCLC immunological checkpoint inhibitors are still in the exploratory phase. The aim of this prospective study was to investigate the prevalence and prognostic roles of soluble PD-L1(sPD-L1) protein in the blood of patients with lung cancer. **Method:** A total of 94 patients with SCLC who were diagnosed by histopathology or cytopathology between March 2018 to November 2018 were enrolled. Blood samples plasma were collected at the time of diagnosis. 17 samples of healthy subjects matching in sex and age from the Health care Center of the hospital were also studied as control. The level of sPD-L1 protein in the blood was measured using an enzyme-linked immunosorbent assay (ELISA). And the correlation of sPD-L1 expression with tumor stage, distant metastasis, and pro gastrin releasing peptide (ProGRP) was analyzed. **Result:** Expression of sPD-L1 in SCLC patients was significantly higher than healthy people(P<0.05).A cut-off value of 1.362ng/ml was distinguished in patients according to Receiver operating characteristic curve (ROC). Dynamic changes of sPD-L1 are associated with progressive disease(PD)a, partial response(PR)a and stable disease(SD)b in SCLC patients(a P<0.01,b P>0.05).The expression of sPD-L1 in serum was positively correlated with ProGRP.

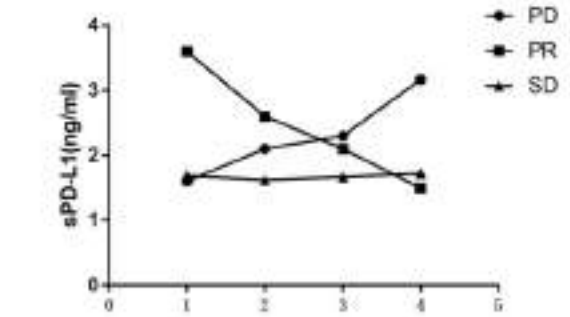

Figure 1 Trend of sPD-L1 in patients with small cell lung cancer during treatment

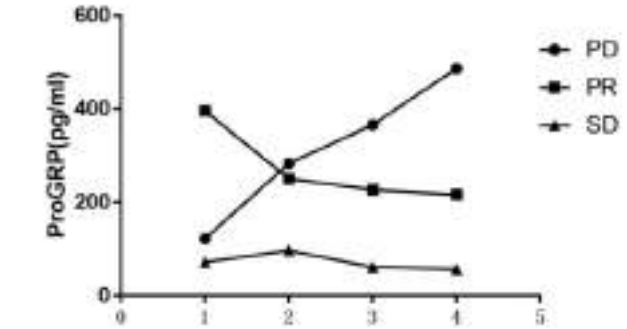

Figure 2 Trend of ProGRP in patients with small cell lung cancer during treatment

Conclusion: Our results indicated that changes of plasma SPD-L1 levels in SCLC patients are associated with prognosis. Plasma sPD-L1 protein is a great biomarker in SCLC and may play an important role in sifting the beneficiaries of immunotherapy.

Keywords: pro gastrin releasing peptide (ProGRP), small cell lung cancer (SCLC);, soluble programmed death ligand 1 (sPD-L1)

P2.12-17 TREATMENT PATTERNS IN SMALL CELL LUNG CANCER (SCLC): AN OBSERVATIONAL STUDY OF 2016–2018 EHR DATA

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Background: SCLC is an aggressive neuroendocrine malignancy with a poor prognosis. Treatment for SCLC has remained largely unchanged for more than two decades, and treatment options for patients remain limited. Recently, immune checkpoint inhibitors have shown efficacy either in combination with chemotherapy in first line or as monotherapy in second or later lines. To better characterize the SCLC treatment landscape, we investigated treatment patterns in a large electronic health record (EHR) dataset. **Method:** Patients ≥18 years of age diagnosed with SCLC from 2016 through 2018 at a US Oncology Network or Onmark community oncology practice were included. Patients enrolled in clinical trials were excluded. Baseline characteristics were compared between treated and untreated patients, and treatment regimens were described by year and by line of therapy. **Result:** A total of 4,589 patients were diagnosed with SCLC during the study period, of whom 85% were treated. Demographics and disease characteristics were similar between treated and untreated groups. Patients were predominately female, former smokers, and residents of the southern United States. Approximately 33% of the treated patients had at least 2 lines of therapy, and 9% had at least 3 lines. The most commonly used treatment regimen in first line across years was platinum + etoposide ± other; in second line, topotecan and nivolumab were most common; in third or later lines, paclitaxel, topotecan, and nivolumab were most common. See Table for details.

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SCLC Treatment Regimens by Year and Line of Therapy						
	2016		2017		2018	
Line	Regimen	n (%)	Regimen	n (%)	Regimen	n (%)
1		N = 1,096		N = 1,427		N = 1,347
	Plat +Eto ± Other	1,042 (95.1)	Plat + Eto ± Other	1,320 (92.5)	Plat + Eto ± Other	1,186 (88.1)
	Plat + Irinotecan	14 (1.3)	Topotecan	23 (1.6)	Plat + Irinotecan	37 (2.8)
	Topotecan	11 (1.0)	Nivolumab	18 (1.3)	Nivolumab	27 (2.0)
2		N = 142		N = 495		N = 651
	Topotecan	66 (46.5)	Topotecan	160 (32.3)	Nivolumab	187 (28.7)
	Plat +Eto ± Other	19 (13.4)	Nivolumab	106 (21.4)	Topotecan	127 (19.5)
	Nivolumab	14 (9.9)	Plat +Eto ± Other	67 (13.5)	Plat + Eto ± Other	114 (17.5)
3		N = 8		N = 181		N = 195
	Paclitaxel	2 (25.0)	Topotecan	28 (23.7)	Nivolumab	78 (40.0)
	Topotecan	2 (25.0)	Nivolumab	25 (21.1)	Topotecan	26 (13.3)
	Irinotecan	2 (25.0)	Paclitaxel	20 (16.7)	Ipilimumab + Nivolumab	18 (9.2)
Plat = platinum-based chemotherapies; Eto = etoposide. Note: Overall number of treated patients is provided for each year and line of therapy. Percentages are calculated by year and line.						

Conclusion: In this database of community oncology practices covering 2016-2018, platinum-based chemotherapy regimens were the most commonly used treatments for patients with SCLC across lines of therapy and years. Other commonly used chemotherapy agents included topotecan, paclitaxel, and irinotecan. Immune checkpoint inhibitors were used predominantly in second and third lines, and utilization increased from 2016 to 2018.

Keywords: Observational research, treatment patterns, small cell lung cancer

P2.12-18 PREVALENCE OF DLL3 EXPRESSION AND ITS PROGNOSTIC ROLE IN EXTENSIVE STAGE SMALL CELL LUNG CANCER

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Background: Extensive stage small cell lung cancer (ES-SCLC) is a highly aggressive disease with a very poor prognosis, and there is a highly unmet need to develop new treatment strategy for them. Rovalpituzumab tesirine (Rova-T), an antibody drug conjugate directed against Delta-like protein 3 (DLL-3) has shown good efficacy in phase I and II clinical trials for the patients with ES-SCLC. We herein examined the prevalence of DLL3 protein expression and its prognostic role in ES-SCLC patients. **Method:** Tumor samples of ES-SCLS were subjected to immune-histochemical staining for DLL3 (AbbVie Stemcentrx). Expression in at least 50% of cancer cells were defined as DLL3-high. The association of patients' characteristics including gender, metastatic sites, and smoking history with DLL3 expression was analyzed by medical chart review. The correlation of DLL3 protein expression status with chemotherapy effect (PFS, OS and response rate) was analyzed. All the statistical analyses were performed by SPSS ver. 18.0 program. **Result:** A total of 56 patients' sample were included in our analysis. The median age was 54 with a range of 44 to 86, and the majority of patients (N=49, 89.1%) are male. Above 90 percent of patients (N=50, 90.9%) received etoposide and cisplatin as chemotherapeutic regimen, and among the 47 patients evaluable for the response, the objective response rate (ORR) was 61.7% (1 complete response and 28 partial response). The median progression free survival (PFS) and overall survival (OS) was 175 days (95% confidence interval (CI), 130.4-220.0) and 250 days (95% CI, 184.0-316.0), respectively. DLL-3 high expression was observed in 91% of patients (N=50). It is not correlated with any of the patients' characteristics and response to chemotherapy. In addition, there was no difference in PFS (242.0 vs. 165.0 days, p=0.900) or OS (160.0 vs. 250.0 days, p=0.975) according to DLL-3 expression. **Conclusion:** Our study showed that DLL3 high expression was found in almost all tumor samples in ES-SCLC. Also, its expression was not correlated with the patients' characteristics and prognosis of them. Further studies are warranted.

Keywords: small cell lung cancer, DLL3, Prognostic factor

P2.12-19 SMALL CELL LUNG CANCER (SCLC) TREATMENT AND SURVIVAL IN PORTUGAL: AN IPO-PORTO ANALYSIS FROM THE I-O OPTIMISE INITIATIVE

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Background: Approximately 15% of lung cancers are SCLC, which is an aggressive disease associated with poor patient outcomes and limited treatment options. As part of I-O Optimise, a multinational research platform providing insights into the real-world management of thoracic malignancies, the IPO-PORTO study aimed to characterise treatment options and their impact on overall survival (OS) in patients diagnosed with SCLC in Portugal's largest oncology hospital. **Method:** IPO-PORTO collects data on patients with various cancers and is linked to the North Region Cancer Registry (RORENO), covering Northern Portugal. This analysis included all adult patients diagnosed with non-resected limited disease (LD)- or incident extensive disease (ED)-SCLC at IPO-PORTO between January 2012 and June 2017, with follow-up to December 2017. ED was defined as metastatic because Veterans Administration Lung Study Group staging was not available. Systemic anti-cancer therapy (SACT) information was available from 2015 onwards. Bespoke and clinically validated rule-based algorithms were applied to describe treatment patterns. The Kaplan–Meier method was used to estimate OS. **Result:** Of 227 patients diagnosed with incident SCLC, 61 (26.9%) had non-resected LD and 166 (73.1%) had ED. Median age was 65 years (range: 59–72) and most patients (83.7%) were male. Most patients with LD-SCLC had stage IIIA/IIIB disease (78.7%). Sites of metastasis in ED-SCLC were bone (47.6%), liver (45.2%), lymph nodes (17.5%), or brain/CNS (13.3%). In patients diagnosed with LD-SCLC from 2015 onwards, 16 of 25 (64.0%) received SACT; among these, 11 received SACT associated with radiotherapy (68.8%). In patients diagnosed with ED-SCLC from 2015 onwards, 53 of 83 (63.9%) were treated with SACT. Among the 69 patients treated with SACT after diagnosis, only 9 received 2nd-line treatment (13.0%). Almost all patients received a platinum-based regimen including cisplatin or carboplatin and etoposide as 1st-line treatment. In patients diagnosed from 2012 onwards, the 1-year OS rate was 54% (95% CI, 43–69) for patients with LD-SCLC and 17% (95% CI, 12–24) for ED-SCLC. Among treated

patients with ED-SCLC who were diagnosed from 2015 onwards, the 1-year OS rate was 18% (95% CI, 9–35). **Conclusion:** Patients with SCLC had a high disease burden; most patients were diagnosed with ED and nearly three-quarters died within a year of diagnosis. The study confirmed that the majority of ED-SCLC patients diagnosed at IPO-PORTO after 2015 were treated with SACT; despite this, 1-year OS rates remained low (<20%).

Keywords: real-world evidence, Immunotherapy, I-O Optimise

P2.12-20 NRG ONCOLOGY/ALLIANCE LU005: A PHASE II/III RANDOMIZED STUDY OF CHEMORADIATION VERSUS CHEMORADIATION PLUS ATEZOLIZUMAB IN LS-SCLC

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Background: Clinical outcomes for limited stage small cell lung cancer (LS-SCLC) remain suboptimal. Standard of care chemoradiation with platinum/etoposide and thoracic radiation to 45 Gy delivered twice daily followed by prophylactic cranial irradiation yields a median overall survival of 30 months. LU005 is a randomized phase II/III trial designed to test the addition of atezolizumab to concurrent chemoradiation (ClinicalTrials.gov Identifier: NCT03811002). **Method:** Patients with LS-SCLC (Tx-T4, N0-N3, M0) are randomly assigned in a 1:1 ratio to either standard chemoradiation, consisting of thoracic radiation (45 Gy twice daily or 66 Gy daily) with concurrent platinum/etoposide chemotherapy, or the experimental arm, consisting of the same chemoradiation regimen plus the addition of atezolizumab beginning concurrently with thoracic radiation, and continued every 3 weeks for 12 months duration. Thoracic radiation begins with the second cycle of chemotherapy in both treatment arms. Stratification variables include radiation schedule (once daily vs. twice daily), chemotherapy (cisplatin vs. carboplatin), sex, and performance status (PS 0/1 vs. 2). Prophylactic cranial radiation is recommended for patients who have a response to treatment. The phase II primary endpoint is progression free survival (PFS) and the phase III primary endpoint is overall survival (OS). It is hypothesized that the addition of atezolizumab will yield a hazard ratio of 0.62 for PFS, for a sample size of 280 patients in the phase II portion of this study. The overall sample size for phase II/III will be 506, with the OS analysis designed to provide at least 85% power to detect a hazard ratio of 0.71 at a 1-sided significance level of 0.025. Secondary endpoints include objective response rates, local control, distant metastases free, and quality of life. This study includes a robust translational science component including blood and tissue based assays to further understand which patients may benefit most from immunotherapy. **Result:** This study activated in May 2019 and is currently enrolling patients. **Conclusion:** NRG Oncology/Alliance LU005 is a randomized II/III trial testing the addition of atezolizumab to standard chemoradiation for LS-SCLC. The estimated date of study completion is May 2024. *Authors Higgins and Ross are co-first authors and contributed equally to this work.

Keyword: small cell lung cancer, immunotherapy, chemoradiation

P2.12-21 OUTCOMES WITH IMMUNE CHECKPOINT INHIBITORS (ICI) FOR RELAPSED SMALL CELL LUNG CANCER (SCLC) IN A SWISS COHORT

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Background: Chemotherapy for relapsed small-cell lung cancer (SCLC) has limited activity. Results from early clinical trials showed promising outcomes in a subset of patients with relapsed SCLC receiving ICI. Therefore, nivolumab +/- ipilimumab, pembrolizumab or atezolizumab have been used off-label in Switzerland. **Method:** 9 cancer centers in Switzerland contributed data to this retrospective cohort of patients who received off-label ICI for relapsed SCLC. Patient characteristics including age, smoking status, stage at diagnosis and previous treatments were collected. Outcomes of ICI were assessed by the local investigators using standard RECIST v1.1 criteria. Tumor tissues were assessed centrally for PD-L1 expression, tumor mutational burden and immune-related gene expression signatures. **Result:** 45 patients were included between November 2016 and January 2019. Median age was 63 years. 73% were males, 4% never smokers and 18% had a performance status (PS) ≥2. ICIs were given as second line treatment in 24 patients (53%). 24 patients (53%) received combination immunotherapy with ipiliumumab and nivolumab. 28 patients (62%) had undergone tumor irradiation (RT) prior to or during ICI. In the entire population, the overall response rate was 31%, while 49% had progressive disease as best response. Median progression-free survival was 2.5 months and median overall survival 6.5 months. There was no significant association between type of ICI (mono vs. combo) or prior RT vs. no RT with survival outcomes in a multivariate analysis. There were no new safety signals. One patient died of immune-related pneumonitis. **Conclusion:** This is the first report of "real-world" data on ICI in relapsed SCLC also including patients with poor PS. We confirm the efficacy and safety of ICI in relapsed SCLC as previously shown in clinical trials. No clinical prognostic marker could be identified. Results on the prognostic value of tissue-based biomarkers will be presented at the meeting.

Keywords: real-world, SCLC, Immunotherapy

P2.12-22 RISK FACTORS FOR BM INCIDENCE IN SCLC: A PREDICTIVE MODEL FOR SCLC PATIENTS ON BRAIN METASTASIS

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Background: As one of the serious complications in patients with lung cancer, brain metastasis (BM) have been demonstrated more common when patients were diagnosing with small-cell-lung cancer (SCLC). After developing a BM, patients' median overall survival will be obviously shorten. Prophylactic Cranial Irradiation (PCI) used to be an optimal therapy to prevent the occurrence of BM in SCLC patients, while recently its status was shaken. This retrospective study aimed to find out the potential risk factor relative to the incidence of BM and construct a predictive mode for SCLC, also to see the efficiency of PCI on SCLC patients' ICPFS. **Method:** Patients pathologically diagnosed with SCLC were consecutively enrolled from May 1st 2006 to February 15th 2019 and reviewed. The intracranial progression-free survival (ICPFS) were calculated by a Kaplan-Meier approach. And the candidate prognosticators of the ICPFS were checked by COX regression analysis. Using these risk factor and its coefficient obtained in the multivariate analysis, a model were constructed to anticipate the incidence of BM. And the

receiver-operating characteristic (ROC) curve was constructed to access the prediction ability. **Result:** Totally 261 SCLC patients were eligible for analysis, including 78 cases had developed a BM (29.9%) after the first diagnosis. We used Cox proportional hazards to analyze and adjust the confounding factor to the incidence of BM, and got the result, that there were five factors showed the significance both in Uni-(P<0.15) and multivariate(P<0.05) analysis, including smoking index <400(P=0.017); vascular invasion (P=0.012); number of primary lesion (P=0.042); staging (P=0.018); and hyponatremia (P=0.05). And a predicative model was constructed by using these factors (except the hyponatremia), with an AUC value of 0.743. And we used this model to distinguish low and high risk group. Two groups' ICPFS showed a remarkable significance (P<0.001). We also simplified it to make it more convenient in clinical work, which also showed an outstanding significance (P<0.001). However, the PCI in our study was not reach the significance, even though it prolonged the ICPFS (P=0.211). **Conclusion:** Factors included smoking index >=400, vascular invasion, number of primary lesion, staging, and hyponatremia, increasing the risk of BM occurrence. In the era of individualized treatment, a predictive model based on smoking status and image science can give some suggestions for clinical work by anticipating the highly risky incidence of brain metastasis on SCLC patients.

Keywords: SCLC, brain metastasis, risk factor

P2.12-23 RADIOLOGICAL FEATURES OF SCLC-LIKE AND NSCLC-LIKE LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)

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Background: Large cell neuroendocrine carcinoma (LCNEC) can be divided in two pathological subtypes: the SCLC-like LCNEC with *RB1* mutations/loss of RB1 staining and the NSCLC-like LCNEC with preserved RB1 staining. The radiological presentations of NSCLC and SCLC are different, with SCLC mainly presenting with bulky disease and a central tumor. Here, we investigated if a distinction between SCLC-like and NSCLC-like LCNEC can be made based on radiological features. **Method:** A survey was developed with chest CT-scans and X-rays of patients with pathological confirmed stage-IV LCNEC (N=52). For reference, images of 10 SCLC and 10 NSCLC patients were randomly included. The survey was distributed among oncology pulmonologists in the Netherlands. Responders could score images as 'SCLC-like', 'NSCLC-like' or 'not possible to determine (nptd)'. Cases were considered as SCLC-like if no more than 1 responder scored NSCLC-like and no more than 67% scored 'nptd'. A similar approach was used to classify NSCLC-like cases. Images not fulfilling both approaches were regarded not applicable (NA). **Result:** The survey was completed by 23 pulmonologists with >5 years of experience, of which 12 had >15 years of experience. 90% NSCLC reference CT-scans were correctly classified, in contrast to only 30% correctly classified SCLC CT-scans (Table). For 36/52 LCNEC RB1 immunohistochemical status was known; 9/36 were RB1 positive and 27/36 RB1 negative. In RB1 positive LCNEC 6/9 scans were allocated to the NSCLC-like group. In RB1 negative LCNEC 2/27 scans were allocated to the SCLC-like group and 17/27 to the NSCLC-like group. If the scan was assessed as SCLC-like, RB1 was negative in 100% of cases. However, in cases assessed as NSCLC-like, only 26% was RB1 positive. No distinction between SCLC-like and NSCLC-like LCNEC could be made based on X-rays (Table).

Results of survey radiological features of LCNEC				
	Pathological diagnosis			
	Controls		LCNEC	
	SCLC	NSCLC	RB1 Pos-neg	RB1 Pos-pos
X-thorax	N=7	N=9	N=21	N=8
Survey SCLC-like	2 (500%)	0 (0%)	0 (0%)	1 (100%)
Survey NSCLC-like	2 (100%)	5 (6.0%)	9 (75%)	3 (25%)
Survey NA	2 (500%)	0 (0%)	12 (75%)	4 (25%)
CT-thorax	N=10	N=10	N=27	N=9
Survey SCLC-like	3 (500%)	0 (0%)	2 (100%)	0 (0%)
Survey NSCLC-like	2 (18%)	9 (82%)	17 (78%)	6 (26%)
Survey NA	5 (83%)	1 (17%)	8 (73%)	3 (27%)

Conclusion: In LCNEC, a CT-scan assessed as SCLC-like is highly predictive for RB1 negative status, whereas a NSCLC-like CT-scan can be both of the RB1 negative and positive subtype. During WCLC results including RB1 status of all 52 LCNEC will be presented.

Keywords: LCNEC, radiological features, Radiology

P2.12-24 UNDERUTILIZATION OF SURGERY FOR LOCALIZED SMALL CELL LUNG CANCER: A NATIONWIDE ANALYSIS

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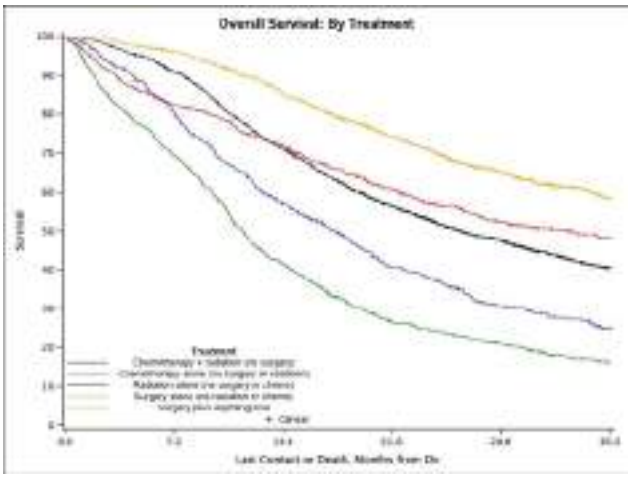
Background: Although surgery has been recommended in node-negative localized small-cell lung cancer (SCLC), utilization has been low (<10%) in the past. Here, we evaluate treatment patterns and outcomes of surgery in localized SCLC over the last decade to determine if routine practice follows the growing literature in support of surgery in localized SCLC. **Method:** We queried years 2006-2014 of the National Cancer Database, a hospital dataset capturing 70% of incident cancers in the United States, to identify adults with Stage IA to IIA (T1-T2N0M0) SCLC who underwent treatment. Temporal practice patterns and multivariable survival outcomes were assessed. **Result:** In the cohort of 5877 patients, 2892 (49%) received chemoradiation, 1300 (22%) received surgery with radiation or chemotherapy, 639 (11%) received chemotherapy alone, 628 (11%) received surgery alone, and 418 (7%) received radiation alone. Amongst patients receiving surgery, 1277 (66%) received a lobectomy or pneumonectomy. Likelihood of receiving surgery in combination with radiation or chemotherapy was higher in later years of diagnosis (15% in 2006 vs 25% in 2014, p<0.001). Stage IA was more prevalent in the group that received surgery alone (77%) or surgery with chemotherapy or radiation (75%) compared to chemoradiation (45%), chemotherapy (49%), and radiation (63%). Median overall survival was most favorable for surgery with chemotherapy or radiation (51.8 months) followed by surgery alone (33.2 months) compared to chemotherapy + radiation (26.2 months), radiation alone (17.8 months), and chemotherapy alone (11.8 months)(p<0.001). In a multivariable Cox model (Table), surgery with chemotherapy and/or radiation was associated with decreased mortality versus chemoradiation (hazard ratio=0.6, P<0.001).

	Hazard ratio	95% CI
Treatment Chemoradiation Chemotherapy alone Radiation alone Surgery alone Surgery + chemotherapy or radiation	Ref 2.1 1.4 0.9 0.6	1.9-2.3 1.2-1.6 0.7-0.9 0.6-0.7
Female sex	0.8	0.8-0.9
Stage IA IB IIA	Ref 1.1 1.2	1-1.2 1.1-1.3

*Model also included age, insurance, median income quartile, Charlson comorbidity score, region, and race (not shown)



POSTERS

Conclusion: Utilization of surgery in localized SCLC remains low, despite its association with improved survival. Future clinical trials may be needed to establish the best therapeutic strategy for these patients.

Keywords: SCLC surgery, early stage small cell lung cancer, ES-SCLC

P2.12-25 SURGICAL MANAGEMENT OF PULMONARY CARCINOID ≤3CM: EXTENT OF RESECTION AND LYMPH NODES EXAMINATION

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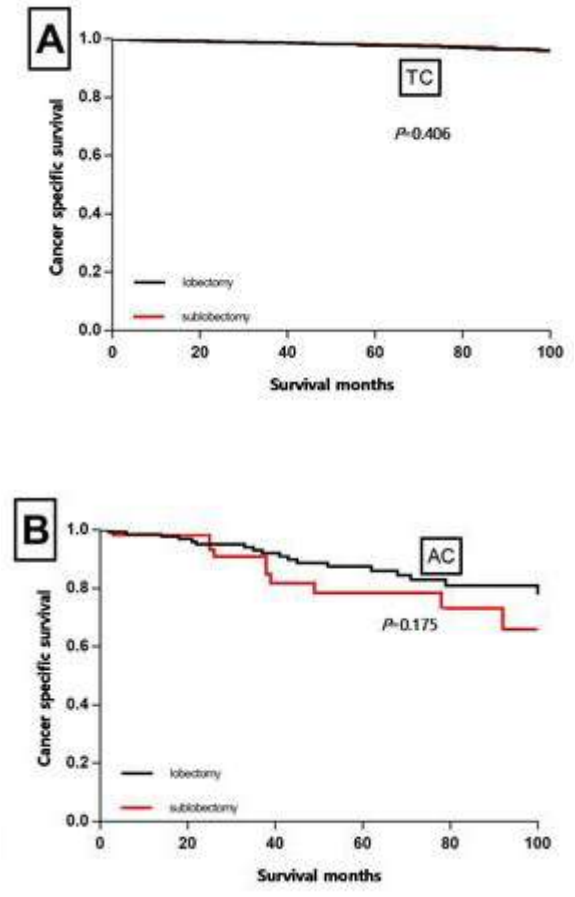
Background: Early stage lung cancer is being detected at a higher frequency with the development of advanced screening programs. We aimed to investigate the optimal surgical approach in pulmonary carcinoid ≤3cm. **Method:** Patients with microscopically confirmed pulmonary carcinoid tumors ≤3cm were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2015. Cancer specific survival (CSS), defined as the survival time from cancer diagnosis to death specific to cancer-related death, was the primary outcome variable. Survival curves were plotted with Kaplan-Meier analysis and the difference in survival was estimated by log-rank tests. Multivariate Cox regression methods determined the independent prognostic factors after adjusting for other confounding factors. **Result:** A total of 2986 patients were included in this study, which comprised 2785 typical carcinoids (TC) and 201 atypical carcinoids (AC). AC histology was associated with larger tumor size and increased risk of nodal metastasis. Lobectomy was performed for bigger carcinoid and correlated with more resected lymph nodes. Sublobectomy was noninferior to lobectomy with regards to CSS. Although lymph nodes involvement conferred significantly decreased survival, lymph nodes resection did not improve survival in either typical or atypical carcinoids.



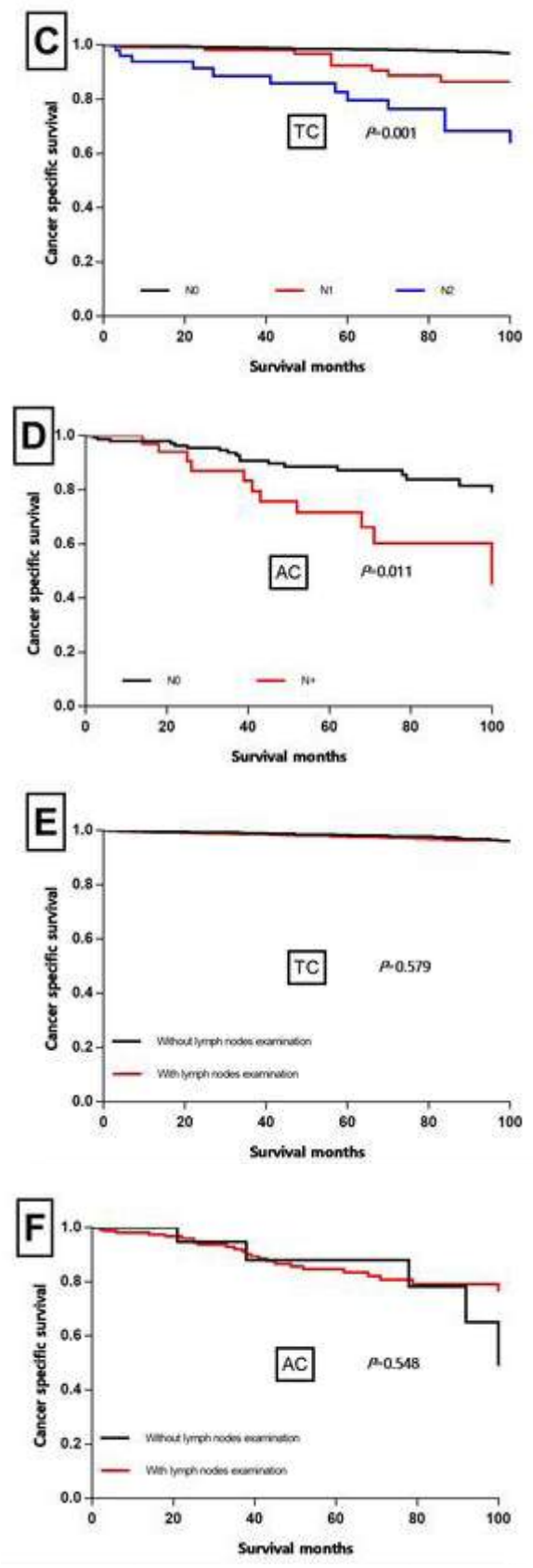


Figure 1 Survival curves stratified by (A) Extent of resection in TC, (B) Extent of resection in AC, (C) Lymph nodes status in TC, (D) Lymph nodes status in AC, (E) Lymph nodes examination in TC, and (F) Lymph nodes examination in AC.

Conclusion: For patients with T1-sized pulmonary carcinoids, sublobar resection results in similar survival rate compared with lobectomy. Lymph nodes examination did not independently predict survival.

Keywords: pulmonary carcinoid tumor, lymph node

POSTERS

P2.12-26 THE IMPACT OF ANLOTINIB FOR RELAPSED SCLC PATIENTS WITH BRAIN METASTASES: A SUBGROUP ANALYSIS OF ALTER 1202

Y. Cheng[1], Q. Wang[2], K. Li[3], J. Shi[4], B. Han[5], L. Wu[6], G. Chen[7], J. He[8], J. Wang[9], H. Qin[10], X.-L. Li[11]

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Background: ALTER1202 trial (NCT03059797), a multicentre, randomized, double-blind phase II study has demonstrated that anlotinib significantly prolonged progress-free survival (PFS) in relapsed SCLC patients as 3rdor further line treatment. Here, we performed a comparative analysis for patients with brain metastases in the placebo and anlotinib arms. **Method:** Eligible either limited- or extensive-stage SCLC pts who failed ≥2 lines of chemotherapy (n=120) were randomized 2:1 to receive anlotinib or placebo (12 mg QD from day 1 to 14 of a 21-day cycle) till progression or intolerable toxicity. The primary endpoint was PFS. This subgroup analysis was based on patients with brain metastases at baseline. **Result:** There are 30 pts with brain metastases in anlotinib and placebo groups (n=21 vs 9). Anlotinib significantly improved PFS (3.84 vs 0.76 months; HR = 0.15; 95% CI, 0.04–0.51; P = 0.0005) and OS (6.08 vs 2.56 months; HR = 0.26; 95% CI, 0.09–0.73; P = 0.0061) comparing to placebo in patients with brain metastases at baseline. In anlotinib group, loss of appetite (47.62%), loss of weight (42.86 %), leukopenia (38.10%) and hypertriglyceridemia (38.10%) were the most common adverse events (AEs); then, in placebo group were emesis (44.44%) and loss of appetite (33.33 %). **Conclusion:** For patients with brain metastases in ALTER1202 trial, significant improvement in OS and PFS were found in anlotinib treated group with a manageable safety profile.

Keywords: Brain metastases, SCLC, Anlotinib

P2.13 STAGING
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.13-01 PET-CT UNDERESTIMATES UNEXPECTED PN2 IN LUNG ADENOCARCINOMA

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Background: Accuracy in lung staging is essential for the management of lung cancer. Positron emission tomography (PET-CT) allows us to identify occult disease and avoid unnecessary surgeries in patients with extended disease. In recent years, the histological distribution has varied in non-small cell lung carcinomas. Historically, squamous carcinoma had been more frequent, but in recent years adenocarcinoma has been progressively increasing its incidence. **Method:** We have retrospectively reviewed all patients that underwent surgery after cN0-N1 staging. Staging studying consisted in chest computed tomography, PET-CT and fiberbronchoscopy. In case of increased mediastinal PET-CT uptake, hiliar lesion, N1 involvement or tumour greater than 3 cm an endobronchial ultrasound (EBUS) and / or mediastinoscopy was performed. Our aim was to study if this histological change has increased our occult pN2 in cN0-N1 patients **Result:** Between January 2010 and March 2016, 484 patients were consecutively operated. 112 patients (92 men and 20 women) had hilar or mediastinal homolateral involvement. The average age was 63.62 years +/- 8.99. The initial nodal involvement was cN0 73.2% (82 patients), cN1 21.4% (24p) and ycN0 after neoadjuvant therapy 5.4% (6p). The following data were analysed: age of the patient, sex, histology of the lesion, staging, location, type of resection performed, laterality and nodal involvement. Subsequently, the statistical analysis was performed with SPSS 25. The most frequent histology was adenocarcinoma in 256 patients (52.89%), squamous carcinoma in 198 (40.9%), other 30 (6.1%). 25.78% adenocarcinoma (66p) and 23.23% squamous carcinoma (46p) presented nodal involvement. By zones, N1 and N2 involvement was 11.71% (30p) and 14.06% (36p) in adenocarcinoma group. 16.16% (32p) and 7.07% (14p) in squamous group (p <0.05). The odds ratio for occult pN2 was 1,988 in adenocarcinoma (p<0.05). **Conclusion:** PET-CT underestimates the presence of unexpected pN2 in adenocarcinoma lung cancer. Further mediastinal investigations may be necessary in these patients prior to surgical resection

Keywords: Lung cancer, PET-CT, staging

P2.13-02 PERSISTENT OCCULT MICROMETASTASES IN MEDIASTINAL LYMPH NODES ARE ASSOCIATED WITH REDUCED SURVIVAL AFTER NEOADJUVANT THERAPY

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Background: This study was undertaken to evaluate the utility of the detection of occult micrometastases (OM) by immunohistochemical (IHC) staining of mediastinal lymph nodes (LN) obtained during surgical restaging after neoadjuvant treatment of NSCLC patients with mediastinal LN metastases. **Method:** In years 2007-2018, 55 patients with pathologically confirmed mediastinal LN metastases were restaged with TEMLA (transcervical extended mediastinal lymphadenectomy) after neoadjuvant chemotherapy or chemoradiotherapy. Routine haematoxylin&eosin staining of harvested mediastinal LN showed no metastases and all patients subsequently underwent curative pulmonary resection. To detect OM, we retrospectively performed IHC staining with anticytokeratin antibodies on all (1613) mediastinal LN obtained during TEMLA. **Result:** Persistent OM were found in mediastinal LN of 7 patients (12,7%). In all cases, only single LN was affected. After a median observation period of 24 months (range 4 to 60) after curative surgery, OM+ patients showed significantly reduced overall survival in comparison to OM- patients (log-rank, p=0.035). In Cox multivariable analysis, OM persistence was independent negative factor for overall survival. **Conclusion:** IHC staining of mediastinal LN obtained during TEMLA allows for more accurate restaging. Persistent mediastinal OM after neoadjuvant treatment are associated with reduced survival after pulmonary resection.

Keywords: restaging, Mediastinal Lymph nodes, neoadjuvant

P2.13-03 IS IT TIME TO REPLACE CERVICAL MEDIASTINOSCOPY WITH EBUS-FNAC IN INVASIVE MEDIASTINAL STAGING FOR NSCLC?

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Background: Cervical mediastinoscopy is considered the gold standard for mediastinal staging in NSCLC. However, the morbidity of this procedure is not inconsiderable and EBUS+/-EUS with guided FNAC is rapidly evolving as a replacement for mediastinoscopy. **Method:** Aim: To evaluate EBUS-FNAC, in invasive mediastinal staging and assess the incremental value of mediastinoscopy. Methods: Retrospective analysis of a prospectively maintained database of patients who underwent EBUS followed by mediastinoscopy and/or surgery within a month for potentially resectable NSCLC from February 2017 to March 2019. Lymph nodes in stations 2 and 4 bilaterally and 7 were sampled, if size 5mm or more/met radiological criteria on ultrasound. Patients with negative EBUS underwent mediastinoscopy and surgery depending on the results. Data regarding PET CECT features, sampling, cytology and final histopathology was analysed. **Result:** During the study period, 126 patients underwent EBUS for staging. Thirty-eight patients had positive mediastinal nodes, 34 with N2 and 4 with N3 disease. Eighty-eight patients were staged as N0 on EBUS, of which 15 received definitive chemoradiotherapy and 8 patients had progression of disease or were lost to follow up before definitive treatment. Sixtyfive EBUS negative patients underwent either mediastinoscopy followed by lung resection(56) or upfront lung resection with systematic mediastinal lymph node dissection(9). Nine of these patients (65) had N2 disease, 5 detected on mediastinoscopy and 4 detected on surgery (three positive in stations not accessible

by mediastinoscopy or EBUS and one in a patient who could not undergo mediastinoscopy). The 5 additional N2 cases detected by mediastinoscopy had sub centimetre lymph nodes with SUV < 3, but had undergone adequate sampling(median-3 passes) on EBUS. **Conclusion:** Presence of metastatic disease in sub centimetre mediastinal lymph nodes with low SUV cannot be excluded by imaging and this may be critical in this era of multimodality management. The sensitivity of EBUS although excellent is further augmented by mediastinoscopy and it remains an integral part of mediastinal staging.

Keyword: EBUS, NSCLC Staging, mediastinoscopy

P2.13-04 MOLECULAR NODAL RESTAGING BASED ON EMBRYONIC MARKERS EXPRESSION ADDS NO RELEVANT CLINICAL INFORMATION IN RESECTED LUNG CANCER

I. Macia[1], G. Aiza[2], R. Ramos[1], F. Rivas[1], A. Ureña[1], S. Aso[1], G. Rosado[3], P. Rodriguez-Taboada[3], C. Deniz[1], E. Nadal[4], I. Escobar[1], G. Capella[5]

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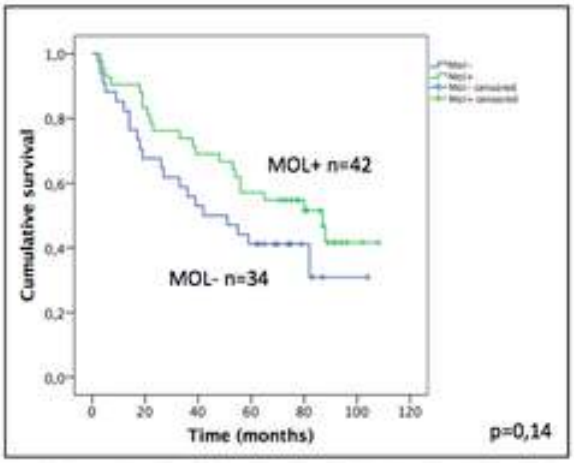
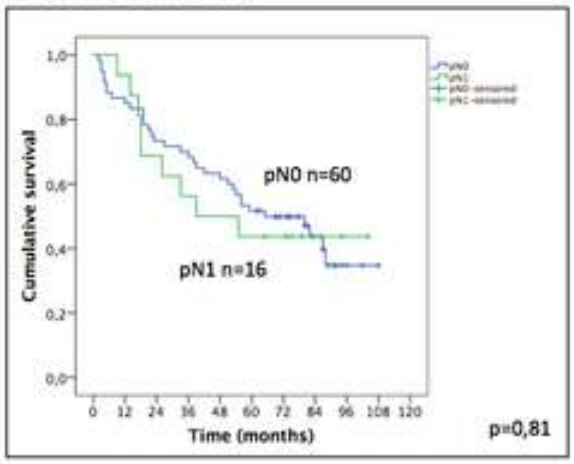
Background: The relapse rate in non-small cell lung cancer (NSCLC) is high, even in localised disease, suggesting that the current approach to pathological staging is insufficiently sensitive to detect occult micrometastases present in resected lymph nodes. Therefore, we aimed to determine the prognostic value of the expression of embryonic molecular markers in histologically-negative lymph nodes of completely-resected NSCLC. **Method:** 76 NSCLC patients undergoing radical resection were included. Primary tumours and 347 lymph nodes were studied. The molecular markers finally were selected based on testing of 27 normal lung and 129 lung tumour samples as well as 25 lymph nodes obtained from non-neoplastic diseases. CEACAM5, FGFR2b, and PTPN11 expression levels were evaluated through mRNA analysis using real-time RT-qPCR assay. Statistical analyses included the Kruskal-Wallis test, Kaplan Meier curves, and log-rank tests. **Result:** CEACAM5 expression levels were scored as high in 90 lymph nodes (26%). The molecular-positive lymph nodes lead to the restaging of 37 (62%) pN0 patients as molecular N1 or N2 and 5 (31%) pN1 cases were reclassified as molecular-positive N2. Surprisingly, molecular-positive patients (42, 55%) associated with a better OS (overall survival, p=0,04) than molecular-negative patients (34, 45%). FGFR2b overexpression was observed in 41 (12%) lymph nodes leading to the restaging of 17 patients (22%). Again a trend was observed towards a better DFS (disease-free survival) in the restaged patients (p=0,09). PTPN11 expression levels were high in 109 (31%) lymph nodes and led to the restaging of 41 (54%) patients who did not correlate with clinical outcome (p=0,61). The combination of CEACAM5-FGFR2b restaged the same number of patients than CEACAM5 only. Accordingly, high expression levels of CEACAM5 or FGFR2b in the primary tumour were related to better DFS (p<0,06; p<0,02, respectively); PTPN11 did not correlate with prognosis (p=0,37).

Disease-free survival



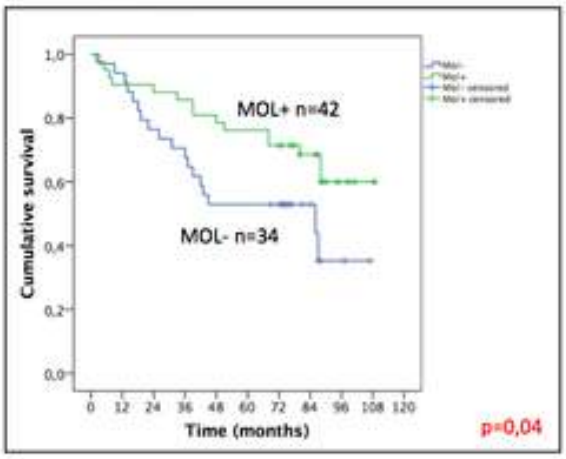
N at risk	0-m	12-m	24-m	36-m	48-m	60-m	72-m	84-m	96-m	108-m	120-m
Mol+	42	38	32	31	28	24	22	13	2	0	0
Mol-	34	28	23	19	17	14	8	2	1	0	0

Disease-free survival



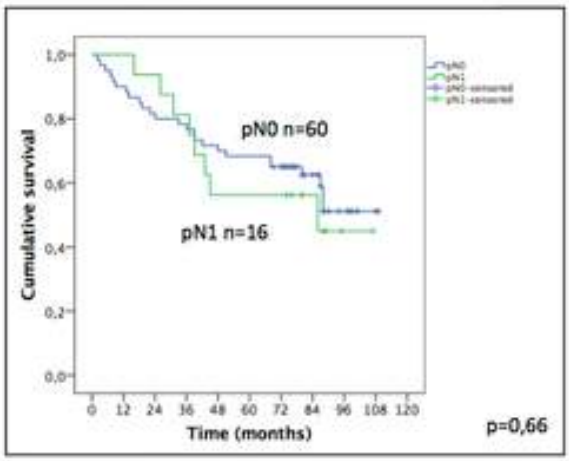
N at risk	0-m	12-m	24-m	36-m	48-m	60-m	72-m	84-m	96-m	108-m	120-m
pN0	60	51	44	41	37	31	24	12	2	0	0
pN1	16	15	11	9	8	7	6	3	2	0	0

Overall survival



N at risk	0-m	12-m	24-m	36-m	48-m	60-m	72-m	84-m	96-m	108-m	120-m
Mol+	42	38	37	36	33	32	29	20	6	1	0
Mol-	34	32	26	23	18	18	16	6	2	0	0

Overall survival



N at risk	0-m	12-m	24-m	36-m	48-m	60-m	72-m	84-m	96-m	108-m	120-m
pN0	60	54	48	46	42	41	36	21	7	1	0
pN1	16	16	15	13	8	7	6	5	1	0	0

Conclusion: Molecular nodal restaging based on expression levels of CEACAM5 and/or FGFR2b, does not add relevant clinical information to pathological staging of NSCLC likely related to the better prognosis of their overexpression in primary tumors.

Keywords: Embryonic marker, Nodal staging, resected non-small cell lung cancer

POSTERS

P2.13-05 ENDOBRONCHIAL ULTRASOUND FOR MEDIASTINAL RESTAGING IN NON-SMALL CELL LUNG CANCER

S. Baeza Mena[1], C. Centeno Clemente[1], P. Serra Mitja[1], C. Martinez-Barenys[2], E. Carcereny[3], T. Moran[4], E. Castella Fernandez[5], J. Jove Teixido[5], A. Rosell[1], F. Andreo García[1]

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Background: The adequate mediastinal restaging following neo-adjuvant therapy (NAT) in operable patients with non-small cell lung cancer (NSCLC) and N2 spread is crucial. Mediastinoscopy is the gold standard for mediastinal restanging, but endosonographic procedures are less invasive and can be an alternative. AIM: Evaluate the role of endobronchial ultrasound-guided transbronchial needle aspirate EBUS-TBNA in mediastinal the restaging of NSCLC. **Method:** Prospective study with 32 patients with CPNCP N2 spread confirmed by TNBA-EBUS, collected from June 2010 to October 2018. These patients were subjected to neoadjuvant treatment (chemotherapy or radio-chemotherapy), subsequently were performed mediastinum restage with TNBA-EBUS. The negative cases were subjected to mediastinoscopy or thoracotomy. **Result:** Of the 32 cases, the basal characteristics are detailed in table 1. Were analysed 229 lymph nodes, 42 of these were malignant (18%). TNBA-EBUS after neoadjuvant treatment showed persistence of N2 spread in 19 cases (52%). In negative cases (n=13; 41%) were performed mediastinoscopy (n=11) or surgery (n=1). After these procedures were confirmed mediastinal disease in 3 cases, 9 lymph nodes of 43 removed. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 86.4%, 100%, 100%, 72.7% and 90% respectively. There was recurrence of the disease in 15 cases (47%). We found a significant difference between recurrence and the type of neoadjuvant treatment (chemotherapy vs. radio-chemotherapy), p=0.047. Table 1.

Basal Characteristics	N (32)
Age	62.1 +/- 9.4
Sex	
Male	23 (72%)
Tumour localization	
Right upper lobe	15 (47%)
Right lower lobe	8 (25%)
Left upper lobe	8 (25%)
Left lower lobe	1 (3%)
Histology	
Adenocarcinoma	15 (47%)
Squamous carcinoma	12 (37%)
NSCLC not typified	5 (16%)
Neoadjuvant treatment	
Chemoradiotherapy	26 (81%)
Only chemotherapy	6 (19%)

Conclusion: TBNA-EBUS is an appropriate semi-invasive tool in mediastinal restage after neoadjuvant treatment, with high diagnostic accuracy. Nevertheless, in negative cases is still necessary support with invasive procedures.

Keyword: restaging, lung cancer, EBUS

P2.13-06 FINDING A PLACE FOR PATHOLOGICAL NEAR COMPLETE RESPONSE PATIENTS FOLLOWING NEOADJUVANT/INDUCTION THERAPY IN THE TNM STAGING

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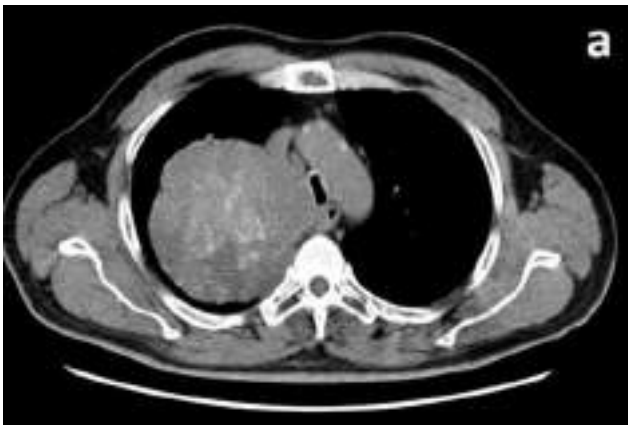
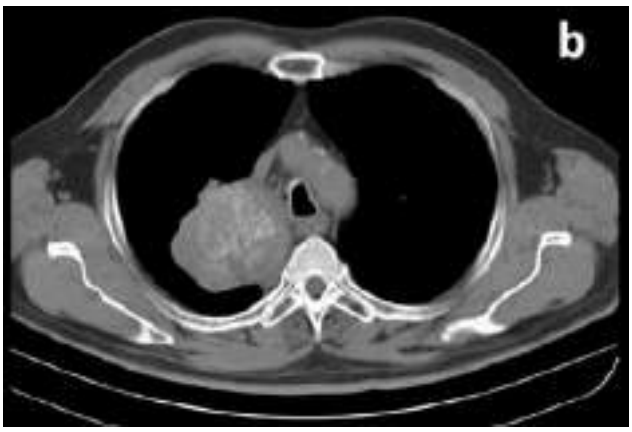
Uludag University, Bursa/Turkey

Background: It has been shown that 10% or less in the number of live tumor cells in patients who underwent surgery after neoadjuvant/induction (N/I) treatment for locally advanced non-small cell lung cancer (NSCLC) is a more important prognostic factor than the tumor diameter. Therefore, to improve the accuracy of TNM staging, the IASLC recommends calculating the new pathological ypT stage by multiplying the percentage of viable tumor cells with the total tumor size (Picture 1). The aim of this study was to determine the effect of this recommendation on long-term survival rates. **Method:** Data of 1190 patients who underwent segmentectomy or larger lung resections for NSCLC in our academic center between 1996 and 2017 were prospectively recorded and evaluated retrospectively. Four hundred and sixty-nine (39.4%) patients who underwent surgery after N/I treatment for locally advanced NSCLC were included in the study. The patients were divided into 3 groups; Pathological complete response (CR, Group 1) as defined as no viable tumor cells regardless of tumor size, group 2 was accepted as near complete response (nCR), where the tumor contained ≤%10 live tumor cells, tumor size > 5 cm without lymph node metastasis, group 3 consisted of ypStage1 patients. The long term survival and its impacting factors were analyzed. **Result:** In histopathological examination, 16.6% (78/469) patients had CR, 4% (19/469) had nCR, 17.7% (83/469) had ypStage 1a and 7.7% (36/469) had ypStage 1b. Five-year survival; 72.5% in Group 1, 30% in Group 2 and 63.4% in Group 3. **Conclusion:** The best survival was observed in patients with pathological CR. Although, IASLC suggests that the nCR should be considered as Stage 1, because of the significantly low survival figures, T3-4 seems to be the more appropriate classification than the IASLC proposal.





Picture 1. A 48y male patient with 12-cm mass adjacent to the trachea (1a). Diagnosis of NSCLC was confirmed. Major response was observed after chemoradiotherapy (1b). After negative mediastinoscopy, right upper lobectomy and lower lobe superior segmentectomy was performed with a bronchoplasty. Histopathological examination revealed a tumor size of 7.5x6 cm

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with live tumor cells ≤5% without lymph node metastasis. The IASLC recommends (T stage = Tumor Size x Number of Live Tumor Cells (5%)) patient's stage as ypStage 1.

Keyword: Neoadjuvant Therapy, Induction Therapy, complete response, staging, TNM

P2.13-07 CT STAGING FOR SUSPECTED LUNG CANCER; SHOULD WE ROUTINELY IMAGE THE PELVIS?

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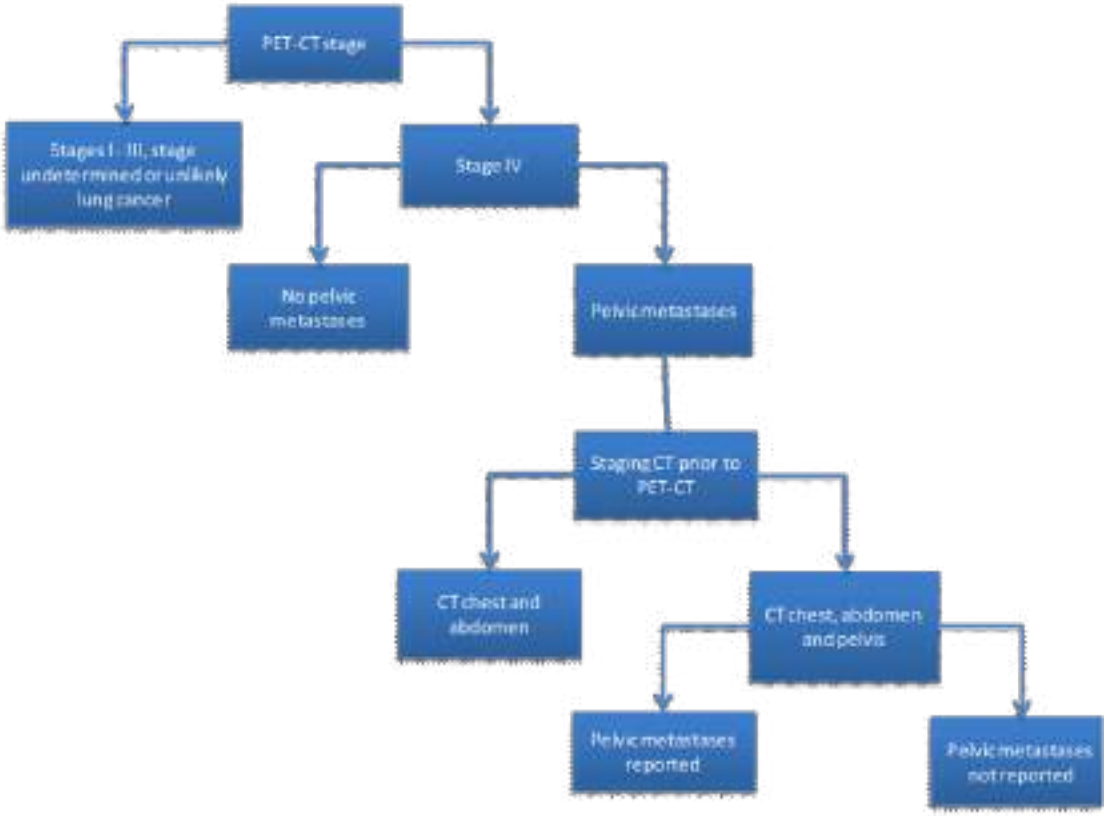
Background: Hospital trust imaging protocols for CT staging of suspected lung cancer vary with regard to inclusion of the pelvis. Imaging the pelvis allows for potential detection of pelvic metastases and appropriate subsequent management, but exposes the patient to a higher radiation dose. This study was designed to determine whether current practice could be improved and standardised. **Method:** Retrospective study across 11 hospital trusts in the United Kingdom. All patients who had a PET-CT scan in 2014 for a new diagnosis of lung cancer were identified from hospital databases. PET-CT reports were reviewed and categorised by the lung cancer stage given in the report. Stage IV disease was further subcategorised into stage IV with pelvic metastases or stage IV without pelvic metastases.The initial staging CT was reviewed in all stage IV patients with pelvic metastases on PET-CT. The CT protocol was documented in addition to whether or not the pelvic metastases were identified. **Result:** Pelvic bony metastases were identified in 4% of PET scans (66 patients). 11 of these 66 patients initially had a contrast-enhanced CT chest, abdomen and pelvis staging scan; 3/11 scans reported pelvic metastases. The remaining 55 patients did not have pelvic imaging prior to PET. Overall radiation exposure and costs were calculated; routine imaging of the pelvis during staging CT could result in an 18% increase in radiation exposure to the population and a 2% reduction in overall cost if subsequent PET imaging decreased by 4%. **Conclusion:** Trust imaging protocols for CT staging of suspected lung cancer vary with regard to inclusion of the pelvis. Pelvic metastases from primary lung cancer are an uncommon finding on PET-CT scans (4%). CT chest and abdomen scans are sufficient for staging lung cancer given the low incidence of pelvic metastases and significant radiation exposure associated with pelvic imaging.

Keywords: lung cancer staging, pelvic metastases, CT staging scan



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P2.13-08 WHICH IS THE RELIABLE PROGNOSTICATOR FOR EARLY METASTASIS AND RECURRENCE OF NON-SMALL CELL LUNG CANCER, RELATED WITH STAS?

S.-Y. Ham[1], D.Y. Kang[2], B. Ko[3], Y. Lee[1]

[1]*Kangbuk Samsung Hopsital, Seouyl/Korea, Republic of,* [2]*Kangbuk Samsung Hopsital, Seoul/Korea, Republic of,* [3]*Ulsan University Hospital, Ulsan/Korea, Republic of*

Background: In recent years, many studies had investigated the correlation between STAS and the clinical parameters and prognosis of lung cancer. The majority of these studies focused on AdC, and a number of tumor-related factors were considered to be influenced by STAS. The incidence of STAS in AdC ranged from 14.8% to 56.4%, and STAS was demonstrated to have an association with AdC histologic type. For proper magement of lung cancer, correct perioperative evlauation and assessment is crucial, Recently the concept and signoficance of STAS has great interest. . **Method:** Materials and methods We retrospectively reviewed 171 non-small cell lung cancers, analyzed 45 cases, underwent lobectomy or pneumonectomy with pathology report and medical record. Tumor STAS was defined as detached tumor cells within the air spaces in the lung parenchyma beyond the edge of the main tumor clinicopathological factors, including clinical outcome. Comparison was done with visceral pleural invasion and lymphovascular invasion. **Result:** STAS was identified in 12 of 45 patients (26.6%). The patients with STAS had a significantly worse 5-year recurrence-free survival (RFS) in stage I, but not in stage II and III. A multivariate analysis showed that the presence of STAS was an independent predictive factor of and an independent prognostic factor (hazard ratio = 3.01; 95% confidence interval, 1.54-5.89; p = 0.0013) in stage I. Positive for STAS, and lymphovascular invasion was 10/45 and positive for STAS, and viscera pleural invasion was 6/45 and all positive lung cancers were 3/45 **Conclusion:** We found that STAS was detected in 26.6% of surgical resected non-small cell caricnomas, and it was associated with recurrence and worse prognosis in early stage lung cancers. Therefore, we suggest that STAS is a reliable prognosticator and play promising roles for the lung cancer managements.

P2.13-09 THE IMPACT OF THE 8TH EDITION OF IASLC STAGING IN PATIENTS WHO UNDERWENT SURGICAL TREATMENT OF LUNG CANCER

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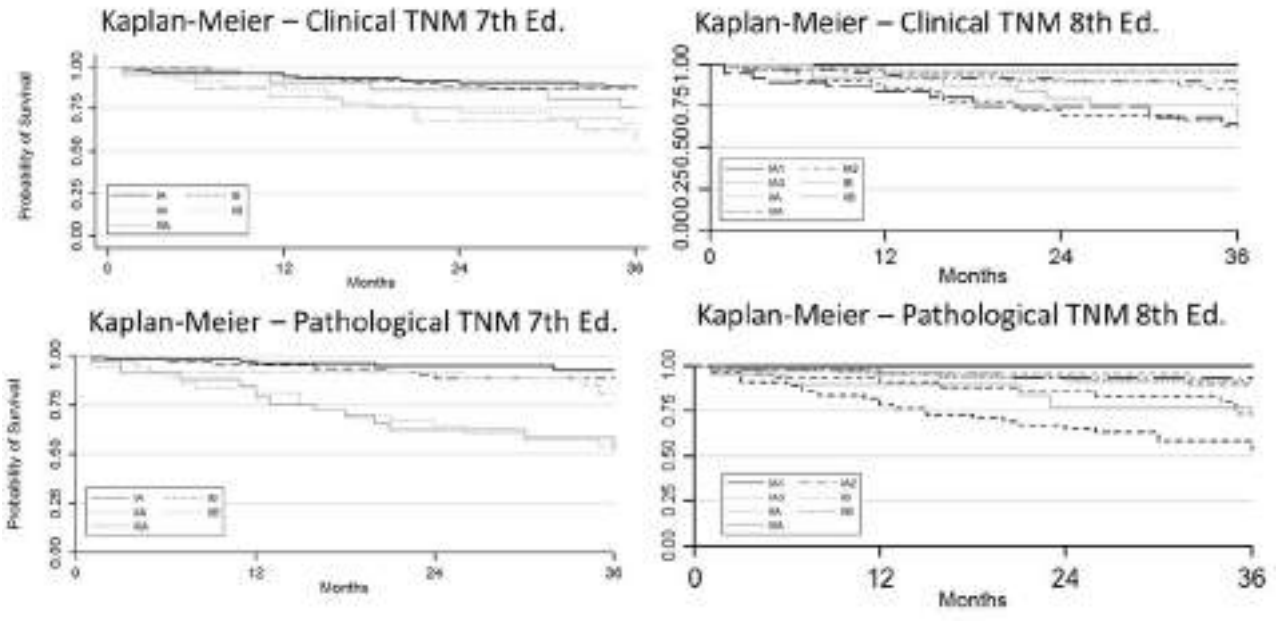
Background: TNM cancer staging main function is to unify the language of patient´s evaluation. It is supposed to be a global initiative, however participation of latin american patients in the IASLC database is limited and the performance of staging in such a population is unknown.Our study aims to describe the performance of TNM 7th and 8th editions in predicting survival of patients with lung cancer who underwent surgical treatment in a latin american country. **Method:** This is a retrospective study conducted in a Oncologic hospital of São Paulo, Brazil. We selected the patients who underwent surgical treatment of lung cancer between January 2011 and December 2015. Clinical data was obtained from the institutional database including exactly the same variables as the IASLC database. Patients were classified according to the TNM clinical and pathological staging system, both in 7th and 8th editions. Then we performed a survival analysis in 36 months according to each classification using the Kaplan–Meier method. A Cox regression was made with the clinical and pathological staging as variables, in order to determine which classification was more precise in risk prediction. **Result:** The mean age was 63,9 (±11.6), female predominance (53%), and strong association with current or former smoking (74%). The most common histological type was invasive adenocarcinoma (54%) followed by squamous cell carcinoma (22%). Both TNM classifications stratified risk adequately as demonstrated in Image 1.

Image 1



According to the Cox regression, TNM 8th edition had a better performance in survival prediction. Clinical 7th ed (LL=-329.14095; LR=6.29) versus Clinical 8th ed (LL=-25.91923; LR=12.73). Pathological 7th ed (LL=-318.82608; LR=26.92) versus Pathological 8th ed (LL=-315.19067; LR=34.19). **Conclusion:** TNM 7th and 8th editions predicted adequately survival in patients of a Latin American country, suggesting that these classifications are generalizable for such a population. 8th edition had a better performance when compared to 7th edition.

Keywords: staging, Latin America, Survival

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P2.13-10 LYMPH NODE UPSTAGING EVALUATION AFTER ROBOTIC RESECTION FOR NSCLC IN BRAZIL

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[1]*Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, São Paulo/Brazil,* [2]*Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR., São Paulo/Brazil,* [3]*Pontifícia Universidade Católica do Rio de Janeiro - PUC-Rio, Rio de Janeiro/Brazil,* [4]*Universidade Estadual do Rio de Janeiro, Rio de Janeiro/Brazil,* [5]*Cirurgiões Torácicos Associados do RJ., Rio de Janeiro/Brazil*

Background: An adequate lymph node staging plays a key role in the management of Non-Small Cell Lung Cancer (NSCLC) having great value in determining the necessity for adjuvant therapy. Inasmuch as the development of surgical robotic devices and robotic lobectomy is prominent, it is important to study if the robotic approach is capable of yielding the same or better lymph node staging as open or video assisted technique(VATS).The prevalence of nodal upstaging has been used as an adequate evaluation of the completeness of lymphadenectomy. The aim of this study was to determine the prevalence of lymph node upstaging in patients treated for NSCLC using robotic approach during the initial adoption of this method in Brazil. **Method:** It was a descriptive analysis with retrospective collection of data from patients submitted to treatment for NSCLC with curative intention using robotic technique in different centers in Brazil. All data regarding demographics in addition to clinical and pathological details about nodal staging were collected. Patients with incomplete records about staging were excluded. **Result:** We included 172 patients operated on from January 2015 to March 2019 . The average age was 65.7 years, 87 were female and 85 male. The most frequent histologic types were adenocarcinoma with 131(75.7%) cases, carcinoid tumors with 22(12.7%) cases followed by 17(9.8%) squamous carcinomas, 2 (1.1%) large cell carcinomas and 1 (0.5%) adenosquamous carcinoma. One of the patients had 2 tumors with different histotypes (large cell carcinoma and adenocarcinoma). The most frequent stage was IA both in clinical (118,68.6%) and pathological (114, 66.2%) and the average tumor size was 20mm. There was upstaging in 34 (19.7%) cases and down staging in 30(17.4 %) cases. Lobectomy was the most frequent type of resection with 140 cases. On average 11.9 lymph nodes were resected and 5.8 node categories were addressed. Nodal upstaging occurred in 17 cases (9.8%) of which 8(4.6%) were N1-2 upstaging 6(3.4%) N0-1 upstaging and 3(1.7%) N1-2 upstaging. The incidence of nodal upstaging found was comparable with others studies. **Conclusion:** In our experience, the treatment for NSCLC using the robotic approach was able to perform an adequate lymphadenectomy with prevalence rate comparable to previous data in literature.

Keywords: Lung cancer, Robotic Surgery, Upstaging

P2.13-11 PREDICTING MICROMETASTASIS IN MEDIASTINAL LYMPH NODES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

S. Erus[1], H. Süer[2], M. Kapdağlı[3], S. Tanju[1], Ş. Dilege[1]

[1]*Koç University School of Medicine, Istanbul/Turkey,* [2]*Koç University, Istanbul/Turkey,* [3]*VKF American Hospital, Istanbul/Turkey*

Background: Non-small-cell lung cancer staging is the most important factor affecting both the potential treatment and the prognosis. The evaluation of non-small cell lung carcinoma staging uses the TNM classification (tumor, node, metastasis). The N factor plays a more critical role in staging than T and M factors, because of its unpredictability. We know that undiagnosed micrometastatic nodal disease has a poor prognosis. Detecting micrometastasis is expensive and time consuming, so that's why we aimed to investigate the factors predicting micrometastatic mediastinal disease. **Method:** We collected all the lymph nodes from the patients that we operated between July 2012 and July 2013. We excluded all the patients who had an induction treatment and preoperatively diagnosed with mediastinal metastasis. We studied the expressions of three biomarkers; EpCAM, CEACAM5 and KRT19 using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) in lymph nodes and compared the expressions with healthy controls. If all three of them are positive, we have accepted it as micrometastasis. We compared the presence of micrometastasis with the pathological data to identify possible predictive factors. **Result:** We analyzed 86 lymph nodes from 32 patients. Twenty seven out of 86 lymph nodes (%31.4) were positive for micrometastasis. Eighteen out of 32 patients (%56.3) became micrometastatic and 16 out of 32 patients are upstaged. Four of them are upstaged from N1 to N2 and 12 of them are upstaged from N0 to N2. Micrometastatic patients tend to have poorer survival compared to non-micrometastatic patients but without an statistical significance. However micrometastasis was found significantly higher in tumors with less than 2 cm (p: 0.03) and lower in tumors without lymphovasculary invasion (p: 0.03). **Conclusion:** In our study tumors with smaller than 2cm in diameter and without lymphovascular invasion have significantly higher micrometastatic potential. In order to validate these parameters as predictive markers this experiment should be performed in a larger cohort with increased control population.

Keywords: micrometastasis, qRT-PCR, NSCLC

P2.13-12 ENDOBRONCHIAL ULTRASOUND FOR DIAGNOSIS AND STAGING OF LUNG CANCER: OUR EXPERIENCE

A. De Palma[1], G. Garofalo[1], E. Maiolino[1], T. Panza[1], F. Signore[1], A. Fiorella[1], O. Pizzuto[1], X. Trabucco[2], G. Marulli[1]

[1]*Section of Thoracic Surgery, University of Bari, Bari/Italy,* [2]*Division of Pathology, University of Bari, Bari/Italy*

Background: Surgical treatment of non-small cell lung cancer (NSCLC) can only be achieved in 20-25% of affected patients. Staging, deriving from the TNM classification, is the most relevant element for the selection of patients and N parameter is an essential prognostic factor. In recent years, in order to assess the N parameter with an endoscopic approach, ultrasound probes of small size have been assembled at the tip of the videobronchoscope (EBUS: Endobronchial Ultrasonography), allowing to perform real-time, ultrasound guided, transbronchial needle aspiration (TBNA) and/or transbronchial needle biopsies (TBNB) of hilar and mediastinal lymph nodes. This invasive examination of the tracheo-bronchial tree is nowadays of primary importance for the diagnosis and staging of lung cancer. We report our experience with this innovative endoscopic technique. **Method:** We retrospectively analyzed data of patients submitted to EBUS-TBNA/TBNB at our Section of Thoracic Surgery, from September 2008 to December 2018, considering the following factors: gender, EBUS-TBNA/TBNB positivity/negativity, duration of the procedure, number of samples taken from each lymph node station, complications related to the procedure. **Result:** EBUS was performed in 131 patients (95 men, 36 women) and repeated twice in 5/131 patients, for a total number of 136 EBUS procedures. Ultrasound evidence of lymph nodes was positive in 120/136 cases, in which TBNA/TBNB was performed, with the following cyto/histopathological results: positivity in 61 cases (51%), negativity in 23 cases (19%), inadequate material for diagnosis in 28 cases (23%), suspect/doubt in 6 cases (5%), no results in 2 cases (2%). Mean duration of the procedure was 30 minutes (range 15-60 minutes) and mean number of samples for each lymph node station was 3. No intra- or postprocedure complications were observed. Only 19 on 36 cases without diagnosis could undergo diagnostic surgery with the following results: 9 sarcoidosis, 6 lung cancer, 1 lymphoma, 1 epitelioid hemangioendotelioma, 1 paraganglioma, 1 antracosis. **Conclusion:** In our experience, EBUS-TBNA/TBNB resulted a safe and free from major complications procedure, easily repeatable, in a standardized way, after an adequate "learning curve" and it can avoid more invasive diagnostic technique such as mediastinoscopy. In fact, according to the current guidelines of the ESTS (European Society of Thoracic Surgeons) EBUS-TBNA should be used as the first diagnostic test in patients with hilar-mediastinal lymphadenopathy with or without the presence of a suspect lung mass, in order to obtain both staging and diagnosis.

Keyword: endobronchial ultrasonography, N staging, lung cancer

P2.13-13 SHOULD VISCERAL PLEURAL INVASION BE PROGNOSTIC FACTOR IN PATIENT WITH SMALLER SIZED ADENOCARCINOMA?

K. Park

DCMC, Daegu/Korea, Republic of

Background: Visceral pleural invasion(VPI) is an adverse prognostic indicator as T2 irrespective of size in case of 3cm and less in 8th AJCC staging system. We analysed the effect of VPI status on recurrence in 3cm or less sized resected adenocarcinoma with another clinicopathological parameters. **Method:** We retrospectively reviewed a total of 97 patients with 3cm smaller sized stage I adenocarcinoma that underwent curative resection and MLND. The risk factors were statistically analyzed using Cox proportional hazard model and the Kaplan meier method. **Result:** The median follow-up period was 43.4months (range 7.0-188.7). In univariate analysis, the significant variables for recurrence were ever smoker at the time of surgery, sex, pathologic tumor size, SUVmax in PET-CT, solid predominant histologic subtype. In multivariate analysis, pathologic tumor size(p=0.049, HR=3.52, CI 1.01-12.31) was the independent risk factor for higher probability of recurrence. The 5-year overall survival rate was 77.0%. **Conclusion:** VPI was not a prognostic factor in 3cm sized pathologic stage I adenocarcinoma. 3cm size tumor or less with VPI may be designated as T1 not T2. But further study should be needed to validate.

Keywords: adenocarcinoma, visceral pleural invasion, staging

P2.13-14 THE UTILITY OF THREE-DIMENSIONAL CT FOR PREDICTION OF TUMOR INVASIVENESS IN CLINICAL IA LUNG ACENOCARCINOMA

Y. Kawaguchi, M. Nakao, J. Ichinose, Y. Matsuura, S. Okumura, M. Mun

Cancer Institute Hospital of JFCR, Tokyo/Japan

Background: In the evaluation of clinical T factor, there are some cases that the measurement of the solid component diameter of the tumor is difficult in conventional two-dimensional computed tomography (CT) because of heterogeneity and indistinctness of tumor density. So there is a problem in the preoperative estimation of the tumor invasiveness in these cases. Three-dimensional image analysis software, Synapse Vincent can quantify the volume of solid component of the lung nodule based on the CT value semi-automatically.The purpose of this study was to investigate the relationship between the histological grade of adenocarcinoma and the solid component volume by three-dimensional CT. **Method:** We enrolled 195 cases of cIA adenocarcinoma resected at our hospital in 2017. Two observers measured the solid component diameter of the tumors after consultation. The relationship of solid component diameter (2D), solid component volume (3D) and pathological subtypes (AIS, MIA or invasive cancer) were analyzed. We additionally performed the same analysis with a focus on 57 cases (29.2%) in which we judged that 2D measurement of the tumor was difficult. The cut-off value of each item was determined using the ROC curve. **Result:** The number of AIS / MIA were 86 and of invasive cancer were 109 cases respectively. The median value of 3D was 442.2 mm3 (0-7044 mm3). About the prediction of invasive cancer by 2D, the sensitivity was 95.4% and the specificity was 64.0%. In the analysis of 3D, the sensitivity was 93.6% and the specificity was 69.6% assuming that the 3D cutoff value was 225 mm3. They were not statistically higher than that of 2D. In subgroup analysis for 57 cases with difficulty in 2D measurement, when the cutoff value of 3D is 225mm3, the sensitivity is relatively good at 92.9% and the specificity 65.5%, and the accuracy is almost the same as the usual tumors with measurable solid components for invasive cancer prediction. In the analysis of 2D, the sensitivity was good at 92.9%, but the degree of specificity clearly decreased at 44.8%, and the diameter of the solid component tended to be overestimated. **Conclusion:** Measurement of the solid component diameter by two-dimensional CT tends to over-estimate shadows that are difficult to measure. Three-dimensional CT, semi-automatic measurement of solid component volume, can be performed easily, and the usefulness of it was suggested, especially in cases with the tumors which are difficult to measure the solid component diameter by two-dimensional CT.

Keywords: three-dimensional CT, pathological subtypes, adenocarcinoma

P2.14 TARGETED THERAPY
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.14-01 REAL WORLD TREATMENT OUTCOMES IN CHINESE PATIENTS WITH RET-REARRANGED LUNG CANCER

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Background: One global, multicenter study has identified available multi-targeted kinase inhibitors has limited activity in patients with RET-rearranged non-small-cell lung cancer (NSCLC). However, there is limited molecular and clinical data with RET-rearranged NSCLC in China. **Method:** Retrospective real-world analysis of clinical, molecular, and treatment outcome of a web-based patient registry and hospital chart review in China. **Result:** By 28/03/2019, 73 patients with RET-rearranged lung cancers from multiple hospitals in China were registered. The majority of patients were female (56.5%), never smokers (62.9%) with NSCLCs (98.4%). 15 different molecular subtypes of infusion partners were identified in which twelve subtypes were not reported before. KIF5B-RET was the most common (51.6%) followed by CCDC8-RET (25.8%). Two patients coexist with ALK fusion, one patient with EGFR mutation, and one patient with C-MET amplification. Median OS was 20.8m (95%CI 14.9-96.4) for 46 stage IV NSCLCs. Median PFS was 7.0m (95%CI 2.7-11.7) in patients who received 1st-line treatment including chemotherapy and multi-targeted kinase inhibitors. Patients with CNS (N=14, 30.4%) had significantly shorter PFS with those without CNS (N=32, 69.6%) (4.4m vs 9.1m; p=0.04, HR 2.343[1.040-5.279]). There was no statistically significant difference in PFS in terms of upstream fusion partners (KIF5B v other partner) (p=0.059). Besides, sixteen patients received one or more lines multi-targeted kinase inhibitors: cabozantinib (fourteen patients), vandetanib (two patients) and anlotinib (three patients). The median line of systemic therapy of the first RET TKI administered was as second line (range, first to third line). The median PFS of multi-targeted kinase inhibitor therapy in patients with CNS was 9.0m (95%CI 2.5-15.5m). **Conclusion:** This is the first real-world study reporting clinical outcomes of Chinese RET-rearranged advanced NSCLC patients by now, which included the most samples, either. Most patients received chemotherapy with unfavorable survival, although several patients may benefit more from available multi-targeted kinase inhibitors. CNS is an important risk factor whereas upstream fusion partners are not. More and novel targeted therapies for RET-rearranged patients are urgently needed in China.

Keywords: real-world study, non-small-cell lung cancer, RET-rearranged

P2.14-02 INTERIM SURVIVAL ANALYSIS OF GEFITINIB PLUS VINORELBINE IN ADVANCED EGFR-MUTANT NON-SMALL CELL LUNG CANCER (GENOA TRIAL)

C. Genova[1], G. Rossi[1], A. Pezzuto[2], G. Valmadre[3], E. Rijavec[4], F. Biello[5], G. Barletta[1], M. Tagliamento[1], M.G. Dal Bello[1], S. Boccardo[1], S. Coco[1], A. Alama[1], C. Sini[6], G. Burrafato[5], C. Maggioni[1], E. Bennicelli[1], L. Cerbone[1], L. Zullo[1], A. Ricci[2], F. Grossi[4]

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Background: Patients affected by advanced non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (*EGFR*) are eventually destined to experience disease progression in spite of initial benefit from EGFR Tyrosine kinase inhibitors (TKIs). Preclinical studies have suggested that combining cytotoxic agents with EGFR TKIs to treat *EGFR*-mutant tumors may increase their inhibitory effect; in a preclinical study conducted within our Institution, the administration of vinorelbine

followed by gefitinib resulted in increased activity due to synergistic effect of the combined drugs. Here we present the interim analysis of GEfitinib plus viNorelbine in Advanced EGFR mutated NSCLC (GENOA TRIAL), which was designed to investigate the role of oral vinorelbine followed by gefitinib for the management of treatment-naïve patients affected by *EGFR*-mutant NSCLC (Clinicaltrials.gov: NCT02319577). **Method:** This was a multi-centric, open-label, randomized phase II trial designed to explore activity and tolerability of vinorelbine followed by gefitinib compared to gefitinib alone in patients affected by *EGFR*-mutant NSCLC. The estimated enrolment was equal to 80 patients; enrolled patients were randomized (1:1) to receive oral vinorelbine (60 mg/m2) on days 1,8 followed by gefitinib (250 mg) on days 9-21 (Arm A) or gefitinib alone (250 mg) on days 1-21 (Arm B) in three-weekly cycles. The primary end-point of the study was to determine the increase in terms of 6-month progression free survival (PFS) rate with Arm A compared to Arm B, while median PFS and median overall survival (OS) were secondary end-points; PFS data were defined according to response evaluation criteria in solid tumors (RECIST) v.1.1. Safety was assessed according to common terminology criteria for adverse events (CTCAE) v. 4.0. **Result:** Data from 44 patients (Arm A= 23; Arm B= 21) are available for this interim analysis, with a median follow up of 19.1 months. All the patients had advanced lung adenocarcinoma with *EGFR* mutation (exon 18=2; exon 19= 16; exon 21= 21; multiple exons= 5). The 6-month PFS rate was 48% for Arm A compared to 66% for Arm B (Fisher p= 0.24). Median PFS was 6.2 months for Arm A vs. 9.5 months for Arm B (Log Rank p= 0.17), while median overall survival (OS) was 18.2 months for Arm A and not reached for Arm B (Log Rank p= 0.12). Response rate was 47% for Arm A vs. 55% for Arm B (Fisher p= 0.76). Severe adverse events (AEs) were similarly uncommon in both arms; more specifically, two patients in Arm A experienced grade 3 white blood cells reductions, and two patients in Arm B experienced grade 3 increase of liver alanine aminotransferase. No treatment-related deaths were reported. **Conclusion:** At the interim analysis of GENOA Trial, the combination of oral vinorelbine plus gefitinib was not associated with increased 6-month PFS rate over gefitinib alone; similarly, no advantages in terms of response, PFS or OS were observed in the experimental arm. With regards to safety, no significant difference in terms of AEs was reported, nor unexpected toxicity was observed. The study was interrupted on the basis of this interim analysis.

Keywords: gefitinib, vinorelbine, EGFR

P2.14-03 PREDICTIVE FACTORS OF OSIMERTINIB AS SALVAGE TREATMENT FOR METASTATIC EGFR T790M POSITIVE LUNG ADENOCARCINOMA

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Background: EGFR T790M mutation is a robust biomarker for the efficacy of osimertinib. But its clinical efficacy is very limited in a part of patients with non-small cell lung cancer harboring EGFR T790M mutation, suggesting primary resistance. The purpose of this study was to discover clinical predictive factors for the efficacy of osimertinib **Method:** This retrospective study analyzed patients with stage IV, EGFR T790M positive lung adenocarcinoma given osimertinib as salvage treatment. Various baseline clinical factors were investigated according to favorable or unfavorable osimertinib efficacy group. Unfavorable efficacy (primary resistant) group was defined as progression-free survival (PFS) < 6 months with osimertinib. **Result:** Thirty patients were eligible for this analysis (19 of favorable and 11 of unfavorable efficacy group). PFS of favorable and unfavorable efficacy group with osimertinib were 9.9 months (95% CI 9.5-10.3) and 3.3 months (95% CI 2.4-4.2), respectively (p<0.001). Response rate of osimertinib was 89.5% vs. 18.2% (p<0.001). The cases with age at the time of lung cancer diagnosis ≥ 60 years, baseline (before starting osimertinib) Neutrophil to Lymphocyte Ratio (NLR) ≤ 3.5, pre-osimertinib treatment with first generation EGFR-TKI (gefintinib or erlotinib) rather than second generation EGFR-TKI (afatinib) were more frequent in the favorable efficacy group (p=0.058, 0.058, and 0.088, respectively, chi-square test). Age at the time of lung cancer diagnosis, ECOG performance, baseline NLR, pre-osimertinib EGFR-TKI generation, and PFS with previous EGFR-TKI were revealed as potential predictive factors through Kaplan-Meier PFS estimation. Finally, Cox proportional hazard regression analysis confirmed age at the time of lung cancer diagnosis ≥ 60 years (HR 0.292, 95% CI 0.104-0.819, p=0.019) and baseline NLR ≤ 3.5 (HR 0.238, 95% CI 0.083-0.677, p=0.007) were good predictive factors for the efficacy of osimertinib **Conclusion:** Relatively old age and low neutrophilic inflammation were associated with favorable efficacy of osimertinib.

Keywords: Osimertinib, resistance, predictive factor

P2.14-04 CLINICAL VALIDATION OF LARGE NGS GENE PANEL USING RESIDUAL SPECIMEN

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Background: Precision medicine based on driver oncogenes is now developed for non-small cell lung cancer (NSCLC). A large number of next-generation sequencing (NGS) gene panels with various characteristics have been developed, and it is important to use properly according to the purpose. TruSight™ Oncology (TSO) 500 is an NGS tumor profiling assay that targets over 500 genes to analyze cancer-related biomarkers including SNVs, indels, fusions, splice variants, tumor mutation burden (TMB) and microsatellite instability (MSI). **Method:** Of the cases diagnosed with advanced NSCLC at Tottori University Hospital, 30 cases with consent to this observational study were enrolled. TSO500 was performed at the CLIA-certified laboratory (RIKEN GENESIS CO., LTD.) using DNA and RNA extracted from archived formalin-fixed paraffin-embedded (FFPE) lung cancer specimens. These were compared with gene alterations measured in the clinical practice. **Result:** Specimens were collected by bronchoscopy in 21 cases (70%), percutaneous biopsy in 3 cases (10%), surgery in 3 cases (10%), cell block of pleural effusion in 2 cases (7%) and thoracoscopy in 1 case (3%). The success rates of DNA analyses, including TMB and MSI analysis, and RNA analyses were 83% (25/30 cases) and 97% (29/30 cases), respectively. In the 30 cases analyzed, a total of 25 actionable gene alterations (13 EGFR mut, 4 ALK fus, 2 KRAS mut, 2 BRAF mut, 2 MET ex14 skipping, 1 RET fus, 1 PIK3CA mut) were detected in 24 cases (80%). Of the 21 cases that actionable gene alterations were identified in the clinical practice, TSO500 detected similar gene alterations in 20 cases (95%) except for one case that RNA analysis was failed. In addition, TSO500 detected BRAF V600E mutation in one case that had not been tested for BRAF mutation. TMB analysis succeeded in 26/30 cases (87%) and 9/26 cases (35%) were TMB-high when 10 mutations per mega base was set as the threshold. **Conclusion:** Despite analyzing small biopsy specimens with a large NSG panel, TSO500 could detect not only gene alterations for clinical use but also exploratory gene alterations.

Keywords: Precision medicine, Next-generation sequencing, driver oncogene

P2.14-05 EGFR MUTATION STATUS AND PROGNOSTIC IMPACT IN PATIENTS WITH SURGICALLY RESECTED LUNG ADENOCARCINOMA

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Background: Epidermal growth factor (EGFR) gene mutation status in lung adenocarcinoma has been demonstrated to reflect the therapeutic efficacy of tyrosine kinase inhibitors (TKIs). In this study, we investigated the association of EGFR mutation status with prognostic impact. **Method:** From January 2010 to December 2018, we retrospectively reviewed 450 patients with resected lung adenocarcinomas who underwent EGFR mutation status analysis. Clinicopathological factors analyzed included age, sexgender, smoking history, serum carcinoembryonic antigen (CEA) levels, lymphatic invasion (Ly), vascular invasion (V), histological grade, malignant component, pathological stage, and EGFR mutation. Univariate and multivariate analyses of overall survival (OS) and recurrence-free survival (RFS) were conducted. **Result:** The study group comprised 450 patients (260 men, 190 women; age range: 32–88 years; mean age: 67.6±9.9 years). The median follow-up period was 35.4 months. A total of 282 patients were smokers

and 168 were nonsmokers. EGFR mutation analysis identified 186 patients with EGFR mutation and 264 patients with wild-type EGFR. Preoperative CEA was elevated in 117 patients. Ly, V, high grade, high malignant component and advanced stage were observed in 72, 73, 209, 120 and 102 patients, respectively. The 5-year OS in patients with EGFR mutation was 80.6% compared with 75.6% for those with wild-type EGFR (p=0.011). The 5-year RFS in patients with EGFR mutation status was 77.1% compared with 66.8% for patients with wild-type EGFR (p=0.036). There were no significant differences in OS and RFS between patients with exon 21 L858R, exon 19 deletion and other mutation subtypes. In addition, there was no survival difference in patients with EGFR mutation who received TKI or not after lung cancer recurrence. In multivariate analysis for OS, EGFR mutation status was an independent significant prognostic factor, as well as age, Ly, and pathological stage. **Conclusion:** EGFR mutation status is an independent good prognostic factor in patients with resected lung adenocarcinoma regardless of TKI use. EGFR mutation subtypes did not show significant differences in prognosis.

Keywords: lung adenocarcinoma, EGFR mutation, risk factor

P2.14-06 THE STUDY OF RAC3 MOLECULAR MECHANISM THROUGH ERK SIGNALING PATHWAY IN LUNG ADENOCARCINOMA

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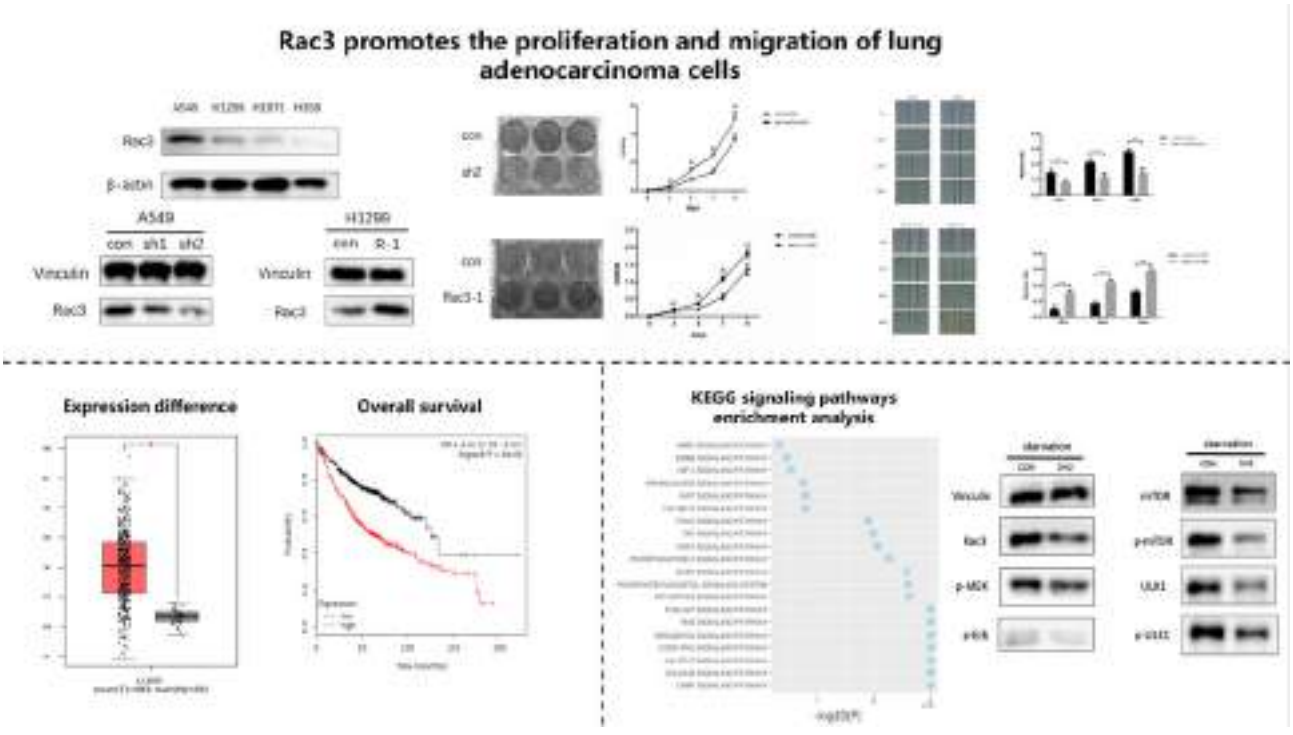
Background: To find out the relationship between Rac3 gene and prognosis of lung adenocarcinoma, the role of Rac3 in the proliferation and migration of lung adenocarcinoma cells, and the mechanism of Rac3 promoting the proliferation and migration of lung adenocarcinoma cells. **Method:** 542 patients with lung adenocarcinoma in the TCGA database were selected for analysis, the expression of Rac3 in cancer tissues and normal lung tissues were compared. Kaplan-Meier Plotter database was selected to analyze the relationship between Rac3 expression and 5-year overall survival rate of patients by Kaplan-Meier method. Human lung adenocarcinoma cell lines A549 and H1299 were used to build Rac3 knockdown and high-expression cell lines. The role of Rac3 in the proliferation and migration of lung adenocarcinoma cells was detected by cell proliferation and healing-wound test. The Rac3 knockdown cell lines were used to detect the changes of intracellular signaling pathways by serum starvation test and Western Blot experiment, screening out the signaling pathways with significant differences and study the biological function of them. **Result:** The results of TCGA database analysis showed that Rac3 expression in 542 patients with lung adenocarcinoma was significantly higher than that in normal lung tissues, and the result is statistically significant (P<0.01). Kaplan-Meier survival analysis showed that patients with high Rac3 expression had a significantly shorter 5-year overall survival than those with low Rac3 expression (P<0.0001). In A549 and H1299 cell lines, Rac3 shRNA is used to build Rac3 knockdown and high expression cell lines by lentivirus infection. The proliferation and migration of lung adenocarcinoma cells were detected by cell proliferation test and healing-wound test. Compared with the control group, the proliferation and migration ability of Rac3-shRNA group was significantly decreased, while that of Rac3 high expression group was significantly increased (P < 0.01). Serum starvation test and Western Blot results showed that in A549 cell lines, the phosphorylation of ERK pathway was significantly reduced after Rac3 expression was knocked down by shRNA compared with the control group.



Conclusion: Rac3 is highly expressed in lung adenocarcinoma. The overall survival (OS) of patients with high Rac3 expression was significantly shorter than those with low Rac3 expression. Rac3 promotes the proliferation of lung adenocarcinoma cells. Rac3 promotes the migration of lung adenocarcinoma cells. Rac3 probably regulates the ERK signaling pathway to promote the proliferation in lung adenocarcinoma cells.

Keywords: Rac3, lung adenocarcinoma, ERK signaling pathway

P2.14-07 EFFICACY OF SINGLE BEVACIZUMAB INTRAPLEURAL OR INTRAPERICARDIAL INJECTION IN THE TREATMENT OF LUNG CANCER-MEDIATED MALIGNANT EFFUSION

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Background: Malignant pleural or pericardial effusion is common in lung cancer, and drug intrapleural and intrapericardial injection plays an important role in the treatment. Local injection drugs include chemotherapy drugs and sclerosing agents. Patients with chemotherapy are vulnerable to bone marrow suppression and gastrointestinal side effects, and sclerosing agents would cause severe local side effects and be forbidden in the intrapericardial injection. The level of vascular endothelial growth factor (VEGF) in the malignant effusion increases significantly, therefore injecting bevacizumab locally may achieve a good response. So we investigated the efficacy and safety of single bevacizumab intrapleural or intrapericardial injection in the treatment of non-small cell lung cancer (NSCLC)-mediated malignant effusion. **Method:** This prospective, open-labeled, single arm, phase II clinical trial was undertaken at the First Affiliated Hospital of Guangzhou Medical University, China. Eligible patients had histologically or cytologically confirmed NSCLC with malignant pleural or pericardial effusion. Patients unsuitable for or rejecting the systemic therapy were included in. Patients could receive TKI continous treatment after TKI-resistance while only emerging malignant effusion. And lung cancer related symptoms were caused mainly by malignant effusions. Patients were administrated by single bevacizumab 100mg intrapleural or intrapericardial injection after the drainage of effusions. Lung cancer symptom scale (LCSS), efficacy and safety were evaluated before and after the treatment. **Result:** Twenty patients with lung adenocarcinoma and two patients with lung squamous cell carcinoma were included in the study from January 2014 through March 2019. LCSS after the treatment (score 494±78, mean±SD) were significantly improved compared with that before the treatment (score 377±77, mean±SD) (paired differences: score 117±64, mean±SD, 95% CI: score 89-145, P<0.001). Malignant effusions decreased obviously three weeks after the treatment compared with those before the treatment (P<0.001). The median duration of response was 91 days (127±40 days, mean±SD) in the 14 patients receiving intrapleural injection, and 111 days (91±11days, mean±SD) in the 8 patients with intrapericardial injection. There was no significant difference in the remission time of local injection between malignant pleural and pericardial effusions (P=0.987). Moreover, no severe side effects emerged, only one patient had mildly dizziness. **Conclusion:** Single bevacizumab intrapleural or intrapericardial injection is effective and safe in the treatment of lung cancer-mediated malignant effusion, while rapidly improving the malignant effusion-related symptoms in NSCLC patients. Certainly further more clinical trials were needed to confirm the results.

Keywords: malignant effusion, local injection, Bevacizumab

P2.14-08 BANF1 PREDICTS LUNG CANCER SURVIVAL AND SENSITIVITY TO PLATINUM-BASED CHEMOTHERAPY

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Background: Barrier to autointegration factor 1 (BAF/Banf1) is a small, 10 kDa protein that functions as a non-specific DNA-binding homodimer and localises to the nuclear envelope during mitosis where it tethers DNA loops to the nuclear envelope. Mutations in Banf1 are associated with the severe premature ageing syndrome, Néstor–Guillermo Progeria Syndrome. Previously, key proteins associated with other progeria syndromes have been shown to play a role in both tumourigenesis and ageing, and now more recently, Banf1 expression has been associated with poor gastric cancer survival. With lung cancers being the leading cause of cancer-related deaths worldwide, identifying markers of improved prognosis, particularly in association with specific chemotherapy treatments, is essential to maximising drug effectiveness and promoting patient survival. **Method:** A variety of cell and tissue biology techniques including cellular Banf1 protein depletion and overexpression in a panel of lung cancer cell lines, drug treatments, immunofluorescence, immunoblotting and tissue microarray analysis, have been utilised in this study. **Result:** Kaplan-Meier analysis of mRNA datasets from 1926 patients diagnosed with lung cancer show a statistically significant association (p=7.8e-12) between "low" Banf1 mRNA and increased median overall survival of patients at 88.7 months, compared with the 52-month median survival of the "high" Banf1 mRNA cohort. Depletion of Banf1 in a panel of Non-Small Cell Lung Cancer (NSCLC) lines followed by cisplatin drug treatment demonstrated a heterogeneity of response, with a subset of cell lines experiencing improved survival while others displayed increased sensitivity to the drug compared with control cells. **Conclusion:** Banf1 is a candidate marker of lung cancer patient prognosis with Banf1 depleted cells having altered sensitivity to cisplatin treatment. Understanding the mechanism by which Banf1 affects lung cancer cell sensitivity to this drug is an ongoing research process that may have major implications for lung cancer treatment. Identification of patient Banf1 expression levels may contribute to improved therapeutic tailoring while modulation of Banf1 expression may ultimately lead to significantly increased survival of diagnosed patients.

Keywords: Survival, Banf1, cisplatin

P2.14-09 CONCURRENT TP53 MUTATION ADVERSELY IMPACT THE EFFICACY OF CRIZOTINIB IN ROS1-REARRANGED LUNG CANCER PATIENTS

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Background: ROS1 tyrosine kinase inhibitors (TKIs) are now standard of care for patients with advanced *ROS1*-rearranged NSCLC. But factors that may affect the efficacy of ROS1 TKIs remain to be explored. **Method:** We conducted a retrospective multicenter study of lung cancer patients with *ROS1* rearrangements. Treatment and survival follow-up was done and clinical records were reviewed. PFS distribution was analyzed by Kaplan-Meier method with log-rank test. **Result:** In total, we included 94 lung cancer patients with *ROS1* fusion genes profiled by next-generation sequencing from May 2016 to September 2018. Fifty of them were female. The median diagnosis age was 54 (25-83). The most common histologic type was adenocarcinoma, which was confirmed in 75 of 78 patients with available pathological results. The most common fusion partners were CD74, EZR, SDC4 and SLC34A2 identified in 42, 19, 12 and 8 patients respectively. Concurrent actionable mutations were uncommon for *ROS1* fusion-positive patients. The most frequent concomitant mutated gene was *TP53*, which was detected in 33% of all the patients. After excluding 29 patients who were lost to follow-up at the very start, the median follow-up time was 8.5 (0-28) months from the moment when mutation profiling was performed. Thirty-nine patients received treatment with crizotinib, among whom 27 were treatment-naïve patients. The median PFS of the 39 patients with crizotinib was not reached yet. Patients with baseline CNS metastasis tend to have shorter PFS compared to patients without (median, 12 *vs* NR, p = 0.0073). Besides, concurrent *TP53* mutations were correlated with worse PFS (median, both NR, p = 0.0417). Mutation profiles of 10 patients were derived from ctDNA testing. No difference was found in PFS between these 10 patients with others whose genomic profiles were based on fresh tissue or FFPE specimens, suggesting that plasma ctDNA serves as good specimen source for mutation profiling to monitor clinical treatment. **Conclusion:** Concurrent *TP53* mutation and presence of CNS metastasis are associated with decreased PFS of *ROS1*-positive patients treated with crizotinib.

Keywords: ROS1, TP53, crizotinib

P2.14-10 IDENTIFICATION OF FREQUENT, ACTIVATING HER2 MUTATIONS AND HER2 INHIBITOR RESPONSE AND RESISTANCE IN CANINE LUNG CANCER

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Background: Naturally occurring primary canine lung cancers share clinical and pathologic features with human never-smoker lung cancer, but their genetic and biologic underpinnings have been unknown. We mapped the genomic landscape of canine lung cancer, discovering somatic HER2 (*ERBB2*) mutations in ~38% of canine pulmonary adenocarcinomas (cPACs). We describe our genomic findings, effects of HER2 mutations on cell signaling and HER2 inhibitor response/resistance, and results of pharmacokinetic (PK) studies of the HER2 inhibitor neratinib in healthy dogs. **Method:** We performed multi-platform genomic analysis of 92 primary canine lung tumors or cell lines. We evaluated HER2 signaling by Western blot. Neratinib and lapatinib responses were assessed in HER2-mutant and wild-type cPAC cell lines *in vitro*. HER2-mutant cell lines were continuously treated with IC50 neratinib doses to select for drug resistance, then evaluated for resistance mutations. Neratinib tolerability and PK were evaluated in healthy, mixed-breed, middle-aged dogs given a single 6 mg/kg oral neratinib dose with or without maropitant citrate or loperamide. Plasma samples for PK were collected pre-dose and timepoints from 0.5-24h after dosing. **Result:** Canine lung cancers exhibited low tumor mutation burden. HER2 was the most commonly mutated gene in cPACs, occurring in ~38%, but was absent from canine adenosquamous or squamous cell carcinomas. HER2 hotspot V659E transmembrane domain (TMD) mutations were most common and comparable to activating TMD mutations in human cancer. HER2 V659E correlated with constitutive phosphorylation of Akt in cPAC cell lines. HER2 V659E lines displayed hypersensitivity to neratinib and lapatinib relative to wild-type lines. Continuous treatment of HER2-mutant cell lines led to rapid development of resistance. Characterization of resistance-driving alterations is ongoing, as are efficacy studies in mouse xenografts. A dose of 6 mg/kg neratinib in healthy dogs showed that neratinib was tolerable and achieved therapeutic levels from IC50 studies. Evaluation of neratinib tolerability and efficacy in dogs bearing HER2-mutant lung cancer is ongoing. **Conclusion:** HER2 TMD mutations are common in otherwise low-mutation-burden primary canine lung cancers. They confer constitutive HER2 signaling and HER2 inhibitor response in cell lines. Dosing and tolerability studies in healthy dogs have shown that therapeutically relevant doses are achievable. Study of HER2 inhibitor response/resistance in cell lines and mouse xenografts is ongoing as is clinical evaluation of neratinib activity in dogs with spontaneous lung cancer. These data offer immediate diagnostic and therapeutic opportunities for pet dogs and bear implications for comparative understanding of human never-smoker lung cancers and other HER2-mutant cancers.

Keyword: HER2 (ERBB2), Never-Smoker Lung Cancer, Novel Translational Models

P2.14-11 RETREATMENT WITH EGFR-TKI FOR 541 NSCLC PATIENTS WITH EGFR MUTATION

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Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) is remarkably effective against non-small cell lung cancer (NSCLC) harboring *EGFR* activating mutation. However, tumors almost inevitably develop resistance approximately after one year of EGFR-TKI treatment. In addition, some patients can not tolerate an EGFR-TKI treatment because of adverse events and result in discontinuation of the treatment. In such cases, the same or other EGFR-TKI may be re-administered. However, its efficacy is not fully evaluated. **Method:** We retrospectively investigated patients who received EGFR-TKI between January 2008 and August 2017. Among these patients, the response rate and time to treatment failure (TTF) for each re-administered TKI were assessed. We assessed each TTF for patients who discontinued the prior EGFR-TKI because of progressive disease (PD group) and patients who discontinued TKI because of adverse events (AE group). We also evaluated the overall survival (OS) for the patients who received the retreatment with EGFR-TKI and who did not. **Result:** A total of 1400 patients from 11 institutions were enrolled in this study. Among them, 570 patients received retreatment with EGFR-TKI, and 541 were eligible. Among the 395 patients who discontinued prior EGFR-TKI because of disease progression, the response rate and the median TTF of subsequent Gefitinib/Erlotinib/Afatinib were 8%/8%/18%, and 4.9/3.2/4.3 months, respectively. The median TTF for the AE group was significantly longer than that for the PD group (10.8 months vs 3.8 months, p<0.0001). In the AE group, The OS for patients receiving retreatment with EGFR-TKI was significantly better than the OS for patients without retreatment (Hazard Ratio = 0.256, p < 0.0001). Similarly, in the PD group, the OS for patients receiving retreatment with EGFR-TKI was significantly better than the OS for patients without retreatment (Hazard Ratio = 0.456, p < 0.0001). **Conclusion:** Retreatment with EGFR-TKI was shown to be effective for both patients who discontinued prior EGFR-TKI because of disease progression as well as adverse events.

Keyword: retreatment, EGFR-TKI, resistance

P2.14-12 TYROSINE KINASE INHIBITOR RESISTANCE MECHANISMS IN EGFR T790M-POSITIVE LUNG CANCER: THE UNIVERSITY OF CHICAGO EXPERIENCE

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Background: Acquired resistance to osimertinib in epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) is a poorly understood phenomenon and presents an ongoing challenge. Previously described mechanisms include emergence of mutations at *EGFR* C797S, *MET* amplification, transformation to small cell lung cancer, and *BRAF* mutation. Next-generation sequencing (NGS) of tumors at progression through osimertinib may help to illuminate novel mechanisms of resistance to osimertinib. **Method:** We surveyed University of Chicago Medicine case records for osimertinib-treated NSCLC patients treated who progressed through therapy. Panels utilized for NGS included, among others, the University of Chicago's validated panel (the UCM-OncoPlus, surveying greater than 1,100 genes) and Guardant (Guardant Health; Redwood City, CA). Patients were stratified according to presence of *EGFR* T790M mutation at the initiation of osimertinib therapy. **Result:** 28 patients were identified to have progressed through osimertinib. 23 patients (82.1%) had next-generation performed at the time of progression. Among osimertinib-resistant patients who had NGS, 17 (73.9%) demonstrated at least one resistance mechanism, of which 8 (34.8% of tested patients) were subsequently treated with tyrosine kinase inhibitor-containing regimens or clinical trial of targeted therapy. Mutational profile at progression through osimertinib included: 2 patients (11.8%) with *EGFR* C797 mutation, 2 patients (11.8%) with *MET* amplification, 2 patients (11.8%) with *RET* fusion protein, 2 patients (11.8%) with *MET* point mutation, 1 patient (5.9%) with *EGFR* amplification, and 1 patient (5.9%) with small cell transformation. Newly identified resistance mechanisms (n = 1 for each) included mutation to *EGFR* G724 and L718 residues, *ROS1* fusion protein, and in the same patient *CBLB* Q371* and *SMAD4* loss. Of the 23 patients undergoing NGS at progression, 11 (47.8%) harbored *EGFR* T790M mutations prior to treatment, 3 (27.3%) of whom demonstrated resistance mutations susceptible to additional tyrosine kinase inhibitor therapy. **Conclusion:** On the basis of these data, we confirm many previously described mechanisms of osimertinib resistance, including *EGFR* amplification, *MET* amplification, fusions involving *RET*, and transformation to small cell lung cancer, as well as novel resistance mechanisms including

ROS1 fusion protein. We demonstrate the utility of NGS at the time of progression through osimertinib in our practice, regardless of the patient's *EGFR* T790M status. We conclude that re-biopsy and utilization of NGS identifies a significant subset of osimertinib-resistant patients in whom well-tolerated tyrosine kinase inhibitor therapies remain an option and, in the interests of both patient well-being and clinical trial enrollment, should be considered standard practice at progression.

Keywords: therapeutic resistance, tyrosine kinase inhibitor, Epidermal growth factor receptor

P2.14-13 ELEVATED EXPRESSION OF EUKARYOTIC TRANSLATION INITIATION FACTOR 3 SUBUNIT C CONTRIBUTES TO EGFR-TKI RESISTANCE IN LUNG ADENOCARCINOMA

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Background: The treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib, in patients with *EGFR*-mutant lung adenocarcinoma causes tumor regression and improved prognosis. However, drug resistance and tumor relapse eventually occur, and the molecular mechanisms remain to be fully revealed. In this study, we elucidated the novel mechanism of EGFR-TKI resistance and clarified the clinical significance using erlotinib-resistant lung adenocarcinoma cell lines and patient specimens. **Method:** The erlotinib-resistant cell line, PC9/ER was obtained from PC9 cell line by exposing to increasing concentrations of erlotinib for 6 months. The sensitivity of erlotinib was evaluated by the MTT assay. In order to identify erlotinib-resistance related factors, we performed a proteomics analysis, followed by western blotting. To evaluate the roles of the candidate factor, we performed gene knockdown analysis using siRNAs. The autophagy activity was assessed by the amount of LC3B-II protein or visualization of autophagosomes using LC3B-RFP expression vector. Immunohistochemical staining was performed on tumor biopsies obtained from lung adenocarcinoma patients with activating mutation in *EGFR*, and we examined the correlation between the staining intensity and clinical EGFR-TKI resistance. **Result:** Initially, we performed the sequencing analysis of *EGFR* exons 18 to 21, which cover the tyrosine kinase domain, and found that there was no difference between PC9 and PC9/ER cells. The proteomics analysis revealed ribosomal and translation-related proteins were abundantly identified in PC9/ER cells, compared with PC9 cells. Among them, we found that eukaryotic translation initiation factor 3 subunit C (eIF3c) was overexpressed in PC9/ER cells. The knockdown of eIF3c expression with siRNA improved the sensitivity of EGFR-TKI in PC9/ER cells. Additionally, we observed that LC3B-II increased in PC9/ER cells, but decreased by the knockdown of eIF3c. Consistently, the overexpression of eIF3c upregulated the number of autophagosomes. Moreover, the inhibition of autophagy with chloroquine attenuated erlotinib-resistance in PC9/ER cells. Finally, the frequency of eIF3c-positive samples was higher in biopsy specimens from the patients' refractory to EGFR-TKI therapy than in those from the patients prior to the treatment with EGFR-TKI. Furthermore, patients with eIF3c-positive tumors had shorter progression-free survival in EGFR-TKI treatment than eIF3c-negative patients. **Conclusion:** The increased eIF3c expression conferred the resistance to EGFR-TKI in lung adenocarcinoma cells via enhancement of autophagy. Moreover, the patients with increased eIF3c expression in biopsy samples showed poor prognosis. The inhibition of eIF3c could be a new therapeutic strategy for overcoming EGFR-TKI resistance in lung adenocarcinoma patients.

Keywords: EGFR-TKI resistance, autophagy, eukaryotic translation initiation factor 3 subunit C

P2.14-14 COMPARISON OF MOLECULAR TESTING MODALITIES FOR DETECTION OF NRG1 REARRANGEMENTS IN INVASIVE MUCINOUS ADENOCARCINOMA

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Background: The NRG1 (Neureguline-1) fusion gene has been recently described as a new molecular feature of non small cell lung cancer (NSCLC), strictly related to invasive mucinous adenocarcinoma (IMA) subtype. Despite of *NRG1* fusion partners, all Nrg1 chimeric ligands were predicted to retain the EGF-like domain of the wild-type NRG1 III-β3 isoform that produces oncogenic signals through ErbB2-ErbB3 heterodimers and leads to phosphorylation of ErbB3. To date, the *NRG1* fusions were quite exclusively identified by RNA sequencing and only in few cases confirmed by fluorescent in situ hybridization (FISH) analysis, mainly due to the cellular features of IMA subtypes that produce interference in fluorescent signals detection. An accurate detection of *NRG1* rearrangement/fusions in clinical tumor samples is actually demanded. In this study we compared the performance of two molecular testing approaches to detect *NRG1* breaks in paraffin embedded formalin fixed (FFPE) IMA lung tissues. **Method:** A total of 19 lung FFPE IMAs were screened by immunohistochemistry (IHC) to evaluate the expression of phosphorylated-ErbB3 (pErbB3) receptor. Samples positive for pErbB3 staining were tested by using by break-apart FISH to detect putative *NRG1* rearrangements and RNA-targeted next generation sequencing (NGS) to identify fusion variants. **Result:** Eleven cases showed an increased expression of pErbB3 in cancer cells compared to the adjacent non-involving bronchial epithelium which demonstrated a basal level staining of the protein. pErbB3 positive cases were investigated by FISH and showed <15% of rearranged nuclei (range 17-47%, mean 29%). In addition to the canonical signal split pattern, the FISH *NRG1* assay reveals that cells also showed rearrangement patterns in form of isolated 3' signals, thus indicating a strength analogy with *ALK* and *ROS1* fusions, where a 5' gene deletion was frequently observed. *CD74-NRG1* fusion variant was identified by NGS analysis in four cases, whereas in three cases a 3'/5' *NRG1* imbalance was detected. For both approaches, we identified assay characteristics that likely contributed to false-negative results. **Conclusion:** Our investigations confirm the usefulness of IHC/FISH combined approach for *NRG1* broken tumors identification, but also highlight the crucial role of NGS to identify NRG1 functional chimeric transcripts. Such combined molecular testing should enhance the selection of *NRG1*-positive patients to include in clinical trials with specific compounds designed to inhibit the RTK downstream signal.

Keywords: NSCLC, NRG1, gene fusions

P2.14-15 IMPACT OF COEXISTING GENE MUTATIONS IN EGFR-MUTATED NON–SMALL CELL LUNG CANCER BEFORE TREATMENT ON EGFR T790M MUTATION STATUS AFTER EGFR-TKIS

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Background: The T790M secondary mutation of epidermal growth factor receptor gene (*EGFR*) is the most common mechanism of acquired resistance to first- or second-generation EGFR tyrosine kinase inhibitors (TKIs). We investigated the association between gene mutation profile in *EGFR* mutation–positive non–small cell lung cancer (NSCLC) before EGFR-TKI treatment and T790M status after treatment. **Method:** A total of 57 *EGFR* mutation–positive NSCLC patients who had undergone a repeat biopsy (tissue or liquid) after failure of treatment with a first- or second-generation EGFR-TKI and who had sufficient tumor tissue available from before treatment for genetic analysis was enrolled. The gene mutation profile of tumor tissue obtained before EGFR-TKI treatment was evaluated by next-generation sequencing with a comprehensive cancer gene panel (409 genes). The number of potentially damaging

nonsynonymous mutations was predicted with PolyPhen-2 software. **Result:** Progression-free survival during EGFR-TKI treatment did not differ significantly between patients who developed T790M-mediated resistance and those who developed T790M-independent resistance. The predicted number of damaging nonsynonymous mutations in pretreatment tumor tissue was significantly lower in patients who developed T790M-mediated resistance than in those with T790M-independent resistance (P = 0.024). **Conclusion:** Coexisting mutations in tumor tissue before EGFR-TKI treatment may contribute to the emergence of cell clones responsible for development of T790M-dependent or T790M-independent TKI resistance in patients with *EGFR*-mutated NSCLC. Multiplex genomic testing of pretreatment tumor tissue may thus provide a means of identifying patients likely to develop T790M-mediated TKI resistance and therefore inform treatment selection.

Keywords: EGFR mutation, T790M, co-mutation

P2.14-16 T790M OR C797S CONFERS ACQUIRED RESISTANCE TO TARLOXOTINIB AND POZIOTINIB IN EGFR EXON 20 INSERTION-DRIVEN LUNG CANCER MODELS IN VITRO

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Background: Lung cancers with EGFR exon 20 insertion mutations are refractory to current available tyrosine kinase inhibitors. Recent evidence suggests the therapeutic potential of the novel hypoxia-activated prodrug, tarloxotinib, a potent pan-HER inhibitor, or the repurposed 3rd generation inhibitor, poziotinib in these tumors. However, it is assumed that acquired resistance to these agents will be inevitable. In this study, we explored secondary mutations that may confer resistance to these agents using Ba/F3 models. **Method:** Ba/F3 cells with various EGFR exon 20 mutations (A763insFQEA, V769insASV, D770insSVD, and H773insNPH) were generated by retroviral transfection. TKI resistant clones were established by exposure of parental cells to either tarloxotinib-E (active form of tarloxotinib) or poziotinib after treatment with N-ethyl-N-nitrosourea (ENU) mutagenesis agent. *EGFR* secondary mutations were detected by direct sequencing. **Result:** ENU mutagenesis resulted in 62 tarloxotinib-E-resistant clones and 56 poziotinib-resistant clones using 200 nM of either drug. Ba/F3 cells with A763insFQEA were highly sensitive to these agents and only 1 tarloxotinib-resistant clone (C797S) was obtained. In Ba/F3 cells with V769insASV, all 14 tarloxotinib-resistant clones and 15 poziotinib-resistant clones developed T790M mutation. In Ba/F3 cells with D770insSVD cells, all 24 tarloxotinib-resistant clones and 20 poziotinib-resistant clones developed C797S mutation. In Ba/F3 cells with H773insNPH cells, 22 of 23 tarloxotinib-resistant clones and 21 of 22 poziotinib-resistant clones developed T790M mutation, while the rest of the clones harbored C797S mutation. **Conclusion:** These results suggested that either T790M or C797S could cause acquired resistance to tarloxotinib and poziotinib in lung cancer models with EGFR exon 20 insertion mutations. Interestingly, the type of resistance mutation is likely to be dependent on the context of the original EGFR exon 20 insertion mutation.

Keywords: EGFR-TKI, secondary mutations, prodrug

P2.14-17 CORRELATION BETWEEN CLINIC-PATHOLOGICAL DATA AND T790M DETECTION IN EGFR MUTATED NSCLC PATIENTS PROGRESSING ON 1ST/2ND GENERATION TKIS

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Background: Despite osimertinib is moving to the first-line for advanced NSCLC harboring EGFR activating mutations, some patients still receive a frontline first- or second-generation EGFR-TKI. In this setting, factors predicting the emergence of T790M resistance mutation at progression (PD) are lacking. The aim of this retrospective study was to investigate the correlations between clinic-pathological features and T790M positivity (T790M+) in a single-center cohort of EGFR mutated stage IV or recurrent NSCLC patients, who underwent liquid (LB) or tissue biopsy (TB) at PD when treated with first- or second-generation EGFR-TKIs. **Method:** Data from 122 patients (80 female, 42 male) treated between 2012 and 2019 were considered for the analysis. EGFR mutations were detected with real time-polymerase chain reaction (RT-PCR) on LB and pyrosequencing or next generation sequencing on TB. PD was determined by RECIST 1.1 criteria. Univariate analysis by Fisher exact test was performed to assess any association. **Result:** At diagnosis, 117 patients carried common EGFR mutations (84 exon 19 deletions; 33 exon 21 mutations), 5 had rare mutations (3 exon 18 mutations; 2 exon 20 mutations other than T790M) . At PD, 29 patients (24%) underwent only LB, 29 only TB (24%), 64 both (52%). The overall T790M+ rate was 67% (82/122). T790M+ was significantly higher among patients with exon 19 deletion than in those with exon 21 mutation (77% vs 51%, p=0.008). T790M+ was significantly more frequent in patients with exclusively intrathoracic PD as compared to extrathoracic PD (81% vs 56%, p=0.007). Patients with pleural involvement (PI), considered as pleural effusion or/and pleural disease, as site of PD (n=45) had a significantly higher frequency of T790M+ than those with stable or absent PI (n=77) (82% vs 58%, p=0.009), irrespectively of the pattern of PD. No correlation with other sites of PD was found. **Conclusion:** Exon 19 deletion, intrathoracic PD and PI as site of PD are significantly associated with higher frequency of T790M+ in patients progressing to first-or second-generationEGFR-TKIs. These results, if confirmed by an independent validation cohort, may allow the development of a T790M+ predictive score accounting for type of mutation and sites of progression.

Keywords: NSCLC EGFR mutated, T790M detection, clinic-pathological data and T790M correlation

P2.14-18 UPREGULATION OF AURKA LEADS TO ACQUIRED RESISTANCE IN EML4-ALK NSCLC CELL LINE

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Background: Molecular targeted therapies in NSCLC often results in profound initial patient responses, these responses are short-term due to the development of acquired resistance. In an EML4-ALK NSCLC background, acquired resistance can be developed in two ways ALK dependent (ALK secondary mutations) and ALK independent (alternative oncogenic pathways). In our study, we have shown that increased expression of Aurora kinase A (AURKA) leads to acquired resistance upon treatment with ALK TKI crizotinib. **Method:** In order to determine the mechanism for acquired resistance, we treated the EML4-ALK NSCLC cell line H2228 with increasing dose of crizotinib until cells develop resistance. RNA sequencing was performed in both parental and resistant cell lines to identify differentially expressed genes. Resazurin assay was performed to evaluate cell viability. Protein levels were determined using western blotting. **Result:** In this study, we describe the upregulation of AURKA gene expression leads to acquired resistance in EML4-ALK cell line H2228. The R2: genomics analysis and visualization platform (http://r2.amc.nl) revealed that high *AURKA* expression is associated with poor prognosis in lung adenocarcinoma patients. Based on RNA seq data, we identify upregulation of AURKA in crizotinib resistance cell line when compared to the parental cell line. The resistant cell lines were sensitive to treatment with AURKA inhibitor MLN8237 and underwent apoptosis. **Conclusion:** Our results indicate a new mechanism to acquire resistance upon treatment with ALK TKI crizotinib. Inhibition of both ALK and AURKA activity might be beneficial for ALK TKI resistant tumors with increased AURKA gene expression/activity.

Keyword: EML4-ALK, AURKA, Resistance

P2.14-19 NOTCH3 AND β-CATENIN ARE FREQUENTLY CO-EXPRESSED IN EGFR MUTANT NSCLC

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Background: In the USA approximately 15% of the patients with lung adenocarcinoma have tumors associated with “driver” mutations in the EGFR gene that demonstrate major clinical responses to EGFR

Tyrosine Kinase Inhibitors (EGFR TKIs). However, despite the fact that these mutations are always "truncal" (present in every tumor cell), and dramatic tumor shrinkage is seen initially in almost all patients, EGFR TKIs are never curative and tumors always recur. Some tumors that develop resistance appear to have pre-existing resistant sub clones, but the majority appear to acquire resistance by mutational target reactivation or bypass mechanisms. In order to develop acquired resistance, a subset of cells must survive at initial stage of therapy ("drug persister cells", or DPCs) which are known to serve as a reservoir for accumulation mutation rendering drug resistance. We have demonstrated that Notch3 mediated β-catenin activation enables drug persistence, an essential step for the development of drug resistance. **Method:** We have conducted tumor protein expression analysis on a tissue micro array (TMA) containing 86 NSCLC tumors obtained before therapy. These TMAs were subjected to IHC analysis to detect the expression of Notch3 and β-catenin signaling which is known to regulate drug persistence. We have also performed cell viability and biochemical assays under various perturbations to study drug persistence mechanisms in EGFR mutant NSCLC cells. **Result:** Previously, we have demonstrated that EGFR TKI treatment leads to drug persistence through Notch3 mediated β-catenin activation. Using pre-treatment NSCLC patient tissue micro array (TMA) we identified that there is frequent co-expression of Notch3 and β-catenin (total) proteins in 90% of EGFR mutant NSCLC. We also observed that there are a relatively low proportion (10%) of patients with active β-catenin in these pretreatment samples. This suggests that the EGFR mutant tumors upregulate Notch3 protein expression, but that β-catenin is predominantly transcriptionally inactive before EGFR TKI treatment. We have also identified that Notch3 is a novel transcriptional target of β-catenin which in turn promotes both β-catenin and EGFR stability. These findings suggest that the Notch3 and inactive β-catenin co-expression is characteristic of EGFR mutant tumors, and β-catenin activation at baseline is infrequent. EGFR TKI therapy activates β-catenin signaling in a Notch3 dependent manner, and here we show that both proteins are frequently highly expressed in these tumors. **Conclusion:** The concept of DPCs serving as a reservoir for accumulation of mutations that could cause drug resistance is novel. However, signaling pathways that are associated with the activation of drug persistence are not well characterized. For the first-time, our studies demonstrate that Notch3, β-catenin andEGFR regulate each other and EGFR TKI therapy mediated Notch3 activation leads to β-catenin activation which is essential for the maintenance of drug persister cells in a positive feedback loop. By understanding and targeting the Notch3 - β-catenin axis that control DPCs, these studies can develop therapeutics to prevent resistance to EGFR TKI therapy.

Keyword: NSCLC, EGFR TKI Resistance and drug persistence

P2.14-20 ATORG-003: DACOMITINIB WITH OR WITHOUT DOSE TITRATION AS FIRST-LINE THERAPY FOR METASTATIC EGFR MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Dacomitinib is a second generation EGFR tyrosine kinase inhibitor (TKI) with irreversible pan-HER inhibitory activity. In the phase III ARCHER 1050 trial, median PFS was improved from 9.2 months to 14.7 months in the gefitinib and dacomitinib groups respectively. Significantly, median overall survival (OS) was also improved from 26.8 months to 34.1 months. However, dacomitinib commenced at 45 mg orally daily was associated with increased toxicity, higher rates of dose reductions and treatment discontinuation. Despite this, post-hoc analysis revealed the efficacy of dacomitinib (PFS and OS) was similar in dose-reduced patients and the overall study population. This investigator-initiated trial aims to evaluate an alternative dose titration strategy to improve the safety and tolerability of dacomitinib while maintaining treatment efficacy. The trial is being conducted by the Asian Thoracic Oncology Research Group (ATORG) – a co-operative lung cancer trials group in Asia. **Method:** ATORG-003 is a multi-national, multi-centre, single-arm, open-label, phase 2 clinical trial of dacomitinib in newly diagnosed stage IIIB/IV or recurrent EGFR mutant (exon 19 deletion or L858R mutation) NSCLC patients. Importantly, subjects with asymptomatic central nervous system (CNS) metastases will be eligible. Patients will be administered dacomitinib 30 mg orally daily for one cycle (4 weeks), after which subjects with ≤G1 toxicity attributable to dacomitinib may escalate to 45 mg with shared investigator and patient decision. Dose reductions to 30 or 15 mg daily will be permitted. The primary objective is to evaluate PFS rate at 12 months. Key secondary objectives include OS, objective response rate (ORR), time to treatment failure (TTF) and intracranial objective response rate (iORR). Exploratory objectives include evaluation of dacomitinib resistance mechanism(s) using next-generation sequencing (NGS) on tissue and plasma circulating tumour DNA (ctDNA). Across 15 sites in six Asian countries (Hong Kong, Korea, Malaysia, Singapore, Taiwan, Thailand), a planned 118 subjects will be enrolled. Primary analysis will be conducted on subjects without CNS metastases only, with 94 subjects required to achieve a one-sided significance level of 5% and 90% power to detect a 15% improvement in 12 month PFS rate for dacomitinib versus historical control for gefitinib (i.e. 55% versus 40%) using the intent-to-treat (ITT) analysis population. Enrollment is due to begin in July 2019. **Result:** Section not applicable. **Conclusion:** Section not applicable.

Keywords: dacomitinib, EGFR mutant NSCLC, Targeted therapy

P2.14-21 LIQUID BIOPSY IN LUNG CANCER: COMPARISON BETWEEN REAL-TIME PCR AND MALDI-TOF FOR CTDNA MOLECULAR PROFILING

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Background: Circulating cell free DNA (cfDNA) could now be used for lung cancer molecular testing when tissue is limited and/or insufficient. Tests' sensitivity and mutation coverage could have a great implication for the patient care. In this study we analyzed and compared results of cfDNA from lung carcinoma patients tested with different technologies. **Method:** 100 cfDNA samples were extracted from blood plasma (Qiagen), DNA quality and quantity were assessed using the LabChip GX Touch 24 (PerkinElmer). We used PCR based Cobas® EGFR Mutation Test v2 (Roche) that identifies 42 mutations in the EGFR gene and UltraSEEK™ Lung Panel on MALDI-TOF based MassARRAY® (Agena Bioscience): 67 mutations in 5 oncogenes: EGFR (43), BRAF (4), ERBB2 (2), KRAS (14) and PIK3CA (4) with a sensitivity down to 0.1%. For UltraSEEK we used 11-40 µl cfDNA (avg. 8.87 ng). For Cobas we initially used 70 µl (avg. 24.39 ng) and re-tested a subset (63 samples) with lower input volumes as were used for UltraSEEK. **Result:** All samples showed the expected fragment-size distribution and no significant abundance of genomic DNA on the LabChip. With high cfDNA input on Cobas we detected EGFR activating mutations in 60 patients with Cobas and in 57 with UltraSEEK and 16 and 18 EGFR T790M with Cobas and UltraSEEK, respectively. In addition, with the UltraSEEK Lung Panel 9*KRAS and 2*BRAF V600E were identified and one more double mutations (G719A/L861QR). For the subset of 63 samples with the same cfDNA input between technologies 4 (6%) were invalid for analysis on Cobas. None were invalid with USK. 85% of patients (50/59) had concordant results for overlapping markers in EGFR. The EGFR T790M mutation was detected in 7 and 10 samples with Cobas and UltraSEEK, respectively (70% concordance). In total, with UltraSEEK 10 additional EGFR mutations (4*Exon 19 deletion, 3*T790M, 1*Exon 20 insertion, 1*L861Q/R, 1*G917A) were detected in 8 of 59 patients (14%). Conversely, 1 EGFR Exon 19 deletion (2%) was detected by Cobas (wild-type in initial analysis by Cobas). The UltraSEEK Lung Panel identified 7 non-EGFR mutations (6*KRAS, BRAF) in 6 patients (10%). **Conclusion:** This study showed that the MassARRAY UltraSEEK Lung Panel improved sensitivity for ctDNA analysis especially for samples with low input in comparison to Cobas EGFR Mutation Test v2, a method widely used in clinical routine. The UltraSEEK Lung Panel could detect more EGFR primary or secondary resistance mutations. Additional mutations to EGFR (KRAS, BRAF) could also be detected in ctDNA and used as guidance for therapy.

Keywords: circulating DNA, molecular analysis, EGFR

P2.14-22 LOSS OF ECT2 EXPRESSION IMPAIRS CELL-MATRIX ADHESION AND FAK/SRC SIGNALING IN LUNG ADENOCARCINOMA CELLS

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Background: Cell adhesion is a crucial step in cancer development and progression. We have previously demonstrated that epithelial cell transforming sequence 2 (Ect2), a guanine nucleotide exchange factor for the Rho family small GTPases Rac1, RhoA, and Cdc42, is overexpressed in early invasive adenocarcinoma. We subsequently showed that suppression of Ect2 significantly reduces cell growth, migration, and invasion of lung adenocarcinoma cells. In the present study, we investigated the potential role of Ect2 on cell-matrix adhesion and adhesion signaling complex in lung adenocarcinoma. **Method:** Cell attachment assay was used to assess the viability of attached Calu-3 and PC-9 cells after suppression of Ect2 using small interfering RNA (siRNA). Adhesion of cells to extracellular matrix (ECM) was examined by adhesion assay, and changes in cell morphology were observed by immunofluorescence. RT-PCR and Western blotting analysis were conducted to examine the effects of Ect2 suppression on molecules involved in the adhesion cascade in Calu-3 and NCI-H2342 cells. To evaluate the effect of Ect2 on adhesion complex formation, immunoprecipitation was performed after treatment with siRNA-Ect2 in Calu-3 cells. **Result:** We found that suppression of Ect2 significantly reduced the viability of attached cells. Furthermore, PC-9 and Calu-3 cells transfected with siRNA-Ect2 showed markedly decreased adhesion to collagen I and fibronectin. In terms of morphological changes, Calu-3 and PC-9 cells showed non-cohesive growth and a clear rounded shape after siRNA-Ect2 treatment. To investigate the underlying molecular mechanism, we examined the levels of expression of several proteins that are directly associated with cancer cell adhesion. We found that focal adhesion kinase (FAK), a key regulator of cell adhesion, was markedly down-regulated at both the mRNA and protein levels after treatment of the lung adenocarcinoma cells with siRNA-Ect2. Consistently, the levels of expression of molecules involved in the adhesion cascade, including integrin β1, paxillin, p-Src (Tyr416), p130Cas, and Crk, were further decreased in siRNA-Ect2. Since FAK/Src signaling can be activated through interaction the adhesion molecules on the cell surface, we speculate that these interactions might be affected by Ect2. Our data showed that Ect2 suppression impairs FAK interaction with Src, integrin β1, and paxillin in lung adenocarcinoma cells. **Conclusion:** We have obtained novel data suggesting that Ect2 suppression leads to attenuation of cell adhesion to ECM, with a consequent impact on adhesion complex formation. These findings further demonstrate that Ect2 plays an essential role in the pathological steps of lung adenocarcinoma progression, and could be a potential molecular target for therapy.

P2.14-23 INITIAL ANALYSIS IN NSCLC PART OF RANDOMIZED TRIAL EVALUATING TOPICAL CORTICOSTEROID FOR THE FACIAL ACNEIFORM RASH BY EGFR INHIBITORS

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Background: Epidermal growth factor receptor (EGFR) inhibitors commonly induce skin toxicities including facial acneiform rash. The incidence of facial acneiform rash with any grade estimetes 60-90% in previous clinical trials. This FAEISS study, NCCH1512, is designed to evaluate the effects of reactive topical corticosteroid therapies with serially ranking down from very strong levels compared with that with serially ranking up from weak levels for facial acneiform rash induced by EGFR inhibitors. **Method:** Patients with EGFR-mutated non-small cell lung cancer (NSCLC) and RAS wild-type colorectal cancer who started treatment with EGFR inhibitors were enrolled first in this study (first-phase). All patients received pre-emptive therapy of oral minocycline 100 mg/day and heparinoid moisturizer from the initiation of EGFR inhibitors. Enrolled patients who developed facial acneiform rash within two weeks were randomised either to group A (ranking-up) and group B (ranking-down) (second-phase) by minimization method for balancing institution, type of EGFR inhibitors, and sex. Primary endpoint in this study was incidence of grade 2 (moderate) or higher facial acneiform rash during the 10-week skin treatment period. Here, we present the initial analysis in NSCLC patients who received EGFR tyrosine kinase inhibitors of afatinib and erlotinib. This study was registered with UMIN-CTR as UMIN000024113 (www.umin.ac.jp/ctr/). **Result:** From November 2016 to August 2018, 51 NSCLC patients treated with afatinib (n=30) and erlotinib (n=21) were enrolled in first-phase. Thirty four patients were female and 17 were male, with a median age of 66 years (range 39-79). Thirty five patients (68.6%) didn't develop facial acneiform rash within two weeks. While facial acneiform rash occurred in 16 patients (grade 1 [n=14, 27.4%] and grade 2 [n=2, 3.9%]). No patients developed severe facial acneiform rash (grade 3 or higher). Nine (30.0%) patients who received afatinib and seven (33.3%) who received erlotinib developed facial acneiform rash within two weeks. One patient treated with erlotinib was excluded due to hepatotoxicity by minocycline and 15 (29.4%) were assigned to second-phase (9 in group A and 6 in group B). Skin adverse events in second-phase (n=15) were non-facial acneiform rash (n=14), pruritus (n=8), paronychia (n=5), and dry skin (n=3). Major non-skin adverse events related to EGFR inhibitors were diarrhea (grade 3 [n=2]), ALT increased (grade 2 [n=2]), stomatitis (grade 3 [n=1]), and pneumonitis (grade 1 [n=1]). **Conclusion:** In NSCLC patients who received EGFR tyrosine kinase inhibitors, pre-emptive therapy of oral minocycline and heparinoid moisturizer could be effective for prevention of facial acneiform rash.

Keywords: EGFR tyrosine kinase inhibitor, facial acneiform rash, pre-emptive therapy

P2.14-24 AN OPEN-LABEL RANDOMIZED PHASE II STUDY OF COMBINING OSIMERTINIB WITH AND WITHOUT RAMUCIRUMAB IN TKI-NAÏVE EGFR-MUTANT METASTATIC NSCLC

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Background: Osimertinib, a third-generation EGFR inhibitor, has become the first-line therapy for patients with metastatic EGFR-mutant NSCLCs since 2018. Osimertinib is well-tolerated, therefore, it opens opportunities to be combined with other therapeutic agents to enhance the treatment outcome. In preclinical models, it has been shown that upregulated VEGF signaling mediates acquired resistance to EGFR therapies. In xenograft models, combination of anti-VEGF medications with EGFR inhibitors were significantly more effective than erlotinib or gefitinib alone. Ramucirumab, a monoclonal antibody targeting VEGF receptor 2, is approved with docetaxel in as second line treatment for NSCLCs. In clinical trial evaluations, the phase 3 RELAY trial (NCT02411448) studying ramucirumab plus erlotinib in patients with metastatic untreated EGFR-mutant NSCLC patients showed a statistically significant improvement in progression-free survival in the combination group compared to erlotinib alone. A phase I study of osimertinib with ramucirumab (NCT02789345) demonstrated safety and feasibility of this combination. With strong preclinical and clinical evidence showing dual inhibition of VEGF/EGFR signaling prolongs progression-free survival for EGFR-mutant lung cancers, and demonstrated safety, we are conducting a phase 2 trial to evaluate the osimertinib ramucirumab combination's efficacy in treatment-naïve EGFR-mutant NSCLC. **Method:** The OSI+RAM trial is a randomized phase 2 study with the primary endpoint being progression-free survival in osi+ram group as compared to osimertinib monotherapy group. The major inclusion criteria include patients with metastatic NSCLC harboring EGFR mutations (L858R/Exon 19 del). The major exclusion criteria include prior anti-EGFR or anti-

VEGF treatments. Patients with stable CNS metastasis are allowed. Based on the results from erlotinib bevacizumab (NEJ026) study, we expect an improvement of PFS from 18.9 months to 29.7 months, corresponding to a hazard ratio of 0.65. The trial plans to enroll total of 150 patients, with 100 allocating to osi+ram arm and 50 to osimertinib monotherapy. Total of 9 study sites in the USA are planned. Hoosier Cancer Research Network will facilitate the execution of the trial. The trial protocol has received IND exemption from US FDA and has been approved by IRB at MD Anderson Cancer Center. The first subject is expected to be enrolled in May 2019. A planned interim analysis will be performed after the first 75 subjects are enrolled. NCT03909334. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: EGFR, Ramucirumab, CNS metastasis

P2.14-25 LORLATINIB INDUCED PROTECTIVE AUTOPHAGY VIA THE AKT–MTOR PATHWAY IN ALK-REARRANGEMENT LUNG CANCER CELLS

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Background: Lorlatinib, also known as PF-6463922, is a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor that had been approved clinic treatment with patients who failed previous ALK inhibitors. However, the growth inhibitory effects of Lorlatinib on NSCLC and the underlying mechanism. **Method:** The growth inhibitory effects of Lorlatinib were investigated in H3122 and H2228 cell lines. Cell death and proliferation were assessed with MTT and Colony formation assay. Flow cytometry assays was performed to study the cell apoptosis. Cyto-ID® immunofluorescence staining was performed to study the cell autophagy. Signaling transduction was demonstrated with western blot. **Result:** We observed that Lorlatinib induces cytotoxicity in H3122 and H2228 cells. trigger autophagy in both H3122 and H2228 cells by increasing the expression of phosphatidylethanolamine-modified microtubule-associated protein light-chain 3 (LC3) and decreasing the expression of p62, still can trigger apoptosis by increasing the expression of B cell lymphoma 2 interacting mediator of cell death (Bim). In the presence of the autophagy blocker (chloroquine) and autophagy enhancer (rapamycin), enhanced the cytotoxicity of Lorlatinib and the Lorlatinib -induced increase in Bim was further augmented. The levels of total and phosphorylated ALK can decrease by Lorlatinib. Lorlatinib inhibited the phosphorylation of AKT and the main autophagy repressor mammalian target of rapamycin (mTOR), pharmacological inhibition of AKT by MK-2206 enhanced Lorlatinib-induced cell death, and it increased LC3 and Bim level. **Conclusion:** We demonstrated that the growth inhibitory effects of Lorlatinib on NSCLC via induced autophagy and apoptosis through AKT/ mTOR signaling pathway, and Pharmacological Intervention of Lorlatinib -induced Autophagy Enhances the Cytotoxicity of Lorlatinib. Our findings provided preliminary data for therapeutic strategies to enhance Lorlatinib efficacy in NSCLC patients.

Keywords: lorlatinib, autophagy, Lung cancer

P2.14-26 OUTCOMES IN PATIENTS WITH COMPOUND EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS AFTER TREATMENT WITH TYROSINE KINASE INHIBITORS (TKIS)

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Background: TKIs targeting EGFR have changed the therapeutic paradigm for patients (pts) with non-small cell lung cancer (NSCLC) harboring classic sensitizing mutations in *EGFR (L858R and Exon 19del).* Less is known about the efficacy of TKIs when a sensitizing mutation is co-existent with another, not resistance-associated EGFR mutation (compound *EGFR* mutations). We report the outcomes of pts with *de novo* compound *EGFR* mutations treated with TKIs. **Method:** We identified pts with compound *EGFR* mutated NSCLC (plasma or tissue detection) treated at a single center. All disease-associated EGFR mutations were included with the exception of T790M and C797S. Time to treatment failure (TTF) was calculated from the start of TKI therapy until treatment discontinuation for any reason (i.e. disease progression, toxicity, pt choice or death). Overall survival (OS) was calculated from the start of TKI until death. Median OS (mOS) and TTF (mTTF) were estimated from Kaplan-Meier curves. **Result:** 24 pts with compound *EGFR* mutations were identified (median age 60, 67% female, 29% never smokers) between 2011 and 2018 (Table 1). Of the 16 (67%) who received a TKI, the most common mutation was G719X (n=9). Exon 19 deletions (del) were present in 2 patients (1 with G719X). L858R was found in 5 patients. Of the 8 pts who did not receive a TKI, 4 had early stage NSCLC that never progressed, 2 had local recurrence treated with surgery/radiation and 2 had metastatic recurrence. Among those treated with a TKI, the mTTF was 13.6 months (mo) and mOS was 32.7 mo. There was no difference in mTTF between erlotinib (n=10) and afatinib (n=6) (13.6 vs. 8.8 mo, log rank p=0.67). Median follow up was 33 mo. In 7 pts who had both baseline tissue and plasma testing, plasma detected all non-classic mutations. **Conclusion:** The mOS and mTTF in this cohort of pts with compound EGFR mutations compare favorably to the historical progression free survival and mOS for pts with classic sensitizing mutations in *EGFR* treated with erlotinib or afatinib. Table 1: Compound EGFR mutations (n=24)

		Exon 3	Exon 18	Exon 19	Exon 20		
		R108K	E709X	del	S768I	V769M	R776H
Exon 18	G719X		5	1	8	1	1
Exon 19	del					1	
Exon 21	L858R	3	2				
	L861Q				1	1	

Keywords: compound EGFR mutations, EGFR, NSCLC

P2.14-27 EFFICACY AND PROGNOSTIC FACTOR OF APATINIB PLUS EGFR-TKI IN TREATING ADVANCED NON-SMALL-CELL LUNG CANCER WITH EGFR-TKI RESISTANCE

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Background: Treatment failure frequently occurs in patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) who respond to EGFR-TKIs initially. Apatinib is an oral TKI against VEGFR-2 and is effective as third- or later-line treatment in advanced NSCLC. EGFR and VEGF/VEGFR pathways are interrelated. We conducted this study to investigate the efficacy and safety of apatinib plus EGFR-TKI as second-line treatment in patients with advanced NSCLC. **Method:** From August 2017 to December 2018, 23 patients of advanced NSCLC acquired resistance for EGFR-TKI (gefitinib 250mg qd:erlotinib 150mg qd:icotinib 125 mg, bid) treated with original targeted drugs plus Apatinib (250 mg, qd, orally). Treatment was continued until disease progression or unacceptable toxic effects. **Result:** In 23 patients, there were 17 patients available for efficacy and safety evaluation. the objective response rate (ORR) was 17.6 % and the disease control rate (DCR) was 82.4 %. The median progression-free survival (PFS) was 8.0 months, patients with and without hypertension was 6.8 months and 4.1 months, respectively. The median overall survival had not reached. The most frequent treatment-related adverse events were hypertension (64.7 %, 11/17), hand-foot syndromes (29.4 %, 5/17) and fatigue (11.8 %, 2/17). **Conclusion:** Apatinib plus EGFR-TKI is efficacious in treating patients with advanced NSCLC after EGFR-TKI treatment failure, with acceptable toxic effects. Hypertension could be an effective prognostic factor for in apatinib-treated NSCLC patients.

Keyword: Apatinib, Prognostic factor,NSCLC

P2.14-28 REAL-WORLD MANAGEMENT AND OUTCOMES OF UNCOMMON EGFR MUTATION-POSITIVE NSCLC PATIENTS AT TWO TERTIARY CANADIAN CANCER CENTRES

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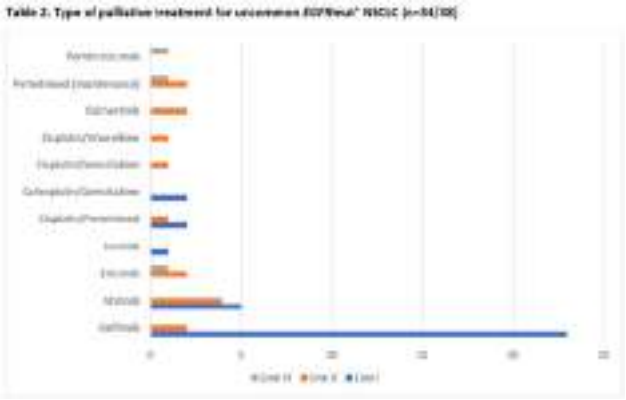
Background: The evolution of targeted therapies has transformed the management of *EGFR*–mutation positive NSCLC patients, especially for those with exon 19 deletion and exon 21 (L858R). However, uncommon *EGFR*-mutation carriers represent a unique group with differential sensitivities and dynamic responses to treatment. We aimed to analyze the demographic profile, management patterns and outcome of these patients. **Method:** Data were extracted from the institutional Glans-Look Lung Cancer database. Adult patients diagnosed with uncommon *EGFR* mutation(s) and treated in the palliative setting during 2010-2017 were included. Demographics and clinical characteristics were reviewed retrospectively (Table 1). **Result:**

Table 1. Demographic and clinical profile (n=38)

Variable	No	(%)
Age, years		
Median	72.7	
Range	50.2 - 88.3	
Sex		
Female	24	(63.2%)
Male	14	(36.8%)
Ethnicity		
Asian	8	(21%)
Non-Asian	28	(73.7%)
Canada-born	21	(75%)
Other	7	(25%)
Not reported	2	(5.3%)
Smoking history		
Current/-Former	23	(60.5%)
Never	15	(39.5%)
Disease stage (initial diagnosis)		
Early-Stage(I-II)	5	(13.2%)
IIIB	4	(10.5%)
IV	28	(73.7%)
Not reported	1	(2.6%)
Disease stage (palliative chemotherapy)		
IV	38	(100%)
Uncommon *EGFR* mutation		
Exon 18 (G719X)	7	(18.4%)
Exon 20 (S768i)	1	(2.6%)
Exon 21 (L861Q)	11	(28.9%)
Exon 20 insertion	4	(10.5%)
[β]Complex dual/-triple mutation positivity	15	(39.5%)
T790M testing (n= 8/38)		
T790M $^{+}$ / $^{-}$	2 (25%) $^{+}$ | 6 (75%) $^{-}$	
PD-L1 testing (n= 5/38)		
PD-L1 $^{+}$ / $^{-}$	3 (60%) $^{+}$ | 2 (40%) $^{-}$	

Table legend: β – G719S &S768I; Ex 19 del & L861Q; G719X & L861Q; G719A, G719C & S768I; S768I & G719X; Ex 19 del, S768I & V774M, G719A & S768I, G719X & Ex 19 del, G719S & Ex 19 del, G719A & E709K,



Uncommon *EGFR* mutations were observed in 38 patients, comprising approximately 10% of all *EGFR*mut+ NSCLC patients (348) diagnosed and treated in Alberta, Canada (2010-2017). Of the total 38 patients, 63% were female, 60% had a smoking history, and 75% were Canada-born. Dual/-triple mutation positivity was found in 40% of patients. 4/38 patients expired prior to receiving any form of palliative treatment. Upon classifying patients as per TKI treatment, it was found that most received gefitinib (67%) as first line systemic palliative treatment (Table 2). Median OS of the entire cohort was 15.1 months; meanwhile those with complex double/-triple mutations experienced longer mOS of 24.9months vs 11.8months for single uncommon carriers. **Conclusion:** This Canadian study supports that uncommon *EGFR* mutation carriers are infrequent in clinical lung cancer practice. Of note, they represent a unique sub-population amongst *EGFR*mut+ NSCLC patients, and experience differential sensitivity and varied responses to treatment. We observed favorable responses to *EGFR*-TKIs in patients with double/-triple uncommon mutations, supporting that these patients may benefit from *EGFR*-TKIs.

Keywords: uncommon EGFR mutation, Target therapy, EGFR TKI

P2.14-29 CLINICAL IMPACT OF NEXT-GENERATION SEQUENCING (NGS) IN BLOOD LIQUID BIOPSIES FOR TREATMENT DECISIONS IN ADVANCED NSCLC

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Background: Blood-based NGS is emerging as either complementary or alternative to standard tissue genotyping in metastatic non-small-cell lung cancer (NSCLC). In cases where tissue is not enough to complete standard EGFR, ALK, and ROS1 testing, or when patients are tested as triple-negative for these genetic alterations, additional tumor genotyping can lead to the detection of further actionable mutations. Moreover, NGS provides valuable genomic information that could be used to select for immunotherapy in metastatic NSCLC. We aimed to describe the molecular findings obtained by liquid biopsy of a cohort of advanced NSCLC patients with unknown/negative EGFR, ALK and ROS1 and how the results modified treatment decisions. **Method:** We performed a retrospective study of advanced NSCLC patients that were analyzed with NGS as part of a molecular pre-screening for clinicals trials in our institution in Madrid (Spain) between October 2016 and March 2019. Patients >18 years-old, PS ECOG 0-2, stage IIIC-IV NSCLC were routinely tested for EGFR, ALK, and ROS1, in addition to PD-L1 (22C3). Those wild-type for EGFR, ALK, or ROS1, or without enough tissue to perform the triple testing were considered for blood-based NGS. The different diagnostic assays for ctDNA NGS used depended on clinical trial molecular pre-screening protocol: Foundation One® Liquid or Guardant360®. We analyzed the frequency of oncogenic drivers, the proportion of patients treated with genotype-directed therapy, and survival. **Result:** We analyzed 95 NSCLC pts with valid NGS results from ctDNA (blood sample). We detected 14 oncogenic driver mutations (15%): 5 EGFR (5.2%), 1 ALK fusion (1%), 1 BRAF V600E (1%), 2 METex14 (2.1%), 2 RET fusion (2.1%) and 3 HER2 mutations (3.2%). We also found 16 KRAS mutations (16.8%), and genetic alterations in tumor suppressor genes: 39 TP53 (41%), and 6 NF1 mutations (6.3%). So far 8/14 patients were treated with genotype-directed therapy (8.4%), 2 of them under clinical trial: 5 pts were treated with an anti-EGFR treatment, 2 pts received alectinib (1 pt for ALK rearrangement, 1 pt for RET rearrangement) and 1 pt with tepotinib (MET splice mutation) Of the 6 patients with NF1 mutations, 4 pts were women (66%), 5 pts were current smokers (83%), median age at diagnosis was 69 years (66-80), and 5 pts had non-squamous histology (83%). PDL1 tumor expression was determined in 4 patients: 2 pts >50%, 1 pt 10%, and 1 pt 0%. NF1 was co-mutated in 4 pts with RAS (66%), 1 with both RAS and TP53, and 1 HER2 A775:G776insYVMA. 3/6 NF1 mutant patients were treated with single agent ICI: 2 pts with first-line pembrolizumab, and 1 pt second-line pembrolizumab. In addition, one patient with germline NF1 mutation was treated with 2nd line atezolizumab. All 3 pts obtained responded to ICI (1 pt with atypical response). We will present updated data on PFS and OS. **Conclusion:** Blood-based NGS can guide treatment decisions in metastatic NSCLC, with special interest in those patients without enough tumor tissue, or wild-type

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to standard-tissue diagnostic tests. NF1 mutations in NSCLC could predict responses to immune-checkpoint inhibitors, and warrants further evaluation.

Keywords: Next-generation sequencing, liquid biopsy, Targeted therapy

P2.14-30 PREDICTIVE VALUE OF CTDNA IN PATIENTS WITH EGFR POSITIVE NSCLC RECEIVING 3RD GENERATION TKI

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Background: The third generation TKI (osimertinib) according to AURA III trial results achieved longer PFS compared to standard platinum based chemotherapy in patient's resistant to 1-2 generation TKIs due to T790M mutation (8.5 vs 4.2 months). The evolution of resistance profile during thins therapy can be analyzed based on ctDNA. **Method:** In this study patients with metastatic EGFR mutated NSCLC, with a confirmed disease progression during treatment with 1/2 generation TKIs, T790M positive which included patients received osimertinib 80 mg daily. Before the treatment and then every 2 months, whole blood was taken, for qualitative assessment of ctDNA dynamics by RT-PCR. The aim of the study was to assess the relationship between the disappearance of T790M + ctDNA and the time to progression on osimertinib. **Result:** From August 2016 to December 2018 22 patients with T790M positive progression were identified. 18/22 (81.9%) were women, 4/22 (18.1%) - men. The mean age was 61.2 years (50-75). Only 1/22 had a smoking history > 30 pack/years. Primary activating mutations in EGFR gene were ex19del, L858R and G719S + S768I in 16, 5 and 1 patients respectively. Median PFS on the first line TKI was 21.7 months (CI 95%, 10.8 – 53.3). In 59.1% (13/22) progressive disease was characterized by the appearance of new metastases and in 40.9% (9/22) by the growth of previously identified metastases. 22 patients were evaluable for response. PR and SD were achieved in 11/20 (50%) and 10/20 (45/5%) respectively. Median PFS was in a whole group 16.7 months (CI 95%, 11.4 - 22.0). T790M in ctDNA was negative after 2 months of osimertinib treatment in 12/22 patients. Median PFS was 18.9 months (CI 95%, 14.8–19.7) in patients with undetectable T790M in ctDNA after 2 month of therapy compared to 8.0 months (CI 95%, 4.2 – 11.8) in patients remaining ctDNA T790M positive. No clinical factors were associated with the disappearance of ctDNA by statistical analysis. **Conclusion:** The disappearance of T790M + ctDNA after 2 months osimertinib therapy is predictive of greater PFS in patients with EGFR mutation positive NSCLC, receving of 2nd line.

Keywords: Osimertinib, ctDNA, resistance

P2.14-31 MELATONIN INHIBITS PROLIFERATION AND INVASION THROUGH DOWNREGULATING CIRCRNA NID1 IN NON-SMALL CELL LUNG CANCER CELLS

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Background: Melatonin could product anti-cancer effects via several mechanisms, including by induction of apoptosis. In this way, it has been shown to be of use, in combination with chemoradiotherapy, for cancer treatment. More and more circular RNAs (circRNAs) revealed to play a critical role in the initiation and progression of cancer, however, the effects of circRNAs on non-small cell lung cancer (NSCLC) remain largely undetermined. The study described here has evaluated effects of melatonin on dysregulated circRNAs and how to affect cell viability, proliferation and apoptosis in human lung adenocarcinoma cell lines (A549, H1299, and H460), which previously had only limited data. **Method:** The dysregulated circular RNA after melatonin treatment was examined. Cells were treated with melatonin alone at 1 nM, 1 μM and 100 μM concentration for 0, 12, 24, 48 and 72 h in culture. Cytotoxicity was measured by CCK-8 assay. Apoptosis induction was detected by annexin V/PI staining using flow cytometric analysis and DAPI nuclear staining. Transwell assay was used to detect the invasion of lung adenocarcinoma cell lines after treating. Western blot for detection of protein levels regulated by circular RNA. **Result:** In the present study, we screened the dysregulated circRNAs in human lung adenocarcinoma cell lines after treating and identified circRNA NID1 was to be significantly up-regulated in NSCLC and demonstrated it promotes NSCLC progression *in vitro* and in vivo. Then, we revealed the expression of miR-16-5p, a downstream factor of circRNA, was significantly down-regulated in NSCLC and acted as a tumor inhibitor, Yes-associated protein 1 was examined up-regulated in cancer and associated with proliferation. **Conclusion:** Our results highlighted circRNA NID1 promoted NSCLC cell proliferation, invasion, and migration by increasing Yap1 expressions through direct inhibition of miR-16-5p, which may serve as a potential prognostic marker of LUAD.

Keywords: lung adenocarcinoma, melatonin, circRNA

P2.14-32 EPIGENETIC SILENCING OF SPARC IN NSCLCS

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Background: The silencing of *SPARC* gene through methylation of its promoter region has been commonly observed in many solid tumors and is frequently associated with tumor progression and an aggressive clinical outcome. At present, the data concerning the mechanisms of *SPARC* deregulation in lung cancer are almost incomplete and correlation analysis with disease clinical course and specific therapeutic strategies is ongoing. Here we present the epigenetic profile of SPARC gene promoter in a collection of NSCLC cell lines and tissue samples and assess its prognostic value in surgical NSCLC resected patients. **Method:** Four cell lines (3 adenocarcinoma, ADC and 1 large cell carcinoma, LCC) and 66 primary NSCLC tissues from surgically resected patients (30 squamous cell carcinoma, SqCC and 36 ADC) and 11 lung non-neoplastic tissues were epigenetically scanned. Promoter methylation analysis was performed using a quantitative methylation specific PCR assay in real-time (QMSP). The downstream effect of epigenetic silencing was also investigated in A549 and H1573 NSCLC cell lines by 5-Aza-2'-deoxycytidine treatment to demonstrate if the demethylating agent was able to restore SPARC mRNA expression levels. *SPARC* methylation levels were correlated with clinicopathological features. **Result:** A tumor-specific DNA methylation of the *SPARC* gene promoter region was found as a specific feature of NSCLC (p=00643 Mann-Whitney test) and was also observed in all cell lines analyzed. In particular, it was detected in 56% of SqCCs (20/36) and 64% of ADCs (19/30), with SqCC showing the highest levels of methylation. Overall, we found promoter hypermethylation in 59% of NSCLCs. Moreover, a direct correlation with mRNA levels was confirmed by *in vitro* 5-azacytidine treatment. In SqCCs, *SPARC* methylation levels correlated with a negative prognosis (p<0,012 Supremum Test for Functional Form, HR=1,93; 95%CI). **Conclusion:** Our results further suggest that epigenetic deregulation of the SPARC gene could be involved in the cancerogenesis of NSCLC. Additional studies on a larger cohort of NSCLCs and correlation with clinic-pathological features may contribute to disease progression prediction and new molecular basis to codify the response to therapy in lung cancer patients.

Keywords: epigenetic, NSCLC, SPARC

P2.14-33 AN OPEN-LABEL PET-MRI STUDY TO DETERMINE BRAIN EXPOSURE OF OSIMERTINIB IN PATIENTS WITH EGFR MUTANT NSCLC AND CNS METASTASES

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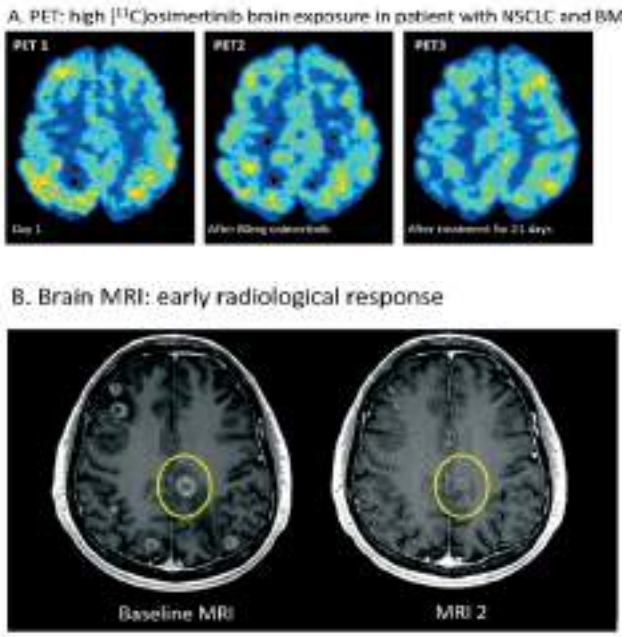
Background: CNS metastases are associated with poor prognosis in patients with advanced NSCLC. Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitising (EGFRm) and EGFR T790M mutations, and has demonstrated efficacy in NSCLC CNS metastases. Osimertinib has also shown superior brain exposure (preclinical/clinical), compared to other EGFR-TKIs. We report preliminary data on brain distribution of 11C-labelled osimertinib ([11C]osimertinib) in patients with NSCLC with brain metastases (BM) using positron emission tomography (PET). Early effects on BM measured by magnetic resonance imaging (MRI) is also presented. **Method:** This open-label, single-centre Phase I study (NCT03463525) enrolled adult patients with EGFR-mutated advanced NSCLC and BM, as confirmed by MRI. Patients could be EGFR-TKI-naïve or have progressed on a prior EGFR-TKI with confirmed EGFR T790M. Intravenous microdoses of [11C]osimertinib and PET examinations were performed pre-dose on Day1, ~6hrs post-dose on Day2, and following ≥21 days of once-daily dosing with osimertinib 80mg. Following the 3rd PET scan, patients completed another MRI scan to investigate early effects on tumour size according to RECIST 1.1 criteria. The primary objective was determination of brain exposure of [11C]osimertinib at baseline and following treatment, in the whole brain. During PET examinations, arterial blood samples were collected to measure radioactivity/radiometabolites of [11C]osimertinib. **Result:** Currently, six patients have been screened. Three enrolled, of whom two completed all imaging visits. PET examinations demonstrated rapid uptake of [11C]osimertinib into the brain and distribution into metastases; MRI scans showed significant decrease in size of brain lesions after 21 treatment days, consistent with partial response according to RECIST 1.1 criteria (Figure).



Conclusion: These early outcomes support the CNS efficacy reported in previous osimertinib studies: high brain-uptake and efficacy after a short dosing period. Further data on distribution, efficacy and PET/MRI imaging will be presented.

Keywords: NSCLC, Brain metastases, Osimertinib

P2.14-34 TYROSINE-KINASE INHIBITORS (TKI) IN FIRST-LINE TREATMENT OF 470 PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) FROM THE CZECH REPUBLIC

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Background: From October 2013 there is a possibility to treat patients with NSCLC and with activated epidermal growth factor receptor (EGFR) mutations with three TKI in the Czech Republic. We have tried to find differences among patient groups treated with single TKI in 1st line of treatment. **Method:** The TULUNG registry was used as a data source for this analysis. This clinical registry is focused on the collection of epidemiological and clinical data of patients with NSCLC treated with target therapy in the Czech Republic. A total of 959 patients treated with TKI inhibitors was enrolled in registry until December 31, 2018. Only patients with EGFR mutation and in which 1st line treatment started in October 2013 and later were included in analysis. With respect to defined inclusion criteria we analysed 470 patients. With gefitinib were treated 234, with afatinib 180 and with erlotinib 56 patients. Descriptive statistics and frequency tables were used to characterize the sample data set. Statistical significance of differences among three TKI inhibitors subgroups was assessed using the Fisher's exact test or Kruskal-Wallis test for continuous variables. OS and PFS were estimated using Kaplan-Meier method and all point estimates include 95% confidence intervals (95% CI). Statistical significance of differences in survival between subgroups was assessed using the log-rank test. All statistical tests were performed at a significance level of α=0.05. **Result:** There was statistically significant difference according to age (< 0.001) and PS (< 0.001), patients treated with gefitinib were statistically significant older and had significantly significant higher PS than patients treated with afatinib and erlotinib There was statistically significant difference in the occurrence of adverse events (p<0.001). Patients treated with gefitinib had a significantly lower incidence of adverse events than patients treated with afatinib and erlotinib. Between these three groups of patients there was no statistically significant difference in sex (p=0.863), in smoking habits (p=0.463, in type of EGFR mutation (p=0.103), in adenocarcinoma proportion (p=0.183). There was no statistically significant difference according to disease control (p=0.183), in response to treatment (p = 0.804), in OS and (p=0.053, in PFS (p=0.06). **Conclusion:** Between these three groups of patients we found a statistically significant difference in age, PS segmentation and in occurrence of adverse events. We have not found any important statistically difference in sex, smoking, in histology type of EGFR mutation, difference in response to treatment, in disease control and OS.

Keywords: Targeted therapy, tyrosine-kinase inhibitors, advanced NSCLC

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P2.14-35 2-DEOXY-D-GLUCOSE SENSITIZES NON-SMALL CELL LUNG CANCER WITH EML4-ALK FUSION TO CRIZOTINIB VIA SUPPRESSION OF HK2 THROUGH AKT/MTOR PASSWAY

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Background: ALK-positive NSCLC cells (ALK+ NSCLC) present high glycolysis. Targeting cancer cell metabolism with the glycolysis inhibitor, 2-deoxyglucose (2DG), is a viable strategy that sensitizes the fist-line ALK-TKI crizotinib; but the effects of combination of 2DG and Crizotinib on ALK+ NSCLC cells and the mechanism of action are unknown. **Method:** ALK+ NSCLC cells H2228 and H3122 were incubated with crizotinib with or without 2DG, and subjected to the MTT. H2228 cells was treated with crizotinib or/and 2DG to explore the impact of cell growth and potential mechanism of action by clones formation, Ki67 incorporation assay, small interfering RNA technology, Western blot analysis. **Result:** A clear synergistic anti-proliferative interaction between 2DG and crioztinib was observed with a combination index value<1 (CI<1).The combination of crizotinib and 2DG effectively inhibited the clones formation and invasion ability of H2228 cells. The glucose consumption and Lactate production of H2228 cell treated with increasing concentration of 2DG was reduced to accompany a markedly decrease of HK2 expression. ALK-positive NSCLC cells showed a higher level expression of HK2 than ALK-negative NSCLC, down-regulation of HK2 by siRNA, obviously enhanced the ability of crizotinib to suppress proliferation activity. The westblot results displayed a significantly inhibition of AKT/mTOR signaling pathway in H2228 cells treatment with combination of 2DG and crizotinib. **Conclusion:** This study demonstrated that 2DG would be a promising drugs to sensitize crizotinib via suppressing HK2 expression to inhibit the activity of AKT/mTOR signaling pathway induced by ALK phosphorylation.

Keywords: EML4-ALK, high glycolysis, crizotinib

P2.14-36 IDENTIFICATION OF GENOMIC FEATURES IN TUMOR-DERIVED ORGANOIDS FROM RESECTABLE NSCLC

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Background: Patient-derived tumor organoids (PDOs) have recently emerged as robust preclinical models. However, few studies were published on lung cancer organoid. This study aims to describe the genomic characteristics of PDOs as a disease model of NSCLC. **Method:** Samples from resected tumors were collected for organoid culture. DNA was extracted from tumor, organoids and matched PBLs samples and sequenced with whole-exome sequencing. **Result:** Seven pts were enrolled, including six LUAD (86 %) and one LUSC (14 %). A total of 1625 somatic mutations were detected in tumors. TP53 (71%), EGFR (43%), and KRAS (29%) mutated most frequently in this cohort, and occurred with frequencies of (57%), (43%) and (29%) in matched PDOs. Based on gene catalog related to lung cancer, the median consistency between tumor and organoid was 87 % (0% ~ 100%). Sample purity was significantly positively related to the variant allele frequency (r=0.82, P=0.0005), and may result in the inconsistence between paired samples. Besides, number of driver gene showed no difference between first- and second-generation organoids.

Table1. Characteristics of the Patients at baseline

Characteristic	Patients (n=7)
Age	
Mean ±SD	63.9±5.5
Median (Range, years)	66(56-69)
Sex-no. (%)	
Female	1(14)
Male	6(86)
Histologic diagnosis-no. (%)	
Adenocarcinoma	6(86)
Squamous-cell carcinoma	1(14)
Clinical disease stage	
I	3(43)
II	3(43)
III	1(14)
Smoking status-no. (%)	
Never	2(29)
Former or current	5(71)

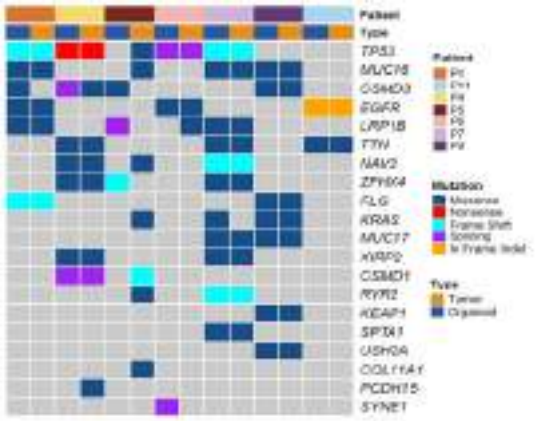

Figure 1. Mutation detected in paired tissues (tumor and organoid) based on gene catalog related to lung cancer (Top20 genes were shown)

Conclusion: This study firstly revealed genomic landscape of NSCLC organoid. In spite of heterogeneity, driver mutations presented high consistency between PDOs and paired tumor. Further study is continuing to evaluate outcomes from patients enrolled.

Keywords: NSCLC organoids, genomic features, whole-exome sequencing

P2.14-37 ANAPLASTIC LYMPHOMA KINASE INHIBITOR INDUCED PNEUMONITIS IN PATIENTS WITH NSCLC: CLINICAL AND RADIOLOGIC CHARACTERISTICS AND RISK FACTORS

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Background: To investigate the clinical and radiologic characteristics and risk factors of anaplastic lymphoma kinase (ALK) inhibitor induced pneumonitis (ALK-IIP) in patients with non-small cell lung cancer (NSCLC). **Method:** A total of 250 NSCLC patients who had been treated with ALK inhibitors from January 2015 to January 2018 were retrospectively enrolled. Clinical characteristics and clinical course were reviewed from the medical records. Chest CT of ALK-IIP was analyzed and classified into four CT patterns, i.e. organizing pneumonia (OP), hypersensitivity pneumonitis (HP), diffuse alveolar damage (DAD), and nonspecific interstitial pneumonia (NSIP), using the American Thoracic Society/European Respiratory Society

classification of interstitial pneumonia. Clinical characteristics including toxicity grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events and treatment course was analyzed in regarding to the classified CT patterns. Clinical characteristics were compared between patients with ALK-IIP and without ALK-IIP. **Result:**

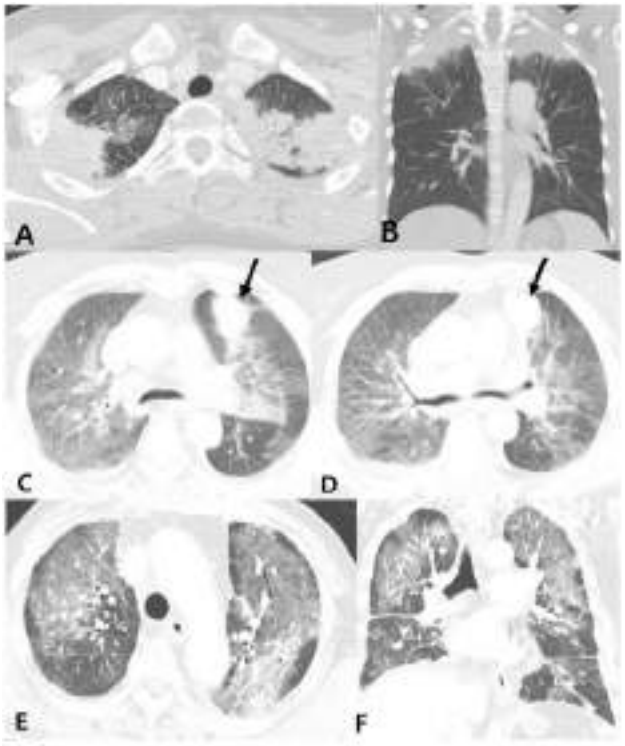

Figure. Spectrum of the CT patterns of ALK-IIP. (A and B), ALK-IIP with an OP pattern in a 56-year-old male patient. Chest CT demonstrated the development of multifocal mass-like consolidations with ill-defined GGO and mild interstitial thickening involving the subpleural areas of both upper lobes and both lower lobes representing the OP pattern. (C and D), ALK-IIP with a HP pattern in a 79-year-old female patient. Chest CT demonstrated diffuse GGO with focal areas of air trapping in both lungs and thus indicative of HP pattern. Lung cancer was noted in the left upper lobe (arrows). (E and F), ALK-IIP with DAD pattern in a 74-year-old male patient. Chest CT axial and coronal images demonstrated diffuse and bilateral gound glass opacity and consolidation with mild thickening of the interlobular septa in both lungs.

ALK-IIP was identified in 11 patients (4.4%). The most common CT pattern was the OP pattern (n = 7, 63.6%) and followed by the HP pattern (n = 2, 18.2%) and the DAD pattern (n = 2, 18.2%). ALK-IIP showed pneumonitis toxicity grade ranged from 1 to 3, and DAD pattern had the highest toxicity grade, followed by HP and OP patterns (median grade: 3.5, 2.5, 1). All of the patients with the OP pattern were successfully treated, while half of patients with the DAD pattern died during treatment. The smoking history and extrathoracic metastasis were more frequent in patients with ALK-IIP ($P < 0.005$). The smoking history was associated with a higher incidence of ALK-IIP [odds ratio: 3.586, 95% confidence interval: 1.058-13.432, $P = 0.049$]. **Conclusion:** ALK-IIP showed a spectrum of chest CT patterns and various toxicity grades, and CT patterns reflected the toxicity grades of ALK-IIP. The OP pattern was the most common CT pattern of ALK-IIP, and patients with ALK-IIP of the OP pattern were successfully treated. ALK inhibitors should be used with caution in NSCLC patients with smoking history.

Keywords: NSCLC, Drug Related Side Effects and Adverse Reactions, Computed Tomography, Spiral

P2.14-38 ATAD2B-ALK, A NOVEL FUSION IN LUNG ADENOCARCINOMA IDENTIFIED USING NEXT-GENERATION SEQUENCING (NGS)

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Background: Anaplastic lymphoma kinase (ALK) rearrangements is an important molecular subtype of non-small cell lung cancer (NSCLC), and patients with this variant are sensitive to ALK inhibitors. Since the discovery of the *EML4-ALK* fusion ten years ago, several fusion partners of *ALK* in NSCLC have been reported, including *KIF5B*, *KLC1*, *HIP1*, *TPR* and so on. According to previous reports, different fusion partner lead to various function and activity of the fusion product. Here, we identified a novel fusion partner for *ALK* in a lung adenocarcinoma patient. **Method:** A 46-year-old smoking Chinese male was diagnosed with lung adenocarcinoma of left lower lobe. In Oct 2017, the patient accepted lobectomy and lymph node dissection, then received 4 cycles of adjuvant chemotherapy. Lymph node metastasis occurred one and a half years after his surgery. The lymph node biopsy sent for genomic testing with a NGS-based pan-cancer 1021-gene panel. Immunohistochemistry (IHC) of ALK was performed to confirm the ALK fusion. **Result:** A novel ATPase family AAA domain containing 2B(ATAD2B)-ALK fusion was identified in the lymph node biopsy tissue. The fusion occurred in intron 1 of ATAD2B gene and intron 19 of ALK gene located on short arm of chromosome 2 (ATAD2B(PMT.IVS1)_ALK(IVS19.END)). ATAD2B is a phylogenetically conserved nuclear protein expressed during neuronal differentiation and it was also reported to play a role in tumorigenesis. As IHC confirmed the expression of ALK, we proposed the fused promoter of *ATAD2B* had driven the expression of ALK kinase domain. The patient is currently treated with crizotinib. **Conclusion:** The novel ALK fusion gene probably served as oncogenic driver of the patient's tumor. This case is the first report of ATAD2B-ALK fusion in clinical tumor samples and could provide a new diagnostic and therapeutic candidate target for patients with lung cancer.

Keyword: ALK, ATAD2B, ALK rearrangement, NGS, lung adenocarcinoma

P2.14-39 EFFECTS OF RENAL FUNCTION ON LORLATINIB SAFETY AND PHARMACOKINETICS

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Background: Lorlatinib (Lorbrena®) is a small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 kinase recently approved at the recommended starting dose of 100 mg once daily in the United States, Japan, and Canada for the treatment of patients with *ALK*-positive metastatic non-small cell lung cancer (NSCLC). In humans, unchanged lorlatinib accounted for less than 1% of dose in urine, indicating minimal urinary excretion of parent drug. Therefore, renal impairment would not be expected to have a major effect on lorlatinib pharmacokinetics (PK) or safety. However, results from a population PK analysis demonstrated that baseline creatinine clearance was a statistically significant predictor of variability in lorlatinib plasma clearance; the median estimated single-dose lorlatinib clearance was 18% and 26% lower in NSCLC patients with mild and moderate renal impairment, respectively. Therefore, it is important to evaluate the potential impact of varying degrees of renal impairment on the safety and PK of lorlatinib via a prospective study. Preliminary results from the ongoing study, B7461010 (NCT03542305), of single-dose lorlatinib in subjects with mild, moderate and severe renal impairment are reported here. **Method:** B7461010 is an ongoing multi-center, open-label, single-dose study comparing the safety and PK of lorlatinib in otherwise healthy subjects with varying degrees of renal impairment. This study was planned to enroll 28–32 subjects (8 each in normal, mild and moderate impairment groups and 4–8 in severe impairment group) who complete PK assessments. Group assignment was based on estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation and as defined in the Kidney Disease Outcomes Quality Initiative guidelines. Subjects with increasing

severity of renal impairment have been enrolled sequentially to allow for safety evaluations. Subjects with normal renal function will be enrolled and matched based on age, sex and weight following completion of dosing of the renal impairment groups. **Result:** As of March 14, 2019, 8 subjects with mild renal impairment, 7 with moderate renal impairment and 3 with severe renal impairment not requiring dialysis have been enrolled. All 18 subjects to date received the clinical dose of lorlatinib 100 mg and completed the study. Among them, 6 subjects experienced adverse events (AEs), which were all transient and of mild or moderate intensity. Only 3 AEs (elevation of blood pressure, myalgia and diarrhea) were deemed related to study treatment. Preliminary analysis of plasma PK in 8 mild renal impairment subjects demonstrated similar exposures (geometric mean [%CV] Cmax of 549.7 [51.7%] and AUCinf of 8609.2 [29.2%]) compared to previous data from patients with normal renal function. **Conclusion:** Data showed that a single dose of lorlatinib 100 mg administered in subjects with mild, moderate or severe renal impairment was well tolerated. No dose adjustment was indicated for mild renal impairment. Updated results will be reported.

Keyword: lorlatinib, NSCLC, renal

P2.14-40 TUMOR-STROMAL MICROENVIRONMENT INTERACTIONS IN A PDX MODEL OF EGFR TKI DRUG TOLERANCE

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Background: Sixty to eighty percent of advanced stage lung adenocarcinoma patients with sensitizing epidermal growth factor receptor (*EGFR*) mutated tumors respond to EGFR tyrosine kinase inhibitors (TKIs). However, the vast majority of patients eventually progress due to acquired resistance. *In vitro* evidence suggests that minor populations of drug tolerant cells (DTCs) may be important for tumors surviving TKI. These studies cannot investigate changes in non-cancerous cell populations found within tumors. Yet, stromal cells have been implicated in protecting cancer cells from treatment-induced death and early stage lung adenocarcinomas responding to neoadjuvant EGFR TKI exhibited DTCs within large areas of fibrosis (NCT00188617). We hypothesize that molecularly characterizing DTCs *in vivo* in comparison to an untreated tumor in a patient-derived xenograft (PDX) model may delineate stromal changes that sustain DTCs, and potentially mimic clinical events. **Method:** DTCs were harvested after one month of chronic erlotinib exposure in a lung adenocarcinoma PDX model harboring an exon 19 deletion; an untreated baseline (BL) tumor was also harvested. Histological characterization and single-cell RNA-sequencing (scRNA-seq) of DTCs and BL tumors were compared. ScRNAseq cell-types were assigned using reference component analysis. RNA expression levels of receptor/ligands were explored in cell populations. **Result:** Post-erlotinib treatment, cell-type proportions within the tumor shifted dramatically, with substantially fewer cancer cells and more fibroblasts, mesenchymal stem cells (MSCs), and natural killer cells (NKCs). Two antigen presenting cell transcriptomic states (APC1 and APC2) were identified in both DTC and BL tumors: APC1s exhibited translation-related gene expression profiles while APC2s exhibited immune-response profiles. BL tumors contained mostly APC1s, whereas DTC tumors exhibited more equal proportions of both APC types. Expression profiles for some cell-types also shifted after treatment. Fibroblasts and NKCs exhibited shifts toward more inflammatory and immune-responsive expression profiles post-treatment. Fibroblasts and endothelial cells demonstrated gene expression shifts towards decreased angiogenesis and vasculature development. Paired ligand-receptor interactions between cancer-stromal cells were increased or decreased congruently post-treatment. Specifically, fibroblasts exhibited a shift from alpha-SMA+ myofibroblastic to more IL6+ inflammatory phenotypes, by mRNA and equivalent immunohistochemistry, post-treatment. Cancer cells exhibited a reciprocal increase in IL6R receptor expression post-treatment. **Conclusion:** Using an *EGFR* mutant PDX model sensitive to EGFR TKIs, we see substantial post-treatment changes after chronic TKI exposure in non-cancerous (stromal) cell population composition involving their proportions, expression profiles, and their inferred communication with cancer cells. Understanding these potentially protective shifts in non-cancerous cell populations post-TKI-treatment may help identify clinically-relevant mechanisms of drug tolerance.

Keywords: drug tolerance, persisters, tumor microenvironment

P2.14-41 RISK FACTORS FOR BRAIN METASTASIS IN PATIENTS WITH EGFR MUTANT NON-SMALL CELL LUNG CANCER

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Background: Brain metastasis is associated with a poor prognosis in patients with EGFR mutant non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) may be an effective treatment, but their influence on brain metastasis development is unclear. We aimed to identify risk factors for brain metastasis in patients with EGFR-mutant NSCLC. **Method:** This retrospective study included 166 consecutive advanced NSCLC patients with EGFR major mutations (Ex 21 L858R or Ex 19 del) who received EGFR–TKI monotherapy at the Nippon Medical School Hospital and Nippon Medical School Tamanagayama Hospital from November 2010 to June 2018. Patients who had brain metastases before EGFR–TKI monotherapy were excluded. We evaluated the cumulative actuarial incidence of brain metastases by Gray's test, univariate and multivariate analyses. **Result:** The median age was 72 years (range, 26-95 years), the majority of patients were female (n=103), and most patients had adenocarcinoma (n=153). Patients carried either an EGFR L858R (n=88) or 19del (n=78) mutation, and had been treated with gefitinib (n=97), erlotinib (n=22) or afatinib (n=47). The time to brain metastasis did not significantly differ between the three EGFR-TKI groups. The time to brain metastasis was significantly shorter in patients <75 years than >75 years (29.0 months versus not reached; HR 4.70; 95% CI 1.72-12.87). Univariate and multivariate analyses showed that age <75 years and non-adenocarcinoma histology were significant predictors of brain metastasis. In patients <75 years, the time to brain metastasis in patients who underwent EGFR-TKI dose reduction or intermittent treatment was significantly shorter than patients with constant EGFR-TKI treatment (24.9 versus 39.9 months; HR 2.40; 95% CI 1.10-5.22). **Conclusion:** Age <75 years is a risk factor for brain metastasis in patients with EGFR mutant NSCLC. We do not recommend EGFR–TKI dose reduction or intermittent administration in these patients.

Keywords: EGFR-TKI, brain metastasis, NSCLC

P2.14-42 EMERGENCE OF CCDC6-RET FUSION WITH MAINTAINED EGFR T790M MUTATION AFTER RESISTANCE TO OSIMERTINIB IN NSCLC: A CASE REPORT

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Background: First- and second-generation EGFR-TKIs have been widely used for advanced patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC); however, acquired resistance to these inhibitors, such as *EGFR T790M* mutation, could be present in resistant cases. Several third-generation EGFR-TKIs including osimertinib, have been explored and approved for conquering this resistance, whereas acquired resistance to osimertinib is evident and resistance mechanisms remain complex and incompletely elucidated. **Method:** A 56-year-old never-smoking Asian woman presenting with back and groin pain for 2 years, and was diagnosed with stage IV lung adenocarcinoma with multiple lung, liver, brain and bone metastases in February 2015. The patient carried *EGFR* exon 19 deletion and clinically responded to initial erlotinib treatment, who progressed on erlotinib after 20 months, and a *T790M* mutation was detected by next-generation sequencing (NGS). Osimertinib treatment was administrated for 13 months during which time the patient remained stable according to the Response Evaluation Criteria in Solid Tumors. The patient progressed with bone metastases in January 2018 and no other mutations were detected by NGS, who then started the treatment with osimertinib, bevacizumab, and complementary radiation therapy. However, the patient discontinued the treatment due to the progress with bilateral lung nodules. In order to probe into the subsequent therapy, circulating tumor DNA (ctDNA) was analyzed using NGS with Acornmed Panel in August 2018. **Result:** The genomic profile of the tumor disclosed actionable mutations including *EGFR* exon 19 deletion, *EGFR T790M* mutation, and *CCDC6-RET* fusion. Osimertinib and bevacizumab discontinued because of

the rapid progress, serious adverse effects of gradeIIsuppression of bone marrow, and shortness of breath. Based on the molecular test results, the patient received treatment with cabozantinib and osimertinib in October 2018, which also failed to slow down the progress of the disease. Further ctDNA test in November 2018 showed *EGFR* exon 19 deletion, *EGFR T790M* mutation, and *CCDC6-RET* fusion were identified again; however, no novel mutations were detected. Unfortunately, the symptoms worsened quickly and the patient died of respiratory failure in December 2018. **Conclusion:** The specifc mechanisms of acquiring drug resistance for EGFR-TKIs have not been fully elucidated. Based on ctDNA-based NGS, we reported a case maintained *EGFR T790M* mutation and acquired *CCDC6-RET* fusion after resistance to osimertinib, which was rare since acquired *RET* fusion was only found in *EGFR T790M* lost patients. More studies about the mechanism should be explored to lead to effective treatment strategies in this population.

Keywords: Acquired Resistance to Osimertinib, CCDC6-RET fusion, maintained EGFR T790M mutation

P2.14-43 COST-EFFECTIVENESS OF 1ST-LINE TREATMENT EGFR-TKIS FOR ADVANCED NSCLC PATIENTS HARBORING EGFR MUTATION IN MEXICO

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Background: As cancer care costs are rising at an unprecedented rate, it is crucial to provide evidence-based justification for promising but expensive therapeutic approaches such as Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). EGFR-TKIs such as gefitinib, erlotinib and afatinib had become the standard first-line treatment for EGFR gene mutation-positive non-small cell lung cancer (NSCLC) improving progression-free survival (PFS) and overall survival (OS) of these patients. However, the economic impact of them remain unclear. Hence, we aimed to assess healthcare costs during and after progression to treatment and to compare the cost-effectivess and safety of the 1st-line treatment with EGFR-TKIs in patients with advanced non-small cell lung cancer (NSCLC) in Mexico. **Method:** The health and economic outcomes of three first-line strategies (gefitinib, erlotinib, and afatinib) among NSCLC patients harboring EGFRmutations were estimated and assessed. Costs in the Mexican setting were obtained from local hospital data and public national purchasing sources. The structure used in this analysis was a Markov model with three possible health states: free of progression, progression and death considering a time horizon of 3 and 5 years. The probabilities of transition and the use of resources used to feed the model were retrospectively collected by reviewing medical records of patients who were treated at the Instituto Nacional de Cancerologia (INCan) of Mexico between April 2013 and June 2017. Probabilistic sensitivity analysis (PSA) was conducted with a Monte Carlo simulation. **Result:** Similar hazards of progression and death were obtained when constrasting afatinib vs. erlotinib, [HR:0.91 (95% CI: 0.59 -2.07) and 0.82 (95% CI: 0.56-2.65), respectively] as well as when contrasting the hazards of progression and death of afatinib vs. gefininib [HR:0.87 (95% CI: 0.87-1.53) and 0.94 (95% CI: 0.74-1.55), respectively]. However, statistically significant differences were identified between the costs of the treatment both the total cost (p<.001) and the daily cost (p <0.001) of treatment. The most expensive treatment was with afatinib, followed by erlotinib and gefitinib. In addition, treatment with afatinib showed the highest cost associated with adverse events. PSA with Monte Carlo simulations showed robustness of estimations.

Cost-effectiveness analysis

Treatment	Overall Mean cost	Incremental cost	Efectiveness	Incremental effectiveness	ICER
Progression-free survival					
Gefitinib	$161,800		8.18		
Erlotinib	$215,700	$53,900	6.7	-1.48	
Afatinib	$348,200	$186,400	9.46	1.28	$145,625.00
Overall survival					
Gefitinib	$161,800		27.1		
Erlotinib	$215,700	$53,900	21.7	-5.4	
Afatinib	$348,200	$186,400	37.1	10	$18,640.00

Conclusion: Although equivalent effectiveness and safety of the three arms of the study was found, substantial differences in treatment costs were observed. Nonetheless, we should highlight that patient selection is absolutely critical for cost-efectiveness analyses; as well as longer follow-up of existing data could substantially alter the conclusions of this analysis.

Keywords: EGFR-TKIs, NSCLC, cost-effectiveness

P2.14-44 TUMOR MUTATION BURDEN AND EFFICACY OF MOLECULAR TARGETED THERAPY IN LUNG CANCER

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Background: Precision medicine based on driver oncogenes is now developed for non-small cell lung cancer (NSCLC). Recently, next-generation sequencing (NGS) has made it possible to analyze Tumor mutation burden (TMB), and it was revealed that TMB is an effective biomarker of immune checkpoint inhibitors. However, the impact of TMB on the effects of targeted therapy for driver alterations is still unclear. **Method:** Of the cases diagnosed with advanced NSCLC at Tottori University Hospital, 30 cases with consent to this observational study were enrolled. TruSight™ Oncology (TSO) 500 was performed at the CLIA-certified laboratory (RIKEN GENESIS CO., LTD.) using DNA and RNA extracted from archived formalin-fixed paraffin-embedded (FFPE) lung cancer specimens. **Result:** Specimens were collected by bronchoscopy in 21 cases (70%), percutaneous biopsy in 3 cases (10%), surgery in 3 cases (10%), cell block of pleural effusion in 2 cases (7%) and thoracoscopy in 1 case (3%). The success rate of TMB analysis was 83% (25/30 cases). In the 25 cases, a total of 23 actionable gene alterations (11 EGFR mut, 4 ALK fus, 2 KRAS mut, 2 BRAF mut, 2 MET ex14 skipping, 1 RET fus, 1 PIK3CA mut) were detected in 22 cases (88%). The median TMB was 7.84 (1.56-21.11) mutations/Mb. 7 of 25 (28%) patients showed high TMB, and the others showed low TMB when 10 mutations per mega base was set as the threshold. 5 of 7 (71%) patients with high TMB had one of the common driver mutations (2 EGFR mut, 2 BRAF mut and 1 PIC3CA mut) and 17 of 18 (94%) patients with low TMB had one of the driver mutations (9 EGFR mut, 4 ALK fus, 2 KRAS, 2 MET ex14 skipping and 1 RET fus). Additionally, no ALK fusion was identified in patients with high TMB. 12 of 15 patients (80%) received targeted therapy with low TMB achieved clinical response, while no patient (0/2 pts, 0%) received targeted therapy with high TMB achieved clinical response. **Conclusion:** TMB might have the impact for the presence of driver alterations and the effects of targeted therapies.

P2.14-45 EML4-ALK FUSION SUBTYPE IS ASSOCIATED WITH THERAPEUTIC EFFICACY IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The aim of this study was to investigate the molecular characteristics of each subtype of the EML4-ALK fusion gene and to evaluate the efficacy of first-line crizotinib or pemetrexed in combination with platinum in the treatment of patients with advanced NSL4-ALK fusion subtypes of advanced NSCLC. **Method:** From August 2015 to September 2018, the clinicopathological data of patients who received driver genes detection for lung cancer in the Affiliated Cancer Hospital of Zhengzhou University were collected,NGS was used for gene detection.The EML4-ALK fusion gene was divided into E13: A20 subtype (variant 1, V1), E20: A20 subtype (variant 2, V2), E6: A20 subtype (variant 3, V3) and Other subtypes (V4) 4 groups. The primary study endpoint was progression-free survival. **Result:** A total of 122 patients with ALK fusion gene-positive NSCLC were screened. Of the 122 patients, 41 (33.6%) had V1 variants, 14 (11.5%) had V2 variants, 35 (28.7%) had V3 variants, and 32 (26.2%) had other variants. There was no correlation between EML4-ALK gene mutation subtypes and distant metastasis (x2=0.570, P=0.903), brain metastasis (x2=4.447, P=0.217) and bone metastasis (x2=1.547, P=0.672). The median was 13.3 months (95% CI: 9.45-17.10) and 6.83 months (95% CI:

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5.30-8.36),respectively, in patients receiving first line Crizotinib and chemotherapy, with statistically significant differences (P =0.001). In the first-line application of crizotinib, the ORR of V1, V2, V3 and V4 variants were 55.56% (10/18), 62.50% (5/8), 44.44% (4/9) and 43.75%, respectively. (7/16), median PFS were 11.96 months, 15.08 months, 12.88 months, and 7.62 months, respectively. There was no significant difference. The ORR of V1, V2, V3 and V4 variants in first-line patients treated with pemetrexe-platinum regimen was 41.18%(7/17), 37.50% (3/8), 36.36%(4/11)and 41.18% (7/17), respectively. The median PFS were 9.13 months, 3.22 months, 7.52 months, and 7.85 months, respectively. There was no statistically significant difference in PFS between V1: V3, V2: V3, and V1: V4. However, the PFS differences in the V1:V2 group (V1:V2=9.13 months: 3.22 months, P=0.007) and the V2:V4 group (V2:V4=3.22 months: 7.85 months, P=0.015) . **Conclusion:** Among all ALK fusion subtypes, E13:A20 subtype (V1 variants) is the most common. Smoking history was a factor affecting crizotinib PFS.Compared with chemotherapy, patients with E20:A20 subtype (V2 variant) showed significant benefit with crizotinib.The median PFS of the pemetrexed combined with platinum regimen was lower than that of the E13:A20 subtype.

Keywords: EML4-ALK fusion gene, Non-Small Cell Lung Cancer, Variant

P2.14-46 TREATMENT OBSERVATIONS AND CLINICAL EXPERIENCE WITH LORLATINIB IN PRETREATED ALK AND ROS1 REARRANGED NSCLC PATIENTS

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Background: Patients with non-small cell lung cancer (NSCLC), showing anaplastic lymphoma kinase (ALK)-or proto-oncogene 1 (ROS1)-rearrangement are routinely treated with tyrosine kinase inhibitors (TKIs). Although treatment is usually very effective resistance invariably develops over time. Lorlatinib a third generation TKI was recently approved by the FDA for patients who progressed on crizotinib and at least one other tyrosine kinase inhibitor. Here we report our experience with this novel brain-penetrant TKI. **Method:** 32 NSCLC patients, heavily pretreated with various chemotherapies and TKIs, have been treated with lorlatinib (100mg daily p.o.) as part of a pre-approval access program (PAA) between June 2016 and April 2019 at the Otto-Wagner-Hospital. We collected patient characteristics including sex, age, race and smoking history. Clinical response rates and progression free survival was assessed in all. **Result:** 21 patients were women and 11 men. The overall mean age was 57.3 years (59.2 female/53.2 male). 20 patients were never smokers (62.5%), 7 were former smokers (21.9 %), 2 were active smokers (6.3%). Smoking history was unknown in 3 patients (9.4%). Of the 32 patients 23 were ALK+ and 9 ROS1+. Lorlatinib was given in various lines of treatment from 2nd up to 6th line while one patient even received it in 11th line. All treated patients were Caucasian. Three patients showed a complete response (9.4%), 8 a partial response (25%), 5 are still showing stable disease (15.6%). Disease progression was noted in 16 patients (50%). The mean PFS (progression free survival) was 8.5 months, whilst treatment of 15 patients is still ongoing. ALK+ patients (n=23) showed a mean PFS of 7.9 months and ROS1+ patients (n=9) a mean PFS 9.8 months. Patients receiving brigatinib before switching to lorlatinib reached a mean PFS of 9.4 months (n=13; 12 ALK+/1 ROS1+) while patients who received lorlatinib after alectinib experienced a mean PFS of 4.93 months (n=8 ALK+). After crizotinib we found a mean PFS of 9 months (n=5; 5 ROS1+) and after ceritinib a mean of 10 months (n=6; 3 ALK+/3 ROS1+). The treatment was generally well tolerated. **Conclusion:** Lorlatinib was overall well tolerated and it was highly effective in these pretreated ALK and ROS1 rearranged NSCLC patients.

Keywords: lorlatinib, Targeted therapy, TKI

P2.14-47 REAL-WORLD MULTICENTER EXPERIENCE OF FIRST-LINE AFATINIB IN PATIENTS WITH EGFR-MUTANT ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Afatinib is an irreversible, second-generation epidermal growth factor receptor *(EGFR)*-tyrosine kinase inhibitor (TKI) that has been shown to be more potent than platinum doublet chemotherapy as well as the first-generation *EGFR*-TKI. This study aimed to look into the efficacy, side-effects and resistance mechanisms of first-line afatinib in the real-world setting. **Method:** This is a multicenter observational study of Malaysian patients with*EGFR*-mutant advanced non-small cell lung cancer (NSCLC) started on first-line afatinib from 1st October 2014 to 30th April 2018. **Result:** Of 85 patients analyzed, *EGFR* mutations harbored by the tumors included *exon 19* deletion in 80.0%, *exon 21 L858R* point mutation in 12.9%, and rare or complex *EGFR* mutations in 7.1%. Among the 85 patients, 18.8% had an ECOG performance status of 2-4, 29.4% had symptomatic brain metastases and 17.6% had abnormal organ function. Afatinib 40 mg or 30 mg once daily was the most common starting and maintenance doses. Only one-tenth of patients experienced severe side-effects and none had grade 4 toxicities.The objective response rate was 76.5% while the disease control rate was 95.3%. At the time of analysis, 56 (65.9%) patients had experienced disease progression (PD) with a median progression-free survival (mPFS) of 12.2 months (95% CI, 8.9-15.5 months). Only 12.5% of the PD patients developed new symptomatic brain metastases. Multivariate analysis demonstrated only patients with *exon 19* deletion had significantly longer mPFS than those with rare or complex *EGFR* mutations (13.5 versus 9.0 months, HR, 0.31; 95% CI, 0.11-0.84; p = 0.021).The overall survival data was not mature. Of the patients who experienced PD while on afatinib, 55.3% were investigated for acquired resistance mechanisms. *Exon 20 T790M* mutation was detected in 42.0% of these patients. **Conclusion:** Afatinib is an effective first-line treatment for patients with *EGFR*-mutant advanced NSCLC with good response and disease control rates as well as long PFS even in patients with unfavorable clinical characteristics. The side-effects of afatinib were manageable and acquired *T790M* mutation was a common mechanism causing treatment failure.

Keywords: Malaysian, Afatinib, real-world

P2.14-48 CLINICAL SEQUENCING USING A NGS-BASED MULTIPLE GENE ASSAY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Patients with non-small cell lung cancer (NSCLC) often harbor driver mutations in multiple oncogenes, including *EGFR, ALK*, *ROS1*, *BRAF*, *HER2*, *MET*, *RET*, etc. The presence of gene alterations can impact the selection of and the response to targeted therapies. Testing of lung cancer for multi-gene alterations is important for identification of potentially efficacious targeted therapies. Therefore, identifying mutations in oncogenes and tailoring therapy become a standard in clinical cancer management. A genetic testing assay based on next-generation sequencing (NGS), named AmoyDx Essential NGS Panel, has been developed for multiplexed and targeted deep sequencing of variants in 10 driver genes. Clinical validation using FFPE tissue was conducted in the present study. **Method:** A total of 294 formalin-fixed and paraffin-embedded (FFPE) tissue samples collected from NSCLC patients were tested by AmoyDx Essential NGS Panel, which enables the simultaneous detection of single-nucleotide variants (SNVs), insertions/deletions and fusions in 10 driver genes (*EGFR*, *KRAS*, *NRAS*, *BRAF*, *PIK3CA*,

ALK, *ROS1*, *HER2*, *RET*, and *MET*) in DNA samples. DNA sequencing was performed on the Illumina sequencer. Golden standard Sanger sequencing was used as a reference method to test the same cohort. The concordance of alterations determined with the AmoyDx Essential NGS Panel was assessed compared to the reference method. **Result:** In total of 294 samples, 98.30% (289/294) of patients were successfully detected by both AmoyDx Essential NGS Panel and Sanger sequencing. 68.86% (199/289) were identified with positive mutation/fusion by NGS assay (Table 1). The overall concordance rate of alterations determined with AmoyDx Essential NGS Panel compared with reference was 90.66%.

Table 1 Alterations detected by NGS

Variant type	Number of patients	Positive rate
EGFR mutation	126	43.60%
KRAS mutation	40	13.84%
NRAS mutation	1	0.35%
BRAF mutation	1	0.35%
PIK3CA mutation	3	1.04%
ALK fusion	22	7.61%
ROS1 fusion	2	0.69%
HER2 mutation	6	2.08%
RET fusion	1	0.35%
MET mutation	0	0.00%
Total	199	68.86%

Conclusion: The NGS analysis with AmoyDx Essential NGS Panel represents an accurate and efficient approach to detect genetic alterations in 10 driver genes with high concordance rate of 90.66% compared with Sanger sequencing.

Keywords: Next-generation sequencing, NSCLC, Multiple gene assay

P2.14-49 MOLECULAR CHARACTERISTICS OF HER2 MUTATIONS IN NON-SMALL CELL LUNG CANCER

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Background: Earlier clinical trials targeting on HER2 exon 20 mutations show promising results. However, target therapy also had shown a favorable effect on non-tyrosine kinase domain (non-TKD) mutations in preliminary studies and case report, while no systemic study was reported about non-TKD mutations in HER2. Hence, The study aims to comprehensively outline the mutation landscape of HER2 in NSCLC. **Method:** HER2 profile data (patients, N=5,222) from thirteen NSCLC studies in the cBioPortal for Cancer Genomics was screened. Finally, after excluding duplicated data (n=2,725) and no HER2 profile data (n=563), 1,934 individuals were enrolled in the analysis. The mutation subtype, mutation type, mutation region, biological effect of mutations referred to OncoKB, and HER2 copy number variation were described. **Result:** 4.3% (84/1934) of NSCLC patients were detected with HER2 mutation, and three patients carried double HER2 mutations, totally eighty-seven HER2 mutations were identified in the study. Fifty-three HER2 mutation subtypes were identified, and the most common mutation subtypes were Y772_A775dup (24%, 21/87), S310F (6%, 5/87), G776delinsVC (5%, 4/87) and G778_P780dup (5%, 4/87) respectively. HER2 fusion was identified in 8% (7/87) of mutations with a tendency to concurrent with HER2 copy number increased (5 amplification, 2 copy number gain). As for mutation region, 43% (37/87) of mutations occurred in TKD, while biological effect was not validated in 16% (6/37) of TKD mutations. Notably, biological effect of 56% mutations was inclusive or unknown. In gain of function subset, 82% (31/38) of mutations located at TKD, 13% (5/38) and 5% (2/38) were located at furin-like cysteine rich region and transmembrane domain.

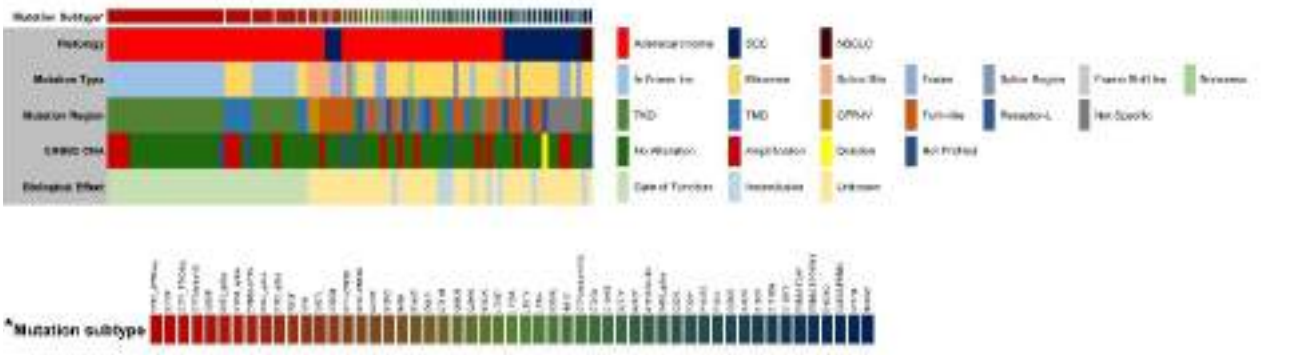

Figure 1. Molecular characteristics of HER2 mutations in NSCLC (n=87).
SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain; TMD, transmembrane domain; GFR-IV, growth factor receptor domain IV; Furin-like, furin-like cysteine rich region; Receptor-L, receptor-L domain; CNA, copy number alteration.

Conclusion: Mutation subtypes were diverse in HER2. Though accounting for more than half of HER2 mutations, the effect of non-TKD mutations was fewly understood rather than TKD mutations. Biological effect and clinical implication of non-TKD mutations need to be further investigated in the near future.

Keywords: Non-Small Cell Lung Cancer, Molecular Characteristics, HER2 mutations

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P2.14-50 LOW TEMPERATURE PLASMA NEEDLE INDUCES CELL CYCLE ARREST OF EPITHELIAL LUNG CANCER CELLS IN VITRO VIA A P21-DEPENDENT PATHWAY

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Background: Low temperature plasma sources which operate at atmospheric pressure produce reactive oxygen species (ROS) and reactive nitrogen species which can cause cancer cell death. In this study we investigated the effect of our low temperature plasma needle system on a non-small cell lung cancer cell line A549 and studied its mechanism of action. **Method:** The housing of the pen lookalike atmospheric plasma source (plasma needle) was made of Teflon. A Pyrex glass tube (o.d. 6 mm and i.d. 4 mm) through which 1 slm of helium was released as the feeding gas was positioned within the housing. The central electrode, a tungsten wire, was powered with a 13.56 MHz sine wave and placed within a ceramic tube inside the glass tube. The central electrode was sticking 1 mm outside of the ceramic and glass tubes, so the discharge occurred on its tip as a weak glow. The cytotoxic activity was determined using MTT assay. The potential of inducing cell cycle perturbations and apoptosis, and changes in the level of ROS was investigated by flow cytometry. The influence of plasma treatment on growth inhibition of multicellular tumor spheroids (MCTS) was also investigated. Evaluation of gene expression was performed by qPCR. All experiments were performed in triplicate, with statistical significance set at p<0.05. **Result:** Our plasma needle exerted a cytotoxic effect with lower sensitivity towards BEAS-2B normal cells than towards A549 cells. A decrease in the number of cells in the G1 phase (up to 45%), increase in the G2 phase (up to 27%), and an increase in the sub-G1 phase (up to 12%) with fragmented DNA was detected upon treatment. The plasma treatment exerted a mild apoptotic effect (around 15% of apoptotic cells), and an increase in the level of ROS in a power dependent manner. There was no significant reduction in growth of MCTS after plasma treatment under investigated experimental conditions. A statistically non-significant proapoptotic effect (increase in Bax, decrease in Bcl2 and decrease in SKP2) was observed at the genetic level. A significant overexpression of the cyclin-dependent kinase inhibitor 1 (p21) was also observed at the genetic level in a power dependent manner. **Conclusion:** Our low temperature plasma needle induced cell cycle arrest of epithelial lung cancer cells through overexpression of p21. The effect of combined plasma treatment with existing treatment modalities (cisplatin, PARP inhibitors) is currently under *in vitro* investigation.

Keywords: cell cycle arrest, plasma needle, p21

P2.14-51 DUAL ALK FUSION PARTNERS AS POOR PREDICTIVE MARKER IN FIRST LINE CRIZOTINIB TREATED ALK REARRANGED NON-SMALL CELL LUNG CANCER

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Background: First line crizotinib response duration time differs with different fusion patterns in *ALK*-rearranged advanced non-small cell lung cancer (NSCLC) patients. Some former researches have elucidate the impact of *EML4-ALK* variants on crizotinib efficacy, however, there was little data about the efficacy of crizotinib considering different fusion partners including one patient with two or more fusion partners or non-*EML4* partners. **Method:** 150 patients with NGS-identified *ALK*-rearranged NSCLC from March 2014 to July 2018 in Hunan Cancer Hospital were enrolled in this study. Among them, 112 patients received crizotinib as first-line treatment. Efficacy of crizotinib was evaluated and categorized according to different fusion partners. **Result:** Among 150 advanced NSCLC patients with NGS-identified *ALK*-rearranged, 181 fusion partners were detected including 43 novel fusion partners. 122 patients (81.3%) were identified with single *ALK* fusion partners, 28 patients (18.7%) were identified with dual or triple *ALK* fusion partner patients. Among 112 patients received first line crizotinib treatment, 89 patients were identified with single fusion partner (79 for *EML4*, 10 for non-*EML4*). 23 patients were identified with dual fusion partner (20 patients with dual fusion partners, 3 patients with triple fusion partners). The overall response rate (ORR) was 85.2% and the median progression-free survival time (mPFS) was 11.7 months. The frequency of brain metastasis was high in dual fusion partner patients. Patients with dual *ALK* fusion partners have a significantly shorter mPFS compared with patients carrying single *ALK* fusion partner (6.1m *vs.* 12.0m, *p*=0.001). Patients with *EML4* partners have a significantly longer mPFS compared with patients carrying non-EML4 fusion partners (12.6m *vs.* 6.1m, *p*=0.004).

Fusion partners	EML4-ALK fusion variants	Number of patient	Percentage of patient(%)
C9orf3-ALK	(	2	1.3%
CLIP1-ALK	(	1	0.7%
CYBRD1-ALK		1	0.7%
DEFA5-ALK	(	1	0.7%
EML4-ALK	V1	31	20.7%
EML4-ALK	V2	10	6.7%
EML4-ALK	V3	47	31.3%
EML4-ALK	V5	11	7.3%
EML4-ALK	V7	3	2.0%
EML4-ALK	E3:A20	1	0.7%
EML4-ALK	E7:A20	1	0.7%
EML4-ALK,APOBALKE	V5	1	0.7%
EML4-ALK,ATXN1ALK	V7	1	0.7%
EML4-ALK,BIRC6AS2-ALK	V3	1	0.7%
EML4-ALK,C1QCALK	V3	2	1.3%
EML4-ALK,COL22A1ALK	V3	1	0.7%
EML4-ALK,COL22A1ALK	V1	1	0.7%
EML4-ALK,DIRC3AS1-ALK,CDC42EP3ALK	V3	1	0.7%
EML4-ALK,EHBP1ALK	V3	1	0.7%
EML4-ALK,-FLJ14082-ALK	V3	1	0.7%
EML4-ALK,LBH-ALK	V1	1	0.7%
EML4ALK,LINC00486ALK	V3	1	0.7%
EML4ALK,LINC01121-ALK	V1	1	0.7%
EML4ALK,LOC102467222ALK	V3	1	0.7%
EML4ALK,LOC388942ALK	V1	1	0.7%
EML4ALK,LOC388942ALK,	V3	1	0.7%
EML4-ALK,LRRTM4-ALK	V3	1	0.7%
EML4-ALK,MBOAT2ALK	V2	1	0.7%
EML4-ALK,MTA3ALK,SP3-ALK	V1	1	0.7%
EML4-ALK,MYH7ALK	V2	1	0.7%
EML4-ALK,PDE6D-ALK	V1	1	0.7%
EML4-ALK,QPCTALK	V1	1	0.7%

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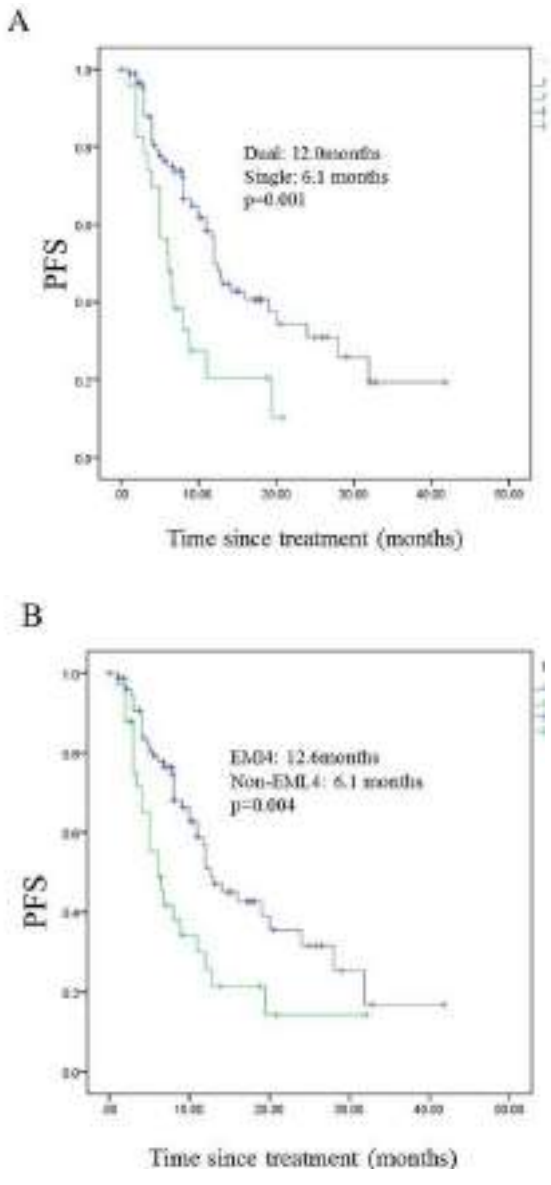
EML4-ALK,RC3H2-ALK	V1	1	0.7%
EML4-ALK,SGPP2-ALK	V3	1	0.7%
EML4-ALK,SIX3-AS1-ALK	V2	1	0.7%
EML4-ALK,SRBD1-ALK	V3	1	0.7%
EML4-ALK,THADA-ALK	V3	1	0.7%
EML4-ALK,TSPYL6-ALK,ABCG8-ALK	V3	1	0.7%
FAM179A-ALK	(	1	0.7%
GBE1-ALK	(	1	0.7%
KLC1-ALK	(	1	0.7%
LOC388942-ALK	(	1	0.7%
NCOA1-ALK	(	1	0.7%
RP11-433C9.2-ALK	(	1	0.7%
RPSA-ALK	(	1	0.7%
SLC8A1-ALK	(	1	0.7%
STRN-ALK	(	1	0.7%
THADA-ALK	(	1	0.7%
UBXN2A-ALK	(	1	0.7%
USP34-ALK	(	1	0.7%
WDR37-ALK	(	1	0.7%



Conclusion: Efficacy of first-line crizotinib in *ALK*-rearranged NSCLC patients differs based on different *ALK* fusion partners. Dual *ALK* fusion partners were poor prognostic factors in first-line crizotinib treatment NSCLC. It also correlated with more brain metastasis compared with single fusion partners.

Keywords: Next Generation Sequencing, ALK, Fusion partners, crizotinib

P2.14-52 THE RESULTS FROM PLASMA EGFR MUTATION ANALYSIS IN NEJ026 STUDY

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Background: EGFR mutation analysis of plasma circulating tumor DNA (ctDNA) has been reported to be useful to detect resistant mutations and to predict the efficacy of treatment. In NEJ026 study, we demonstrated the PFS of erlotinib plus bevacizumab (BE) treatment was significantly superior to the erlotinib alone (E) in NSCLC patients harboring EGFR mutation. Evaluation of plasma EGFR mutations included in NEJ026 study as preplanned analysis. **Method:** At the time points of pretreated (P0), 6 weeks after study treatment started (P1), and confirmed progressive disease (P2), the plasma samples were collected from the patients enrolled to NEJ026 study. The number of enrolled patients were 112 in BE and 114 in E. Plasma ctDNA analysis for detection of the activating EGFR mutation and T790M mutation were performed by modified PNA-LNA PCR clamp method. **Result:** The total numbers of collected plasma samples in BE and E were 108 (96.4%) and 107 (95.5%) at P0, 95 (84.8%) and 97 (86.6%) at P1, and 42 (37.5%) and 53 (47.3%) at P2, respectively. In eligible patients having EGFR activating mutation detected by cytohistological specimens, detection rate of plasma EGFR mutation at P0 was 68% (147/215). The detection ratio of T790M mutation at P2 were similar in both arms: 8 (19.0%) in BE and 11 (20.8%) in E. By detection pattern of activating EGFR mutation, PFS was evaluated among three groups: type A (P0 (-),P1 (-)), type B (P0 (+), P1(-)), and type C (P0 (+), P1(+)). Type A achieved the best response to both TKI [Type A BE: 18.1 M (n = 32, 95% CI, 11.5 to upper limit not reached(NR)), E: 16.7 M (n = 26, 95% CI, 11.2 to NR)]. Type B also had better PFS to TKI and BE is more favorable effect than E compared to other types [type B BE: 15.5 M (n = 48, 95% CI, 12.4 to 23.3), E: 11.1 M (n = 57, 95% CI, 8.5 to 13.7)]. Type C showed worse response to both treatment [type C BE: 6.0M. (n = 12, 95% CI 2.6 to NR), E: 4.3 M (n = 10, 95% CI, 2.8 to 20.2)]. BE had better PFS in all types. **Conclusion:** Frequency of T790M in P2 was similar among BE and E. When patients still had detectable activating EGFR mutation in plasma ctDNA after treatment for 6 weeks, you should consider that they might have poor response to both BE and E.

Keywords: liquid biopsy, EGFR, Bevacizumab

POSTERS

P2.14-53 HIGH MET OVEREXPRESSION DOES NOT PREDICT THE PRESENCE OF MET EXON 14 SPLICE MUTATIONS IN NSCLC: RESULTS FROM THE IFCT PREDICT.AMM STUDY

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Background: *MET* exon 14 splice site (*MET*ex14) mutations were recently described in Non Small Cell Lung Cancer (NSCLC) and reported to correlate with efficacy of MET tyrosine kinase inhibitors. High diversity of these alterations make them hard to detect by DNA sequencing in clinical practice. Because *MET*ex14 mutations induce increased stabilization of the MET receptor, it is anticipated that these mutations are associated with MET overexpression. We aim to determine whether NSCLC with high MET overexpression could define a subset of patients with a high rate of *MET*ex14 mutations. **Method:** From the IFCT Predict.amm cohort of 843 consecutive patients with a treatment-naïve advanced NSCLC who were eligible for a first-line therapy, 108 NSCLC samples with high MET overexpression defined by an immunochemistry (IHC) score 3+ were tested for *MET*ex14 mutations using fragment length analysis combined with optimized targeted next generation sequencing (NGS). *MET* copy number analysis was also derived from the sequencing data. **Result:** *MET*ex14 mutations were detected in two patients (2.2%) who also displayed a TP53 mutation and a PIK3CA mutation, respectively. A *MET* gene copy number increase was observed in 7 additional patients (7.7%). NGS analysis revealed inactivating mutations in *TP53* (52.7%) and *PTEN* (1.1%) and oncogenic mutations in *KRAS* (28.6%), *EGFR* (7.7%), *PIK3CA* (4.4%), *BRAF* (4.4%), *NRAS* (2.2%), *GNAS* (1.1%) and *IDH1* (1.1%). **Conclusion:** The rate of *MET*ex14 mutations in NSCLC with high MET overexpression was similar to that found in unselected NSCLC. Moreover, we observed a high frequency of driver alterations in other oncogenes. Consequently these findings do not support the use of MET IHC as a surrogate marker for *MET*ex14 mutations.

Keywords: Non small cell lung cancer, MET, Receptor tyrosine kinase

P2.14-54 HIGH INCIDENCE OF CNS METASTASES IN ADVANCED OR RECURRENT NON-SMALL CELL LUNG CANCER PATIENTS WITH RET FUSION

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Background: Chromosomal rearrangements involving *RET*, with incidence of 1-2% in non-small-cell lung cancer, define a distinctive molecular subset. Here, we aim to determine the clinicopathological characteristics of patients with advanced NSCLC harboring the *RET* fusion gene. **Method:** We identified 59 consecutive cases with *RET* rearrangements by using break-apart fluorescence in situ hybridization (n=14), next-generation sequencing (n=37), or both (n=8). Clinical data, including baseline characteristics, initial presentation, responses to chemotherapy and/or immunotherapy were retrospectively analyzed. **Result:** The median age was 56 years, and 53% of patients were male. Approximately half of the patients (51%) were never-smokers. Adenocarcinoma was the predominant histologic subtype (90%), followed by pleomorphic (3%), neuroendocrine (3%), squamous cell (2%), and small cell carcinoma (2%). For the 19 patients with small primary lesions (<3cm), 32% (6/19) had N2 and 37% (7/19) had N3 disease. 17 patients (29%) had an intracranial lesion at the initial presentation or at the time of recurrence, and additional 11 patients (19%) developed brain metastasis during follow-up. Cerebrospinal fluid cytology exam confirmed leptomeningeal seeding in four patients (7%) with concomitant parenchymal metastasis. The median time to development of brain metastases was 19.0 months (range 3.8-51.8). Of 30 patients whose fusion partners were identified, kinesin family member 5B (*KIF5B)* was the most common, followed by coiled-coil domain containing 6 gene (*CCDC6*), nuclear receptor coactivator 4 (*NCOA4*), and myosin 5C (*MYO5C*) and lisH domain and HEAT repeat-containing protein KIAA1468 homolog (*KIAA1468*). Additionally, a novel fusion partner, phytanoyl-CoA 2-hydroxylase interacting protein like (*PHYHIPL)*, was reported in one patient. Only two patients harbored concomitant *EGFR* mutation, and no *ALK* alterations were reported. The median overall survival was 35.3 months (95% confidence interval [CI]: 21.7-48.9). In 46 patients who were treated with pemetrexed-based chemotherapy, the overall response rate (ORR) and progression-free survival (PFS) time were 53.0% and 8.5 months (95% CI: 6.3-10.7), respectively. In 13 patients who were treated with immunotherapy, the ORR and PFS were 7.7% and 1.5 months (95% CI: 1.3-1.7), respectively, with no significant difference according to the level of PD-L1 expression. **Conclusion:** Our study revealed the unique clinical characteristics and outcomes of advanced NSCLC patients harboring *RET* fusion gene. Considering the high incidence of CNS metastases, relatively poor response to immunotherapy, and a recent development of *RET* kinase inhibitors (such as cabozantinib and vandetanib), more efforts are warranted for identification of patients with *RET* fusion as a candidate for targeted therapies.

Keywords: NSCLC, RET fusion, CNS metastases

P2.14-55 REAL-WORLD SAFETY AND EFFICACY DATA OF OSIMERTINIB IN PATIENTS FROM JAPAN WITH EGFR T790M-POSITIVE NSCLC

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Background: Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was approved in Japan on 28 March 2016 as second- or later-line treatment for patients with EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on EGFR-TKIs. Post-marketing activities included the Japan-local All-patient Clinical Experience Investigation, reporting Japanese real-world safety and efficacy of osimertinib in the approved indication. **Method:** Overall, 3629 patients investigated at 718 hospitals between 28 March 2016 and 31 August 2018 were included. Adverse events were assessed by attending physicians to determine whether they were possibly causally-related to osimertinib. Osimertinib antitumour activity was evaluated by attending physicians using RECIST version 1.1. Progression-free survival (PFS) and overall survival (OS) were also analysed. The planned observation period was 12 months. **Result:** The median observation period for patients in the safety analysis set (n=3578) was 343 days (range: 1–764). Adverse drug reactions occurred in 58.1% (2079/3578) of patients. Adverse drug reactions (as per Japanese Prescribing Information) of interstitial lung disease, prolonged QT interval, liver disorder, and haematotoxicity were reported in 6.8% (245/3578) (Gr≥3, 2.9% [104/3578]), 1.3% (45/3578) (Gr≥3, 0.1% [5/3578]), 5.9% (212/3578) (Gr≥3, 1.0% [35/3578]), and 11.4% (409/3578) (Gr≥3, 2.9% [104/3578]) of patients, respectively. The objective response rate and disease control rates for patients in the efficacy analysis set (n=3563) were 69.9% (2492/3563; 95% confidence interval [CI] 68.4, 71.4) and 86.7% (3090/3563; 95% CI 85.6, 87.8). PFS rates at 6 months and 12 months were 77.4% (95% CI 75.9, 78.9) and 53.2% (95% CI 51.3, 55.1). OS rates at 6 months and 12 months were 88.3% (95% CI 87.2, 89.4) and 75.4% (95% CI 73.8, 77.0). Selected subgroup analyses of efficacy are presented in Table 1.

Table 1. Selected subgroup analysis of real-world osimertinib efficacy in patients from Japan					
Subgroup	Category	N	ORR % (95% CI)	PFS rate at 6 months % (95% CI)	PFS rate at 12 months % (95% CI)
Age	<75	2458	69.4 (67.6, 71.3)	76.1 (74.2, 77.8)	50.4 (48.1, 52.7)
	≥75	1104	71.1 (68.3, 73.8)	80.7 (78.0, 83.1)	60.1 (56.5, 63.4)
WHO PS	0-1	2894	73.6 (72.0, 75.2)	80.7 (79.1, 82.2)	56.9 (54.7, 58.9)
	2-4	668	54.2 (50.3, 58.0)	60.8 (56.3, 64.9)	34.1 (29.4, 38.8)
EGFRm type	Exon 19 deletion	1757	72.5 (70.4, 74.6)	78.2 (76.0, 80.2)	55.2 (52.4, 57.9)
	L858R	1232	67.1 (64.4, 69.7)	77.0 (74.3, 79.4)	49.7 (46.4, 52.9)
Brain metastasis	No	2728	71.0 (69.3, 72.7)	78.9 (77.2, 80.5)	55.8 (53.6, 58.0)
	Yes (asymptomatic)	601	69.7 (65.9, 73.4)	74.4 (70.4, 77.9)	47.2 (42.6, 51.6)
	Yes (symptomatic)	233	58.4 (51.8, 64.8)	67.3 (60.0, 73.6)	37.2 (29.6, 44.8)
Pleural effusion	No	2623	72.7 (71.0, 74.4)	78.4 (76.6, 80.0)	54.2 (52.0, 56.4)
	Yes	939	62.3 (59.1, 65.4)	74.8 (71.6, 77.7)	50.3 (46.4, 54.0)
CI, confidence interval; EGFRm, epidermal growth factor receptor mutation; ORR, objective response rate; PFS, progression-free survival; PS, performance status					

Conclusion: These data support the currently established benefit–risk assessment of osimertinib in patients with EGFR T790M positive NSCLC.

Keywords: T790M, Japanese, Osimertinib

P2.14-56 OSIMERTINIB OVERCOMES ALECTINIB RESISTANCE CAUSED BY AMPHIREGULIN IN A LEPTOMENINGEAL CARCINOMATOSIS MODEL OF EML4-ALK LUNG CANCER

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Background: Central nervous system (CNS) metastasis, such as brain metastasis and leptomeningeal carcinomatosis (LMC), occurs in 20–40% of all patients with cancer. Anaplastic lymphoma kinase (ALK) is a clinically validated drug target and *ALK* rearrangements are found in approximately 3-5% of non-small cell lung cancer (NSCLC). ALK tyrosine kinase inhibitor (TKI) shows dramatic clinical efficacy in *ALK*-rearranged NSCLC patients, and the second-generation ALK-TKI alectinib is effective against CNS metastasis of *ALK*-rearranged NSCLC. However, the patients with *ALK*-rearrangement acquire resistance to alectinib over time and develop recurrent LMC metastasis. This study aimed to clarify the mechanism of resistance to alectinib in LMC and seek a novel therapeutic strategy. **Method:** Alectinib-resistant cell line (A925L/AR) was established by continuous treatment with alectinib in the LMC mouse model inoculated with the alectinib-sensitive human lung cancer cell line, A925LPE3, which harbors the *EML4-ALK* gene fusion. The tumor level was measured by in vivo imaging system. To clarify the mechanism of alectinib resistance, tumor cell culture supernatants, patient cerebrospinal fluid (CSF), and patient serum were measured using ELISA kits for EGFR ligands. **Result:** A925L/AR cells were moderately resistant to various ALK-TKIs, such as alectinib, crizotinib, ceritinib, and lorlatinib, compared with parental cells *in vitro*. A925L/AR cells acquired resistance through epidermal growth factor receptor (EGFR) activation due to overexpression of its ligand, amphiregulin. EGFR-TKIs and anti-EGFR antibodies re-sensitized A925L/AR cells to alectinib *in vitro*. In the LMC model with A925L/AR cells, combined treatment with alectinib and an EGFR-TKI, such as erlotinib and osimertinib, successfully controlled LMC progression. Imaging mass spectrometry showed accumulation of EGFR-TKIs in the tumor lesions. Moreover, notably high amphiregulin levels were detected in the cerebrospinal fluid from *ALK*-rearranged NSCLC patients with alectinib-resistant LMC compared with those in *EGFR*-mutated NSCLC patients with EGFR-TKI-resistant LMC or patients without LMC. **Conclusion:** We demonstrated that *EML4-ALK* lung cancer cells acquired moderate resistance to alectinib in the leptomeningeal space due to amphiregulin-triggered EGFR activation. Moreover, combined use of alectinib and EGFR-TKIs, including the third-generation inhibitor osimertinib, could overcome resistance in the LMC model. Our findings may provide rationale for clinical trials to investigate the effects of novel therapies dual-targeting ALK and EGFR in *ALK*-rearranged NSCLC with alectinib-resistant LMC.

Keywords: leptomeningeal carcinomatosis, alectinib resistance, Osimertinib

P2.14-57 EFFICACY OF 3RD GENERATION EGFR-TKIS AFTER FAILING FIRST OR SECOND GENERATION EGFR-TKIS IN EGFR MUTATION-POSITIVE NSCLC (ROOT-EGFR)

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Background: Over the past decade, treatment of EGFR mutation –positive NSCLC has been revolutionized with the development of next generation EGFR TKIs. Four epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib, afatinib and osimertinib, are currently available in Korea. Recent trials have compared the available and emerging EGFR TKIs head to head. The highly anticipated findings of the phase III FLAURA trial showed a nearly doubling of PFS with frontline osimertinib, a third-generation TKI, versus erlotinib or gefitinib.The optimal sequence of EGFR TKIs is still controversial. And many countries 3rd generation EGFR TKI is not readily available. The purpose of this study is to analyze the efficacy in patients who received first-line gefitinib, erlotinib, or afatinib and followed by 3rd generation EGFR-TKIs. **Method:** This non-interventional observational study through big data analysis will retrospectively collect de-identified patient data from clinical data warehouse (CDW) using a unique algorithm with Standard Query Language (SQL) called ROOT project. **Result:** Over 10 years, 2,358 patients were diagnosed recurrent or metastatic non-small cell lung cancer and received 1st or 2nd generation EGFR TKIs at Samsung Medical Center. 72.9% (1720/2358) of EGFR mutation-positive NSCLC patients received 1st or 2nd generation EGFR-TKIs as first

line palliative chemotherapy. In total population, 30.8% (727/2358) patients received 3rd generation EGFR TKIs. Among them, patients who received 3rd generation EGFR TKI after 1st or 2nd generation EGF TKIs showed better overall survival (45.0 months (95% CI, 41.8-48.2). Among 1720 patients who received 1st or 2nd generation EGFR-TKIs as first line palliative chemotherapy, 313 patients received 3rd generation EGFR-TKIs as 2nd line chemotherapy and 200 patients received as more than 3rd line chemotherapy. However, there was no difference of overall survival between them (44.0 months vs 47.0months, p-value=0.104). **Conclusion:** This study was meaningful as a study of what can be the best sequence in EGFR-TKI treatment. Updated and detail clinical and exploratory biomarker outcome will be presented at the meeting.

Keywords: NSCLC, EGFR TKI, 3rd generation

P2.14-58 A PHASE IIIB, OPEN-LABEL STUDY OF AFATINIB IN CAUCASIAN EGFR TKI-NAÏVE PATIENTS WITH EGFRM+ NSCLC: AN INTERIM ANALYSIS

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Background: First-line afatinib demonstrated significantly improved median PFS in patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC versus chemotherapy in LUX-Lung 3/6 (HR [95% CI]: 0.58 [0.43–0.78]/0.28 [0.20–0.39]), and versus gefitinib in LUX-Lung 7 (0.73 [0.57–0.95]). Since these trials had strict inclusion criteria, it is important to support these findings with real-world studies of broader patient populations. We report interim results of a Phase IIIb study of afatinib treatment for *EGFR*m+ NSCLC in a patient population similar to real-world practice. **Method:** EGFR TKI-naïve patients with locally advanced/metastatic *EGFR*m+ NSCLC, and ECOG PS 0–2, received afatinib 40 mg/day. Dose reduction was permitted (minimum 20 mg/day). Primary endpoint: adverse events (AEs; descriptive fashion). Efficacy was also assessed. **Result:** At data cut-off (30-April-2018), 479 patients were enrolled and treated (Caucasian/Asian/other: 97%/2%/<1%; ECOG PS 0–1/2: 92%/8%; 1st/2nd/≥3rd-line therapy: 78%/17%/5%; common/uncommon mutations: 87%/13%; brain metastases: 17%). Median time on afatinib: 359 days. Objective response and disease control rates were 46% and 86%, respectively. Other efficacy outcomes are in the Table. The most common grade ≥3 afatinib-related AEs were diarrhoea (16%) and rash (11%). 258 (54%) patients had AEs leading to dose reduction (most frequently diarrhoea [25%]/rash [11%]), and 37 (8%) had TRAEs leading to discontinuation (most frequently diarrhoea [3%]; all others [<1%]). Serious afatinib-related AEs occurred in 39 (8%) patients.

	Median TTSP, months (95% CI)	Median PFS, months (95% CI)
All pts (n=479)	14.9 (13.8–17.6)	13.4 (11.8–14.5)
Line of therapy		
1st (n=374)	15.6 (14.1–18.5)	13.8 (12.6–15.2)
2nd (n=81)	14.7 (11.3–20.6)	13.2 (8.3–17.7)
≥3rd (n=24)	8.1 (3.7–14.4)	6.6 (3.2–12.6)
Baseline brain metastases*		
No (n=395)	15.8 (14.1–18.8)	13.9 (12.7–15.5)
Yes (n=83)	13.7 (9.7–17.2)	10.1 (8.2–13.9)
Baseline mutation type*		
Common† (n=416)	15.9 (14.5–19.1)	14.1 (13.0–15.7)
Uncommon‡ (n=62)	6.7 (5.4–8.3)	5.9 (4.0–7.4)
Baseline ECOG PS*, including age		
0–1 (n=442)	15.8 (14.4–18.8)	13.8 (12.8–15.2)
<65 years (n=221)	14.7 (12.7–17.6)	13.4 (11.6–15.5)
≥65 years (n=221)	18.9 (14.7–21.7)	14.1 (12.6–16.4)
2 (n=36)	8.9 (5.7–13.2)	6.2 (2.5–11.6)
<65 years (n=16)	6.0 (2.4–13.2)	3.2 (1.5–9.1)
≥65 years (n=20)	9.9 (7.6–13.9)	7.7 (5.7–13.9)

*Missing (n=1); †Del 19 and/or L858R with or without uncommon mutation; ‡Includes, n (%, of those with uncommon mutations): ex 20 ins: 37 (60), T790M: 12 (19), G719S/A/C: 12 (19), L861Q: 10 (16), S768I: 9 (15). TTSP, time to symptomatic progression; PFS, progression-free survival

Conclusion: This interim analysis indicated predictable and manageable safety, and encouraging efficacy, with afatinib in a broad patient population. The high proportion of patients with tumours harbouring exon 20 insertions may account for the differences in TTSP/PFS by common/uncommon mutation subgroup. Independent of treatment line, median TTSP/PFS in patients with ECOG PS 0–1 (LUX-Lung trials' inclusion criteria) was 15.8/13.8 months, and, notably, was 18.9/14.1 months in those also aged ≥65 years. These findings by ECOG PS/age are consistent with those of the LUX-Lung trials.

P2.14-59 OSIMERTINIB IN EGFR T790M ADVANCED NSCLC: ANALYSIS OF UNCOMMON/COMPLEX EGFR MUTATIONS IN A REAL-WORLD STUDY (ASTRIS)

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Background: The challenges of treating uncommon/complex EGFR mutations impact treatment decisions in clinical practice. Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitising (EGFRm) and EGFR T790M mutations and has demonstrated efficacy in NSCLC CNS metastases. ASTRIS is an ongoing, international, real-world study of osimertinib in EGFR T790M positive advanced NSCLC (NCT02474355). We report a subset-analysis of patients with

uncommon/complex mutations. **Method:** Patients with stage IIIB/IV T790M positive NSCLC previously treated with an EGFR-TKI were enrolled and received osimertinib 80 mg once-daily. Progression-free survival (PFS), clinical response and time to treatment discontinuation (TTD) were analysed in both full analysis set (FAS) and patients with uncommon/complex EGFR mutations. Uncommon mutation combinations included: T790M+G719X, T790M+S768I, T790M+ex20ins; complex mutations included T790M+two or more mutation(s). **Result:** From 18 September 2015 to 15 October 2018 data cut-off, 3015 patients across 16 countries had received ≥1 dose of osimertinib (FAS), 53(2%) of these patients had uncommon/complex EGFR mutations. Baseline demographics between this patient subset and the FAS were similar (Asian: 55%/69%; female: 57%/64%; median age: 59 [30–80] years/62 [range, 27–92]; WHO performance status 2: 9%/11%, respectively). Baseline EGFR mutation status at enrolment of the FAS is shown in Table 1. Clinical outcomes appeared to be lower in the uncommon/complex mutation subset than in the FAS: response rate (measured in a FAS subset with ≥1 documented response assessment) was 50% [95% CI, 35.2, 64.8] in the uncommon/complex mutation group, and 57% [55.2, 58.9] in the FAS; median PFS was 8.1 [5.4, 10.1] and 11.1 [11.0, 12.0] months; median TTD was 9.0 [6.7, 11.5] and 13.5 [12.6, 13.9] months, respectively. Overall survival data are immature.

Table 1. Baseline EGFR mutation status (full analysis set)

EGFR mutation, n (%)**	Osimertinib (N=3015)
Uncommon/complex EGFR mutations	53 (2)
T790M	3015 (100)
+ Ex19del	1711 (57)
+ L858R	917 (30)
+ S768I (uncommon mutation)	*17 (1)*
+ G719X (uncommon mutation)	*30 (1)*
+ Ex20ins (uncommon mutation)	*4 (<1)*
T790M only	372 (12)
T790M + 1 other mutation	2611 (87)
T790M + 2 other mutations (complex mutations)	*30 (1)*
T790M + 3 other mutations (complex mutations)	*0*
T790M + 4 other mutations (complex mutations)	*2 (<1)*
T790M + 1 other mutation[#]	2611 (87)
+ Ex19del	1690 (65)
+ L858R	900 (34)
+ G719X (uncommon mutation)	*18 (<1)*
+ Ex20ins (uncommon mutation)	*2 (<1)*
+ S768I (uncommon mutation)	*1 (<1)*
T790M + 2 other mutations (complex mutations)[§]	*30 (1)*
+ Ex19del + S768I	*4 (13)*
+ Ex19del + L858R	*10 (33)*
+ L858R + S768I	*4 (13)*
+ Ex19del + Ex20ins	*2 (7)*
+ S768I + G719X	*6 (20)*
+ Ex19del + G719X	*3 (10)*
+ L858R + G719X	*1 (3)*
*T790M + 4 other mutations (complex mutations)***	*2 (<1)*
+ Ex19del + L858R + G719X + S768I	*2 (100)*

*Patients can have more than one mutation and specimens are not necessarily tested for all mutations
#Uncommon/complex EGFR mutations are italicised
§Percentages quoted are as proportion of those with T790M+1 mutation (n=2611)
¶Percentages quoted are as proportion of those with T790M+2 mutations (n=30)
**Percentages quoted are as proportion of those with T790M+4 mutations (n=2)
Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion.

Conclusion: Whilst clinical outcomes appeared to be lower in the uncommon/complex mutation subset than the FAS, they were favourable and support use of osimertinib 80mg in this heterogeneous population.

Keywords: Osimertinib, NSCLC, EGFR

P2.14-60 AFATINIB IN EGFR MUTATION-POSITIVE NSCLC: ACTIVITY IN PATIENTS WITH BRAIN METASTASES, AND IMPACT ON CNS PROGRESSION/SPREAD

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Background: In the LUX-Lung 3 and 6 trials, first-line afatinib significantly improved progression-free survival (PFS) versus chemotherapy in patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC and baseline brain metastases (hazard ratio [HR], 0.50; P=0.0297).1 In LUX-Lung 7, similar PFS improvement with afatinib versus gefitinib was observed in patients with, and without, brain metastases (HR, 0.76 and 0.74; Pint=0.93).2 The aims of this study were to assess: i) the impact of afatinib on central nervous system (CNS) progression or metastatic spread in LUX-Lung 3, 6, and 7; ii) efficacy of afatinib in patients with brain metastases in a similar setting to 'real-world' practice. **Method:** Competing risk analysis of CNS/non-CNS progression or death was performed in patients who received afatinib in LUX-Lung 3, 6, and 7, based on the cumulative frequency of the event of interest versus the competing risk event. Separate analysis was performed of an Asian phase IIIb study, which assessed afatinib in a broad population of EGFR TKI-naïve patients with *EGFR*m+ NSCLC (NCT01953913).3 PFS and time-to-symptomatic progression (TTSP) in patients with baseline brain metastases were calculated by Kaplan–Meier methodology. **Result:** In patients with baseline brain metastases receiving afatinib in LUX-Lung 3 and 6 (n=48; median follow-up: 10.3 months), the risk of CNS progression was 40% lower than the risk of extracranial progression; 31.3%/52.1% of patients had CNS/non-CNS progression, respectively. In patients without baseline brain metastases receiving afatinib in LUX-Lung 3, 6, and 7 (n=485; median follow-up: 13.0 months), the risk of *de novo* CNS/non-CNS progression was 6.4%/78.4%. Cumulative risk of CNS/non-CNS progression was 1.3%/17.2% at 6 months and 2.6%/41.2% at 12 months. In the Asian phase IIIb study, there was no difference in PFS (median 10.9 vs 12.4 months; P=0.18) or TTSP (median 14.8 vs 15.4 months; P=1.0) between patients with (n=92) or without (n=387) brain metastases. **Conclusion:** Competing risk analyses of LUX-Lung 3, 6, and 7 suggest that afatinib delays the onset/progression of brain metastases. Real-world data are consistent with LUX-Lung 3, 6, and 7, and support the use of afatinib in patients with EGFRm+ NSCLC and baseline brain metastases. 1. Schuler, M. et al. J Thorac Oncol 2016;11:380-90 2. Park, K. et al. Lancet Oncol 2016;17:577-89 3. Wu YL, et al. J Thorac Oncol 2017;12(suppl 2):abstract P3.01-036

Keywords: central nervous system, EGFR mutation, Afatinib

P2.14-61 ACQUIRED RESISTANCE TO ENTRECTINIB ASSOCIATED WITH ACTIVATION OF RAS SIGNALING PATHWAY IN ROS1-REARRANGED NON-SMALL CELL LUNG CANCER

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Background: ROS1 is a receptor tyrosine kinase (RTK) that is not usually expressed at high levels in normal lung tissue. The wild-type function of ROS1 is unknown, and a natural ligand has not been identified. *ROS1* gene rearrangements occur in ~1-2% of patients with NSCLC, and have also been identified in colorectal, gastric and ovarian cancers, glioblastoma and cholangiocarcinoma. *ROS1* rearrangements with oncogenic potential have been found to constitutively activate ROS1 signaling, and although it remains unclear exactly how the ROS1 fusion proteins are activated, the PI3K/AKT, MAPK/ERK and JAK/STAT3 pathways are known to be involved. Thus, *ROS1*-rearranged NSCLCs are 'addicted' to ROS1 for cell growth and survival. Knocking down or pharmacologically inhibiting ROS1 has been reported to inhibit growth or induce

apoptosis in *ROS1*-rearranged cell lines. Entrectinib is a pan-tyrosine-kinase inhibitor that targets oncogenic rearrangements in *NTRK*, *ROS1* and *ALK*. The combined results of two clinical trials demonstrated the efficacy of entrectinib in *ROS1*-rearranged NSCLC. Because the development of drug resistance is inevitable, it would be helpful to determine the mechanisms of entrectinib resistance in a *ROS1*-rearranged tumor model so that future therapeutic strategies can be developed. **Method:** To investigate the effects of entrectinib on *ROS1*-rearranged NSCLC, we used HCC78 cells harboring an *SLC34A2-ROS1* fusion. Entrectinib-resistant HCC78 (HCC78ER) cells were newly established in our laboratory through the exposure of HCC78 cells to gradually increasing concentrations of entrectinib (starting at 100 nM and ending with 5 μM) over 6 months. **Result:** Here, we characterized the molecular basis of resistance in entrectinib-resistant *ROS1*-rearranged HCC78 cells (HCC78ER cells). These cells were analyzed by next-generation sequencing and genetic profiling, which revealed the acquisition of *KRAS* G12C and the amplification of *KRAS* and *FGF3*. However, there were no secondary mutations in the ROS1 kinase domain. We also found that sustained ERK activation was involved in entrectinib resistance, and that combined treatment with selumetinib resensitized HCC78ER cells to entrectinib in cell viability and colony formation assays. **Conclusion:** Our data suggest that activation of the RAS signaling pathway can cause entrectinib resistance in *ROS1*-rearranged NSCLC, and is unlikely to be overcome by sequential single agent ROS1-targeting strategies against such tumors. Instead, co-targeting ROS1 and MEK may be an effective strategy for overcoming entrectinib resistance in *ROS1*-rearranged NSCLC.

Keywords: ROS1, Non-Small Cell Lung Cancer, Entrectinib

P2.14-62 EARLY, SUBCLINICAL SCLC TRANSFORMATION IN PATIENTS WITH EGFR MUTANT LUNG CANCER RECEIVING OSIMERTINIB, DETECTED THROUGH CELL-FREE DNA

E. Stewart[1], S. Martins-Filho[1], M. Cabanero[1], A. Wang[2], J. Huang[2], H. Bao[2], X. Wu[2], D. Patel[1], Z. Chen[1], J. Law[1], P. Bradbury[1], F. Shepherd[1], N. Leighl[1], M. Tsao[1], T. Pugh[1], S. Bratman[1], G. Liu[1], A. Sacher[1]

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Background: Liquid biopsies provide a convenient approachfor serial sampling and real-time disease monitoring, leading to the early detection of treatment response, disease progression and drug-resistance. Here,we present genomic profiling of serial liquid biopsies from seven lung cancer patients with activating*EGFR*mutations receiving osimertinib in clinical practice. **Method:** At Princess Margaret Cancer Centre, in the Lung Cancer Outpatient Clinics, plasma samples were obtained from each patient at defined clinical visits (between ~1–5 months in-between visits). Cell-free DNA (cfDNA; with a median of 57 ng; range: 3.5 to 3806 ng) was extracted from plasma samples and profiled using targeted capture next-generation sequencing with the Geneseeq Prime 425-gene panel, at a mean coverage depth of 4892X (with a deduplicated mean coverage depth of 2108X). **Result:** Systemic tumour burden correlated with the detection of genomic alterations in cfDNA: Four of four of the patients with low tumour burden, despite minor disease progression, exhibited minimal EGFR and co-mutation allele frequencies (AFs). Conversely, significant increases in systemic (but not central nervous system) tumour burden led to increases in driver and co-mutation AFs (two our of three patients). EGFR C797S mutation and inactivating mutations in RB1 and TP53 were detected in the cfDNA of one patient nearly four months prior to the development of small cell lung cancer (SCLC) transformation confirmed on tissue biopsy with distinct transformed and untransformed areas. Both of the specific RB1 and TP53 mutations found in cfDNA have been previously associated with SCLC. Subsequent combination cisplatin-etoposide chemoradiation resulted in temporary complete remission of the transformed SCLC, corresponding to loss of RB1 mutation detection by cfDNA testing. **Conclusion:** Profiling of plasma cfDNA using hybrid capture deep sequencing of a large gene panel can detect early subclinical transformation of *EGFR*-mutated lung cancer into small cell lung cancer (i.e., neuroendocrine transformation), leading to earlier diagnosis and management of the transformed disease. Serial liquid biopsy profiling can also be used to monitor disease progression. However, detection sensitivity of tumour cfDNA largely depends on systemic tumour burden.

P2.14-63 COST ANALYSIS OF THE MANAGEMENT OF CNS METASTASES IN PATIENTS WITH ADVANCED ALK+ NSCLC: ALECTINIB VS CRIZOTINIB

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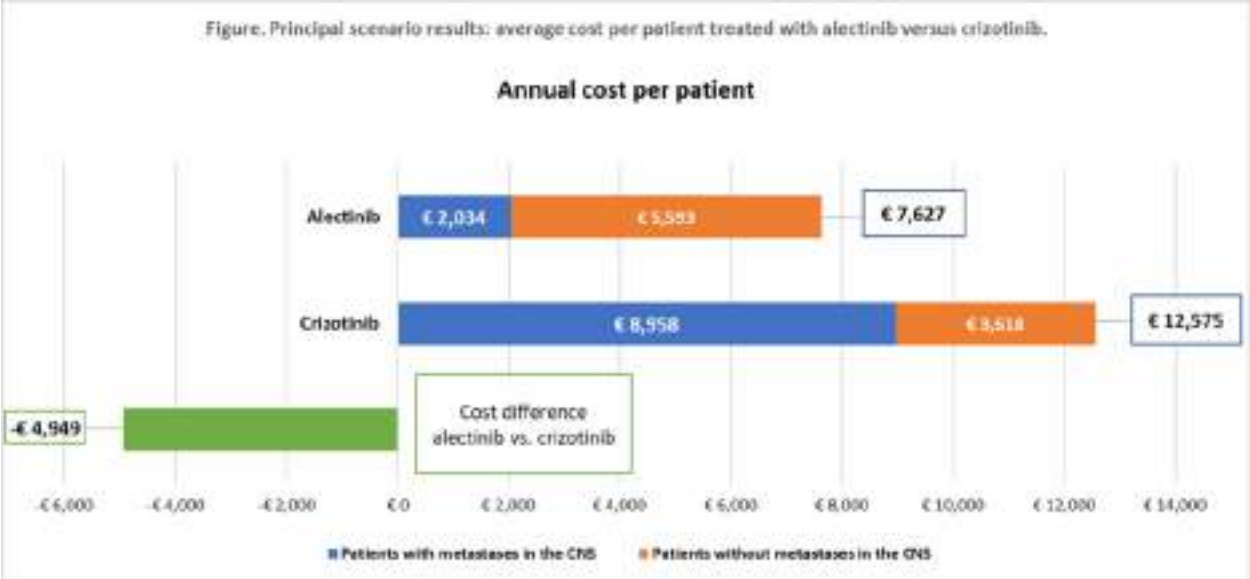
Background: The high prevalence of CNS metastases in ALK+ NSCLC leads to a significant clinical and economic burden. Alectinib demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in untreated patients. Therefore, alectinib could reduce the brain metastasis-related healthcare resource utilization and costs. The objective is to estimate the cost associated with the management of patients with advanced ALK+ NSCLC with and without CNS metastases, and to perform an analysis of the annual cost comparing patients treated with alectinib or crizotinib. **Method:** Using the disaggregated consumption of resources provided by a panel of expert oncologists, the cost/year of the management of patients with ALK+ NSCLC with/without development of CNS metastases was estimated. The cost of management (€,2018) included the quantification of medical visits, hospitalisations, diagnostic and laboratory tests, imaging techniques and radiotherapy procedures. The unit costs of the resources were obtained from eSalud (Spanish database). Using the 12-month cumulative incidence rate of CNS metastases in the ALEX trial for alectinib (9.4%) and crizotinib (41.4%), the annual cost of management with each therapy was estimated and compared. An alternative analysis was performed considering the management of adverse events (AE) observed in the ALEX trial, with costs obtained from the literature. **Result:** The cost/year of managing NSCLC was €6,173.42/patient without CNS metastases and €21,637.50/patient with CNS metastases. In patients treated with alectinib, the average cost per patient was lower than in patients with crizotinib (-€4,948.51 patient/year) in the Spanish healthcare setting. Considering the cost of AE, the average cost/year difference would be -€5,044.26/patient treated with alectinib vs crizotinib.



Conclusion: The delay in the appearance of CNS metastases associated with the treatment of alectinib vs crizotinib may result in a reduction in cost per year in the management of ALK+ NSCLC. Comprehensive approach of cost analysis should be adjusted to each disease characteristics.

P2.14-64 IS ALK INHIBITOR A CONTRAINDICATION FOR SUBSEQUENT IVF PREGNANCY?

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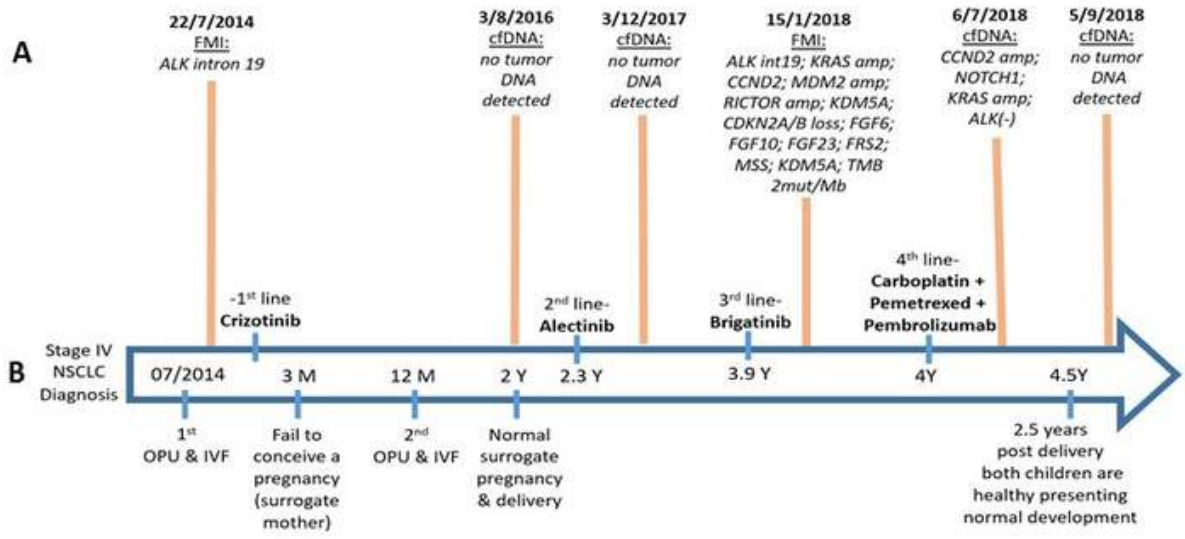
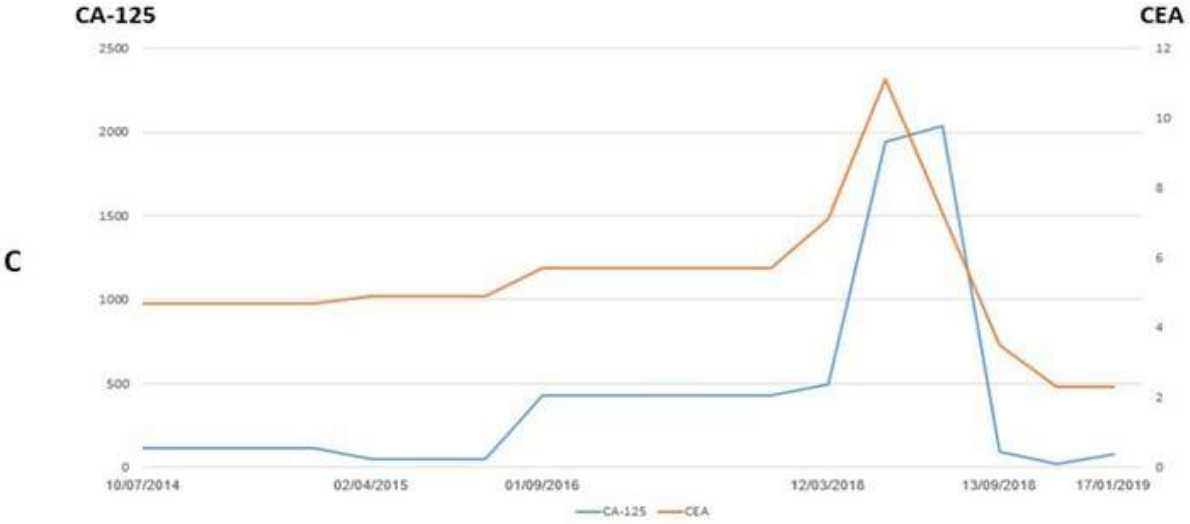
Background: Anaplastic lymphoma kinase (ALK) inhibitors drugs, such as crizotininb, are currently at the focus of treatment for ALK positive metastatic non-small cell lung cancer. Although the FDA statement that crizotinib may be detrimental to fetus development, there is no direct prohibition against the use of crizotinib during pregnancy, neither comment regarding its consumption under assisted reproductive pregnancy. Here we report, for the first time, a normal development of twins that their oocytes were aspirated while undergoing Crizotinib therapy. Furthermore, we discuss some ethical issues raises from this report. Our report along with the rapidly improvement of the ALK inhibitors therapies, raises ethical issues such as, the debate around the right for parenthood while having a progressive uncurable disease and the right for proceeding an assistant reproductive therapy while treated with biological therapies.



Method: "Section not applicable" - I am submitting a case report



Result: "Section not applicable" - I am submitting a case report
Conclusion: "Section not applicable" - I am submitting a case report

Keywords: ALK Positive lung cancer, Tyrosine Kinase inhibitors, *In vitro* fertilization

P2.14-65 EFFICACY OF DABRAFENIB PLUS TRAMETINIB COMBINATION IN PATIENTS WITH BRAF V600E–MUTANT NSCLC IN REAL WORLD SETTING

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Background: Dabrafenib plus trametinib (D-T) combination is approved in Europe Union for *BRAF*V600E–mutant metastatic non-small cell lung cancer(NSCLC) but there is few published data's on this efficacy and tolerance outside clinical trail results. Objective: to assess efficacy and tolerance of D-T in real world setting. **Method:** Retrospective, multicentric study including *BRAF* V600E-positive advanced NSCLC receiving D-T outside a clinical trial. Overall survival (OS) and progression free survival (PFS) were analyzed in all population and according lines of D-T treatment (first line treatment or subsequent line treatments). **Result:** the analysis included 40 BRAF V600E advanced NSCLC patients managed in 14 centers; at diagnosis: mean age 71 ±9.6 years, female 55 %, adenocarcinoma 95 %, currents/formers smokers 17.5%/50 %, At D-T initiation: PS 0-1/2 or+: 86.8%/13.2%, loss weight> 5%: 24%, symptomatic disease: 92%, stage IV: 95%, mean metastatic site: 2.3 (main metastatic sites: pleura: 46%, bone: 33%, respectively).Mean line of treatment before D-T: 1.5. D-T was a first line treatment in 22.5 %, second line or more 77.5% (25% received one BRAF TKI before). Median time between diagnosis and D-T treatment was 0.7 [95%CI: 0.2-1.3] months in first line setting and 17.3 [95%CI: 10.8-27.2] months. At the time of analysis 67.5% patients were in treatment with D-T and median follow up since beginning of D-T treatment was 8.7[95%CI: 5-12] months in whole population [7,5, 95%CI: 1-12.3]months for patients treated in first line). D-T dose was modified for 32.5.0% of the patients and definitively discontinued for 12,5 % because of severe adverse events. Median PFS and OS were not reach and follow up is continued. The mature results of PFS and OS (whole population and subgroups) will be showed to the WLCC meeting. **Conclusion:** Section not applicable

Keywords: braf, Dabrafenib, trametinib

P2.14-66 COMBINATION ALK AND MEK INHIBITION IN ALK-POSITIVE LUNG CANCER

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University of Otago, Dunedin/New Zealand

Background: ALK positive lung cancer can be treated with ALK inhibitors, but resistance typically develops within 1 or 2 years. One strategy to overcome drug resistance is combination therapy. In particular, MEK has been suggested as a target for combination therapy with ALK inhibitors. We investigated this hypothesis with *in vitro* and in vivo experiments. **Method:** Human lung adenocarcinoma cells harbouring the ELM4-ALK rearrangement (H3122) we exposed to varying concentrations of the ALK inhibitor crizotinib, and the MEK inhibitor selumetinib, and cytotoxicity assayed using the SRB assay. Cell cycle, apoptosis, and Western blot assays were used to further investigate mechanisms of co-action. Balb/c mice were then dosed with crizotinib (5 or 25mg/kg, po) and/or selumetib (25 mg/kg, po) for 14 days and toxicity assessed. Nude mice were then injected with H3122 cells to produce a flank tumour, and the effects of treatment with crizotinib (25 mg/kg, po) and/or selumetinib (25 mg/kg, po) ascertained. **Result:** Combination crizotinib and selumetinib killed both crizotinib naieve and crizotininb resistant H3122 cells in a synergistic manner. The combination treatment caused a small increase in apoptosis, and a large decrease in cells in S phase. Western blot showed strong combination effects on suppression of phoshpo-ERK, and cyclin DI, and upregulation of BIM. No toxicity for liver or kidney function was detected with 25 mg/kg crizotinib and selumetinib. In xenograft experiments, the combination suppressed tumour growth to a greater extent than either drug alone. **Conclusion:** This work has successfully replicated recent findings for combination ALK and MEK inhibition in ALK lung cancer experiments, but using different specific drugs than previously. The drugs were were well tolerated in combination. Cell based experiments shed further light on mechanisms of action for this drug combination, and revealed two further druggable targets: BIM and CDK1.

Keyword: ALK, MEK, crizotinib, selumetinib

P2.14-67 METASTATIC RET-REARRANGED LUNG ADENOCARCINOMAS TREATED WITH ALECTINIB: RETROSPECTIVE ANALYSIS OF A SINGLE INSTITUTION

M. Ribeiro, A. Gongora, L. Oliveira, J.V. Alessi, K. Saccardo, B. Zucchetti, F. Barbosa, D. Muniz, A. Shimada, C. De Souza, O. Feher, A. Katz

Hospital Sírio-Libanês, Sao Paulo/Brazil

Background: RET-rearrangements are well-described drivers in lung adenocarcinomas (LADC), identified in nearly 1-2% of the tumors, for which there are no current specific targeted therapies approved. Although several tyrosine-kinase inhibitors (TKI) (e.g vandetanib, cabozantinib, lenvatinib, etc) demonstrate anti-RET activity, poor tolerability and overall response rates less than 50% has been limiting its widespread adoption. The structural homology between the kinase domains of ALK and RET, as well as the documented *in vitro*activity, and well-known toxicity profile makes alectinib an attractive drug for evaluation in clinical trials and, possibly, for off-label use in the setting of progression upon pemetrexed-based chemotherapy. **Method:** Retrospective assessment of the clinical and molecular characteristics, drug efficacy and tolerability of RET-rearranged LADC patients treated with alectinib in a single institution. **Result:** Among the four patients identified, 100% were white, female and non-smokers, between 59-66 years old; 2/4 presented with high carcinoembryonic antigen levels and 1/4 with poorly differentiated LADC. All patients were TKI naïve and underwent evaluation with FoundationOne® next-generation sequencing platform, which showed *KIF5B-RET*fusion in 3/4 (75%) and *CCDC6-RET*in 1/4 (25%) of the cases. Among other alterations shared, 3/4 (75%) presented with *CDKN2A/B*loss; in all cases, the tumors were microssatelite stable (MSS) and had low tumor mutational burden (1-9 muts/Mb). All patients were treated with 600 mg bid of alectinib. Among the four patients assessed, one was not available for radiological response evaluation and the drug was withheld within two months of treatment due to clinical deterioration. The best ORR was partial response in 2/4 (50%), with PFS ranging from 4-5 months. In one patient, after 5 months of therapy, an asymptomatic oligoprogression in soft-tissue was observed; the patient was treated with local radiation therapy and remains on alectinib for 12 months. No grade 3/4 adverse events, dose reductions or discontinuation due to toxicity were observed. **Conclusion:** Although this is a small single center evaluation, alectinib demonstrated clinical activity in RET-rearranged LADC, apart from being a well-tolerated treatment. Nevertheless, the concurrent molecular alterations, its prognostic significance, the ideal dosing regimen and the precise magnitude of benefit are all questions to be addressed in clinical trials, in order to consider alectinib a treatment option for this small subset of patients.

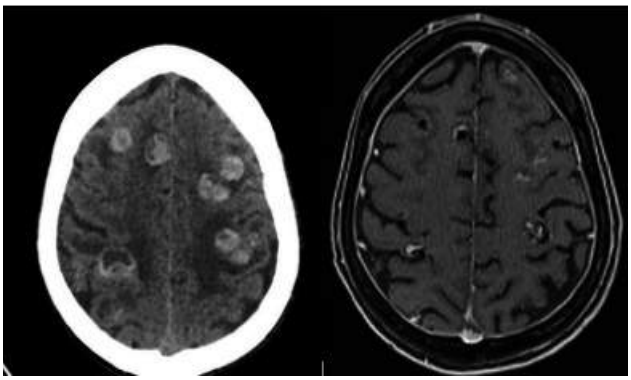
Keywords: alectinib, RET-rearranged

P2.14-68 DRAMATICAL INTRACRANIAL RESPONSE TO OSIMERTINIB IN PATIENT HARBOURING THE UNCOMMUM EGFR G719S/L861Q MUTATION

J.V. Alessi, M. Ribeiro, A. Katz

Hospital Sírio-Libanês, Sao Paulo/Brazil

Background: Almost 10% of EGFR mutations are represented by uncommom mutations, which represents a heterogenous group of rare molecular alterations, where the presence of co-mutations are even more rarely seen. Third generation shows efficacy and safety in these patients (Pt). **Method:** We hereby report a case of dramatic intracranial response to osimertinib in a poor performance status Pt with lung cancer harbouring the uncommom epidermal growth factor receptor (EGFR) co-mutations encoded in exon 18 (G719S) and exon 21 (L861Q). The Pt was a 76-year-old male, smoker (60 packs-year), who visited our hospital with a prior history of 2-weeks mental confusion and seizures. Computed tomography detected several brain lesions with moderate edema, as well as lung, cervical and mediastinal lymphadenopathy, liver, adrenal and bone lesions. A biopsy specimen obtained from his cervical adenopaHty suggested primary stage IVB lung cancer with sarcomatoid differentiation (T2a N2 M1c) and PDL-1 expression of 10%. A MRI-brain was not performed due to the Pt altered mental status and also because his condition prevent the use of sedation. Due to the dramatic nature of the case and a very poor clinical condition, systemic treatment with carboplatin, paclitaxel and pembrolizumab was started while we waited for the results of NGS. There was no clinical evidence of response to this treatment. Just prior to the schedule day of the second cycle of chemotherapy we had access to the NGS result, which disclosed the presence of EGFR G719S (allele frequency of 49.7%) and L861Q (allele frequency of 50.8%). **Result:** Based on recent reported data we started osimertinib 80mg/day. He had unequivocal clinical improvement over the following weeks with relieve of neurologic symptoms. After 42 days of treatment restaging PET-CT demonstrated complete response and brain MRI with remarkable response. Osimertinib has been well-tolerated for the Pt. Before and after 6w of osimertinib



Conclusion: This case report corroborates the promising activity of osimertinib in uncommom EGFR mutation. We have described the first case showing dramatic cranial response in these rare EGFR co-mutations.

Keywords: Osimertinib, EGFR G719S/L861Q

P2.14-69 LORLATINIB RESCUE THERAPY FOR LIFE THREATENING CNS DISEASE IN CRIZOTINIB-RESISTANT ROS1-POSITIVE NON–SMALL CELL LUNG CANCER (NSCLC)

A. Franke, V. Nair, M. Shafique, S. Mokhtari

Moffitt Cancer Center, Tampa/United States of America

Background: C-ros proto-oncogene-1 (*ROS1)* chromosomal translocations result in constitutively activated receptor tyrosine kinase in 1-2% of NSCLC. Although crizotinib, a first-generation Tyrosine Kinase Inhibitor (TKI) of Anaplastic Lymphoma Kinase (ALK) and *ROS1* translocations, has demonstrated efficacy in treatment of *ROS1* NSCLC, patients invariably acquire resistance mutations, with a high incidence of brain metastasis at relapse owing to poor CNS drug penetration. Lorlatinib is a novel, third-generation TKI with improved CNS penetration and preclinical activity against crizotinib-resistance mutations, which recently demonstrated efficacy in a phase I/II trial. We report a patient who developed secondary crizotinib-resistance and was successfully treated with lorlatinib. **Method:** A 73-year-old, female, never-smoker with recently diagnosed stage-IV *ROS1*-rearranged NSCLC presented with refractory seizures and coma. The patient was on first-line treatment with crizotinib for 6-months, with an excellent systemic response at 2 months. Brain MRI after presentation demonstrated multiple intracranial metastasis with vasogenic edema (Fig.1A). Neurologic status was unchanged despite mannitol, steroids and anti-epileptics. **Result:** As salvage therapy, the patient received bevacizumab for vasogenic edema and lorlatinib (100mg/daily). After 48-hours, substantial clinical improvement in neurologic function and mental status was observed. A repeat MRI (D+4) demonstrated a slight interval decrease in the largest metastasis and associated edema. At 1-month follow-up, the patient continued to improve clinically with no evidence of lorlatinib toxicity. Brain MRI showed a decrease in the sizes and/or resolution of all previously noted lesions and no new metastases or significant peritumoral edema (Fig.1B).

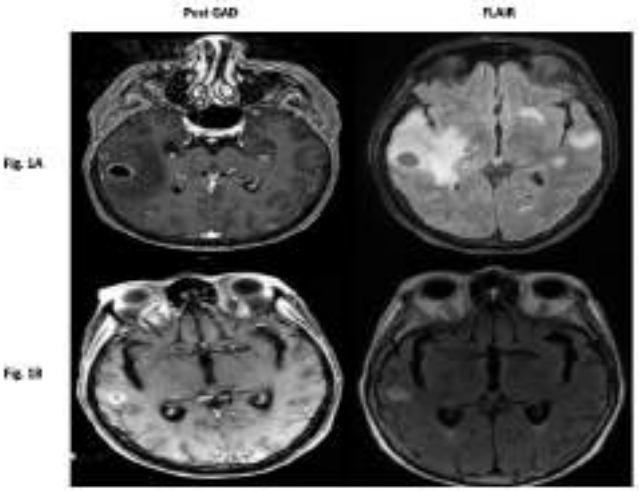


Figure 1. Brain magnetic resonance imaging, pre-treatment baseline post GAD an FLAIR sequences are shown **(Fig.1A)**, followed by near complete resolution of two posterior fossa lesions and associated edema, and significant reduction in tumor volume of a right lateral temporal lobe lesion after 1 month of loralatinib therapy **(Fig.1B)**

Conclusion: Since clinical trials typically exclude patients with symptomatic, untreated CNS disease, efficacy of newer, targeted agents in mutated-NSCLC is unclear. Here we report on a patient with life threatening, acute neurologic deterioration who derived a meaningful clinical reduction in CNS lesions at 1 month, with favorable CNS response at 2 months. In addition, we observed early evidence of tumor regression on MRI after 4 days of lorlatinib therapy. Of note, her rapid clinical response may have in part been attributable to the addition of bevacizumab. Another important consideration for our patient is that she avoided whole-brain radiation in the acute setting, and its potential adverse sequalae. We note a limitation was the absence of available testing for secondary resistance mutations that developed in this patient, which was highly susceptible to lorlatinib. However, current clinical guidelines (NCCN) do not specifically recommend resistance mutation testing upon progression, and outside of a clinical trial, the current algorithm supports lorlatinib as the agent of choice post-crizotinib failure.

Keywords: brain metastasis, ROS1, Non-Small Cell Lung Cancer

P2.15 THYMOMA/OTHER THORACIC MALIGNANCIES MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.15-01 SURGICAL RESECTION OF 61 CASES OF INFLAMMATORY MYOFIBROBLASTIC TUMOR OF THE LUNG

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Background: Inflammatory myofibroblastic tumor (IMT) of the lung is rare soft tissue tumor, with low malignant potential. Here we report 61 cases of surgically resected IMT of the lung. **Method:** Surgically resected IMT of the lung, during the period of September 2004 to July 2010 were retrospectively studied. Of the 61 patients, 40 were male (65.6%), 21 female (34.4%); aged 34 to 77 years old (middle age 55). The symptoms included cough in 32 cases (52.5%), bloody sputum 19 (31.1%), sputum 14 (23.0%), fever 13 (21.3%), chest pain 10 (16.4%), hemoptysis 8 (13.1%), shortness of breath 6 (9.8%), shoulder pain 2 (3.2%), sore throat 1 (1.6%), and asymptomatic 9 (14.8%). Chest CT showed 50 cases (81.2%) were round-ball-like pulmonary nodules, most with smooth and clear borders, while speculated 18 (29.5%), lobulated 13 (21.3%), cavity or vacuole sign 12 (19.7%), calcification 7 (11.5%), pleural indentation 6 (9.8%), and vessel convergence 1 (1.6%). Fibrobronchonscopy was performed in 13 cases but no malignant evidence obtained. CT guided fine-needle biopsy was refused by the patients, and surgical resection was requested. **Result:** Wedge resection was performed in 29 cases (47.5%), and lobectomy in 27 cases (44.3%) (lymph node dissection was performed in 6 suspected cases), segmentomy 5 cases (8.2%). Frozen pathological diagnosis were performed in 59 cases (96.7%), IMT was diagnosed in 38 cases (64.4%) (with alveolar epithelial dysplasia in 14 cases), inflammation or benign disease in 18 cases (30.5%), granulomatous inflammation in 2 cases (3.4%), and malignant in 1 case (1.7%). All patients recovered smoothly except one case received second thoracotomy on the day of surgery due to postoperative hemothorax; no other serious complications happened; all cases were discharged on about the 10th day postoperatively as usual. IMT was confirmed in all these 61 surgical resected cases by the postoperative pathological diagnosis. Follow-up showed all patients recovered well, and no recurrence and metastasis found. **Conclusion:** IMT of the lung has no specific symptoms, lacks specific CT imaging characteristic to distinguish from lung cancer. Surgical resection is of first choice for treatment of IMT of the lung, with no recurrence and metastasis found; wedge resection is recommended; lobectomy and lymph node dissection may be reasonable and necessary for certain suspected cases. Surgical resected IMT of the lung has a good prognosis according to our limited cases and short-time observations. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05, 17-230-9-71)

Keywords: lung neoplasm, Inflammatory myofibroblastic tumor, surgical resection

P2.15-02 PRIMARY SALIVARY GLAND-TYPE LUNG TUMOURS, SURGICALLY TREATABLE RARE ENTITY LUNG CANCER: A SIXTEEN-YEAR EXPERIENCE OF A SINGLE CENTRE

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Background: Primary salivary gland-type lung tumours (PSGT) are uncommon entity, representing 0.09% of overall lung cancer. Due to their rarity, this category of malignancies remain incompletely understood and the role of surgery is poorly known. The primary endpoint of this study was to analyse the impact of surgical treatment on outcome for PSGT lung cancer **Method:** A retrospectively analysis of patients who underwent a surgical treatment for PSGT tumours between January 2001 and January 2017 in a single centre was conducted. Overall survival (OS), disease free survival (DFS) and medical records (for age, sex, clinical conditions, location, surgical treatment, histopathology and tumour grade) were analysed **Result:** Out of a total of 30 PSGT lung tumours, 26 patients (15 female, 11 male) with an average age of 58.1±12.7 years underwent surgical resection with curative intent. Four patients were excluded from this study because of metastatic disease (2) or unresectable masses that underwent only palliative endoscopic treatment (2). Adenoid cystic carcinoma was diagnosed in 14 patients, mucoepidermoid carcinoma in 10 patients, and epithelial-myoepithelial carcinoma in 2 patients. Fourteen patients (54%) were current/former smoker. Twelve tumours originated from main bronchus/trachea, 14 from lobar/sublobar bronchus. The surgical procedure included lobectomy (n = 9, 34.6 %), sub-lobar resection (n=5, 19.2%), tracheal resection (n = 4, 15.4%), pneumonectomy (n = 3, 11.5%), sleeve lobectomy (n = 4, 15.4%), and carinal resection (n = 1, 3.8%). No operative mortality or major complications were reported; minor complications (e.g. air leaking, arrhythmias) occurred in five patients (19.2%). Mean dimension of tumours was 3.67±3.24 cm. Three patients underwent adjuvant therapies (2 radiotherapy, 1 chemotherapy). Cancer recurred in 11 patients (42.3%): 3 were surgically treated, 3 underwent chemotherapy, 1 radiotherapy and 4 combined radio-chemotherapy. With a median follow-up of 70 months, the overall survival was 68.8 months and the disease free survival was 56.8 months. The 5-year OS and DFS were 92% and 68% respectively. Adenoid cystic carcinoma was the most favourable subtype with a median OS of 90 months. Only three cancer-related dead occurred **Conclusion:** Surgical resection of primary salivary gland-type lung cancer is an effective treatment even in case of large tumours that required extended resections. The long-term survival and the DFS after surgical resection are encouraging and redo surgical procedure with a curative intent can be performed in case of local recurrences

P2.15-03 TROPOMYOSIN-RELATED KINASE B CAN BE A BIOMARKER OF PROGNOSIS AND THERAPEUTIC TARGET FOR MALIGNANT THYMIC EPITHELIAL TUMORS

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Background: Thymic epithelial tumors (TETs), mainly thymoma and thymic cancer are most common tumors arise in mediastinum. Histologically, thymoma is divided into Type A, AB, B1, B2 and B3. Clinically, TETs are divided into two groups, benign TETs (bTETs) as Type A, AB, B1 thymoma and malignant TETs (mTETs) as Type B2, B3 thymoma and thymic cancer. Complete surgical resection is vital for the management of TETs, and adjuvant therapy play important roles in the management of recurrent or metastasized cases. But there remains a lack of standard treatment after failure of adjuvant therapy. Development of molecular target therapies for advanced mTETs is a present issue. Tropomyosin receptor kinase (Trk) family is one of tyrosine kinase receptors consists of TrkA, TrkB and TrkC. Among them,TrkB have oncogenic factors in various cancers. **Method:** Patients and case selection We analyzed 48 TETs (43 thymomas and 5 thymic cancers) patients who received curative surgical resection. We divided into two groups due to Masaoka-Koga stage (StageI and II as early stage and StageIII and IV as advanced). Immunohistochemistry Immunohistochemical staining was performed using tissue sections and primary antibodies, TrkA, TrkB and TrkC. We evaluated the immunoreactive cells by Allred score. Anchorage-dependent cell proliferation assay Proliferation assay was performed by using Trk inhibitor K252a, recombinant human BDNF (ligand of TrkB) and siRNA (Control-siRNA, TrkB-siRNA, and BDNF-siRNA). **Result:** Trk expression in TETs. Early stage were 37 cases (77%) and advanced stage were 11 cases (22%). Benign TETs (bTETs) were 29 cases (60%) and malignant TETs (mTETs) were 19 cases (39%). The high expression of TrkA was observed in 5 cases (10%) and TrkB was 7 cases (14%). TrkC expression was not observed in 48 cases (0%). Among the TrkB-high, all the 5 thymic cancer cases indicated TrkB-high expression and remaining two cases were type B2 and type B3 thymoma. The TrkB-high type B2 thymoma was recurrent case. TrkB-high cases showed poor prognosis. Advanced showed significantly higher expression of TrkB than those with early cases (P<0.0001). TrkA and TrkC expression was no correlation with stage (TrkA: P=0.5163, TrkC:-). Cases with TrkB-high expression were significantly more in mTETs than in bTETs (P=0.0004). TrkA-high expression were no correlation with malignancy (P=0.9839). TrkB-high expression cases were significantly shorter overall survival periods (P=0.0482), compared to TrkB-low expression cases. There was no significant correlation between TrkA expression and survival periods (P=0.1484) The BDNF/TrkB signaling involve in proliferation ability of thymic cancer cell Tymic cancer cell, transfected with BDNF-siRNA or TrkB-siRNA showed significantly lower level of proliferation than with Control-siRNA, while administrating rhBDNF to the cell transfected with TrkB-siRNA showed no rising level of proliferation. These indicated knocking down of BDNF or TrkB suppressed proliferation. Cell incubated with rhBDNF showed significantly higher levels of proliferation than without rhBDNF. Administration of K252a and rhBDNF resulted in lower level of proliferation than without administration of K252a. These indicated proliferation was enhanced by rhBDNF and it was abrogated by Trk inhibitor K252a. **Conclusion:** TrkB expression is a biomarker of prognosis and BDNF/TrkB signaling pathway can be a therapeutic target for mslignsnt thymic epithelial tumors.

Keywords: thymic epithelial tumors, TrkB, therapeutic target

P2.15-04 IMPACT OF PROGNOSTIC NUTRITIONAL INDEX ON LONG-TERM OUTCOMES AFTER SURGERY FOR PULMONARY METASTASIS FROM COLORECTAL CANCER

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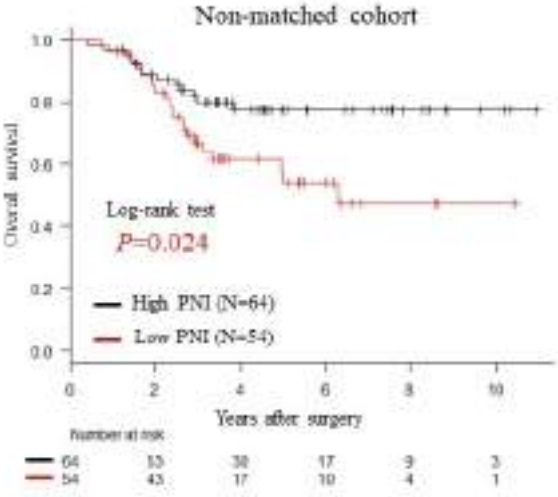
Background: A prognostic nutritional index (PNI), calculated using serum albumin levels and peripheral lymphocyte counts, has been reported as a predictor of prognosis of various cancers. The aim of this study was to investigate the impact of a PNI on postoperative prognosis of lung resection for pulmonary metastasis from colorectal cancer. **Method:** Retrospective review of patients who underwent curative surgical resection for pulmonary metastasis from colorectal cancer (01/2008-12/2015). Exclusion criteria: missing data. Preoperative serum albumin (Alb) and peripheral lymphocyte counts were measured within 1 month just before the initial lung surgery. We calculated PNI as follows: PNI = serum albumin levels (g/dl) × 10 + total lymphocyte count (per mm3) × 0.005. We used the median value as the optimal cut-off value for PNI (47.5) and divided patients into two groups. We evaluated overall survival using propensity score matching. **Result:** A total of 158 patients underwent 187 lung resections for pulmonary metastasis in this study. One hundred eighteen patients were eligible. Low PNI was significantly associated with older age (P<0.001), wedge resection (P=0.041), open approach (P=0.045) and colon origin (P=0.041). In the non-matched analysis, overall survival was significantly better in high PNI group that low PNI group (77.5% vs 54.0% at 5 years; HR 2.21; 95% CI 1.11-4.39; P=0.024). After propensity score matching accounting for sex, age, surgical procedure, surgical approach and site of origin, there were no significant differences in background between both groups. In the matched analysis, overall survival was significantly better in high PNI group than low PNI group (78.2% vs 43.2% at 5 years; HR 3.46; 95% CI 1.33-8.96; P=0.010).

Non-matched cohort

	High PNI (N=64)	Low PNI (N=54)	p-value
Age (years)	59.5 ± 10.8	67.0 ± 11.3	<0.001
Sex (%)			
F	24 (37.5%)	27 (50.0%)	0.195
M	40 (62.5%)	27 (50.0%)	
Surgical procedure (%)			
Wedge resection	41 (64.1%)	44 (81.5%)	0.041
Others	23 (35.9%)	10 (18.5%)	
Surgical approach (%)			
VATS	55 (85.9%)	38 (70.4%)	0.045
Open	9 (14.1%)	16 (29.6%)	
Site of origin (%)			
Colon	22 (34.4%)	29 (53.7%)	0.041
Rectal	42 (65.6%)	25 (46.3%)	



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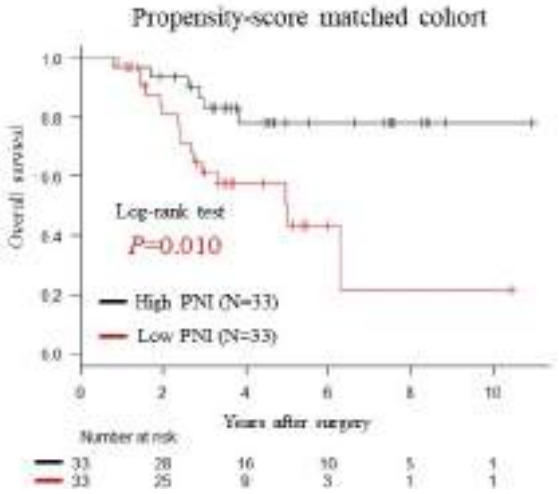
Propensity-score matched cohort

	High PNI (N=33)	Low PNI (N=33)	p-value
Age (years)	62.7± 10.6	63.6± 11.7	0.750
Sex (%)			
F	12 (36.4%)	12 (36.4%)	1.000
M	21 (63.6%)	21 (63.6%)	
Surgical procedure (%)			
Wedge resection	26 (78.8%)	25 (75.8%)	1.000
Others	7 (21.2%)	8 (24.2%)	
Surgical approach (%)			
VATS	25 (75.8%)	25 (75.8%)	1.000
Open	8 (24.2%)	8 (24.2%)	
Site of origin (%)			
Colon	15 (45.5%)	14 (42.4%)	1.000
Rectal	18 (54.5%)	19 (57.6%)	



Conclusion: Preoperative PNI may be a useful biomarker to predict postoperative prognosis of pulmonary metastasis from colorectal cancer.

Keywords: prognostic nutritional index, metastasectomy, pulmonary metastasis

P2.15-05 INVESTIGATION OF THE TRANS-SUBXIPHOID ROBOTIC THYMECTOMY

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Background: We have performed a thoracoscopic thymectomy with a trans-subxiphoid approach and have reported its usefulness. This time, we performed enlarged thymectomy by the trans-subxiphoid approach with the robotic surgery support system (da Vinci surgical system TM; da Vinci TM) and report its improved surgical technique. **Method:** The patient was placed in the supine position with 10-15 degree head-up. A 3.5 cm transverse skin incision was typically made 1-2 cm below the lower edge of the xiphoid. Through this incision, the space among the posterior surface of the sternum and bilateral mediastinal pleura was enlarged blindly with a finger. Additional two 8-mm robotic trocars were inserted to the bilateral 6th intercostal space under the guidance of a finger. Carbon dioxide (CO2) was insufflated at a pressure of 8 mmHg to get a working space to resect thymus. The whole thymus was excised for patients with thymic tumor, and simultaneous resection of surrounding adipose tissues was performed for patients with myasthenia gravis. Clinical characteristics and early surgical outcomes of the patients were collected and analyzed retrospectively. **Result:** From April 2017 until March 2019, Fifteen trans-subxiphoid robotic thymectomy were performed. The average age was 58 years, the average operation time was 238.4 minutes (176 - 452 minutes), the console time was 175.3 minutes (97 -390 minutes), the bleeding volume 13.9 g (2- 75 g), the number of surgical ports were all 3 and the resected specimen weight was 41 g (25 - 58 g). The average drainage period was 1.5 days (1 - 2 days), the postoperative hospital stay was 3.2 days (2 - 5 days), no complications were observed. The final pathologic diagnosis was 10 thymoma, 1 thymic cancer, 2 thymic cyst and 2 thymic hyperplasia. **Conclusion:** Compared with thoracoscopic thymectomy by the trans-subxiphoid approach, surgery using da Vinci TM has longer operation time and more surgical ports. However, even in the narrow space from the neck to the upper mediastinum, da Vinci TM can stably perform accurate operation. Therefore, with good manipulation, using da Vinci TM surgical system for the trans-subxiphoid thymectomy was suggested that safer thymectomy could be performed without surgeon's stress.

Keywords: Thymoma, Trans-Subxiphoid, Robotic-Thymectomy

P2.15-06 PRETREATMENT NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTS SURVIVAL IN THYMIC CARCINOMA PATIENTS

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Background: The host inflammatory response plays an important role in carcinogenesis and disease progression. It has been demonstrated that the neutrophil to lymphocyte ratio (NLR), as a marker of the systemic inflammatory response, was associated clinically meaningful outcomes in patients with a variety of cancers. The objective of this study was to evaluate its prognostic value in thymic carcinoma patients. **Method:** From February 2003 to January 2018, 516 consecutive patients with pathologically confirmed thymic carcinomas were treated at the Shanghai Chest Hospital. Clinico-pathological data were retrospectively reviewed. Survival analysis, stratified by NLR quartiles, was used to evaluate the predictive value of NLR. **Result:** The NLR level cutoff of four quartiles was 1.9, 2.6 and 3.9 in our patients. After adjusting for the factors affecting the survival (sex, age, tumor size, Masaoka-Koga stage, completeness of resection, chemotherapy and radiotherapy), NLR level less than 1.9 (NLR<25th percentile, n = 108) remained an independent significant predictor of overall survival (hazard ratio = 1.824, 95% confidence interval = 1.088-3.058, p = 0.023, Table 1). Patients with NLR level <1.9 has an advantage on 5-year overall survival (p = 0.001, Figure 1) than their counterpart.

Table 1. Multivariate Analysis for Overall and Disease-Free Survival in Patients with Thymic Carcinoma

Variable	HR (95%)	p Value[a]
Overall survival		
Sex	1.164(0.804-1.686)	0.421
Age	1.015(1.000-1.030)	0.055
Tumor size	1.115(1.050-1.184)	<0.001[b]
Masaoka-Koga stage	1.392(0.989-1.959)	0.058
Completeness of resection	1.628(1.302-2.035)	<0.001[b]
Neoadjuvant treatment	1.262(0.805-1.980)	0.311
Chemotherapy	1.799(1.022-3.168)	0.042[b]
Radiotherapy	0.710(0.408-1.236)	0.226
NLR<1.9	1.824(1.088-3.058)	0.023[b]
NLR<2.6	0.892(0.571-1.522)	0.779
NLR<3.9	1.244(0.844-1.836)	0.270
Disease-free survival		
Sex	1.055(0.810-1.373)	0.693
Age	0.999(0.989-1.010)	0.901
Tumor size	1.012 (0.967-1.060)	0.603
Masaoka-Koga stage	1.751(1.368-2.241)	<0.001[b]
Completeness of resection	1.436(1.216-1.696)	<0.001[b]
Neoadjuvant treatment	0.978(0.693-1.383)	0.905
Chemotherapy	0.999(0.712-1.402)	0.996
Radiotherapy	1.013(0.723-1.420)	0.941
NLR<1.9	1.285(0.917-1.746)	0.152
NLR<2.6	0.930(0.679-1.273)	0.651
NLR<3.9	1.036(0.732-1.465)	0.841

[a] Cox proportional hazards regression analysis. [b] Statistically significant.
CI = confidence interval; HR = hazard ratio; NLR = the neutrophil to lymphocyte ratio.

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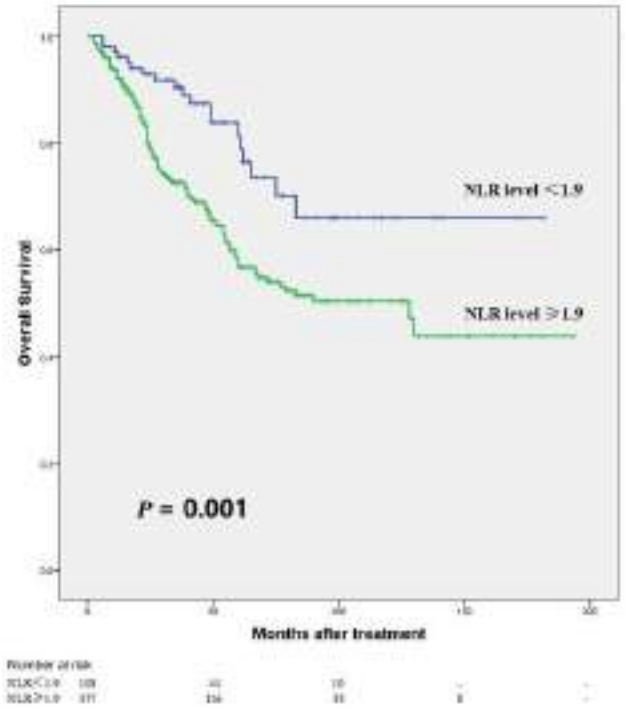

Conclusion: NLR level less than 1.9 measured before treatment is an independent marker of prognosis in thymic carcinoma patients. The NLR does have the advantage of being a routine procedure in clinical practice, feasibility and inexpensive.

Keywords: The neutrophil to lymphocyte ratio, Survival, Thymic cardinoma

P2.15-07 BIMANUAL EXAMINATION IS INDISPENSABLE IN THE SURGERY OF LUNG METASTATIC TUMORS!

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Background: Thoracic computed tomography (Th CT) is used to evaluate the surgical outcome of lung metastatic tumors. However, Th CT is often inadequate on the detection of millimetric lesions and it alone is a problematic for guiding complete resection. It is recommended for complete resection that the intraoperative bimanual palpation of the lung to be used with care and meticulously. In addition, there are studies for minimally invasive surgical methods may be an alternative to thoracotomy where bimanual evaluation is not possible. In this study, we aimed to evaluate the number of radiological and pathological metastases in patients who underwent metastasectomy with muscle conservative thoracotomy (MCT). **Method:** Between 2008 and 2018, 204 patients with metastatic lung tumors who underwent metastasectomy were included in the Department of Thoracic Surgery, Ankara University Faculty of Medicine. Preoperative Th CT imaging of all patients was evaluated in a multidisciplinary council. The relationship between the numbers of metastases detected by pathological examination of patients and the number of pulmonary nodules reported as 'metastasis' in preoperative Th CT was retrospectively analyzed. **Result:** 55% (n: 111) of the patients were F, 45% (n: 93) were M, mean age was 46.4 (13-77). %25 (n:52) of two hundred and four patients had bilateral, 3% (n: 8) of the patients had 3 and 1% (n: 4) of the patients had 4 metastasectomy with MCT due to contralateral lung metastasis or re-metastasectomy. The number of pulmonary nodules detected in Th CT was 740 (mean: 2,6), although the number of pulmonary nodules resected was 1503 (mean: 5,29). In histopathological evaluation of these nodules, 1120 (mean: 3,94) were reported as metastases. 2,03 fold of the nodules detected in Th CT were detected by bimanual intraoperative examination and 1.5 fold of nodules detected in Th CT were pathologically assessed as metastasis. Primary tumor numbers and histologies of 1120 metastatic nodules respectively; 42% (n: 475) were epithelial tumors and 58% (n: 645) were mesenchymal tumors. **Conclusion:** In this study, 740 pulmonary nodules were reported in Th CT of 204 patients. However, 763 additional pulmonary nodules were detected by bimanual palpation. 49.8% (380/763) of 763 additional pulmonary nodules were metastatic. Although minimally invasive surgery is a successful method for the surgery of many thoracic malignancies, bimanuel palpation of the lung with open surgery is still an effective method for the complete resection of pulmonary metastases. Bimanual examination is indispensable especially in the pulmonary metastasectomy of sarcomas.

Keywords: lung metastasectomy, minimally invasive surgery, lung metastasis count

P2.15-08 MULTICENTER EXPERIENCE WITH COMPLETE SURGICAL RESECTION OF PRIMARY PULMONARY ARTERY SARCOMA

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Background: Pulmonary artery sarcoma is a rare and aggressive malignancy and survival is extremely limited without surgical resection. Treatment options for surgical resection are not standardized. We sought to examine our series of complete resections and clinical outcomes over an 18 year experience. **Method:** From 1999 to 2017, we evaluated 17 patients (mean age 56 +/- 12. 9 years) with pulmonary artery sarcoma across three institutions. Fourteen (82.7%) underwent complete surgical resection. **Result:** All 14 patients underwent complete resection of the pulmonary artery sarcoma. Six patients (42.9%) had previously undergone surgical resection and were referred for recurrent disease. Seven patients (50%) underwent neoadjuvant chemotherapy or radiation. Reconstruction of the pulmonary artery trunk was performed with a pulmonary artery allograft, and reconstruction of the right or left main pulmonary artery was performed with a Dacron interposition graft. Additional endarterectomy was performed in two patients with disease extending into the PA branches. Lung resection was performed in five patients (35.8%). Total length of stay was 9.7 +/- 4.6 days including 5.3 +/- 4.2 days in the ICU. Mean survival was 2 +/- 2.8 years. Tumor histology is summarized in table 1.

Pulmonary artery sarcomas	N=17
Male gender	14 (82.65%)
Age at operation (mean ± SD)	56 ± 12.9
Operative	14/17 (82.4%)
Pre-op chemo only	4/14 (23.5%)
Pre-op XRT only	1/14 (5.9%)
Chemo & XRT	2/14 (11.8%)
Recurrent Disease	6/14 (42.9%)
Lung Resection/Pneumonectomy	5/12
ICU Length of stay (mean ± SD)	5.3 ± 4.2
Total length of stay (mean ± SD)	9.7 ± 4.6
Years alive from surgery (mean ± SD)	2 ± 2.8
Histology/Pathology	**Cases (n)**
High Grade Sarcoma	n= 5
High Grade Angiosarcoma	n= 2
Leiomyosarcoma	n= 2
High Grade Intimal Sarcoma	n= 2
High Grade Spindle Cell Sarcoma	n= 1
Pleomorphic Sarcoma	n= 1
Undifferentiated Sarcoma	n= 1

Conclusion: Surgical resection of pulmonary artery sarcomas offers improved long-term outcomes compared to non-surgical management. Complete resection and reconstruction is preferred compared to endarterectomy. Prompt and accurate diagnosis is important for optimal management.

Keywords: Cardiothoracic surgery, Cardiac tumor, Pulmonary artery sarcoma

P2.15-09 CLINICAL FEATURES AND PROGNOSIS OF PRIMARY TRACHEAL CANCER AT OUR INSTITUTION'S EXPERIENCE

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Background: Primary tracheal cancer (PTC) is rare. Although histological components of the trachea are similar to that of the lung, the reason for its low incidence is still unknown. Because of its rarity, there are no standard treatment strategies. **Method:** PTC is not clearly defined. We defined it as a primary malignant neoplasm arising from the sub vocal cord region to the bilateral main bronchi via the bifurcation. The clinical features and prognosis of patients with PTC from 1999 to 2018 at the Kanagawa Cardiovascular and Respiratory Center were analyzed. **Result:** A total of nine cases, 4 males and 5 females with the median age of 62 years (range:29-81), were included in this study. The clinical symptoms were 3 patients with a cough, 2 with expiratory noise, 2 with hemoptysis, 1 with wheezing, and 1 PTC was detected on screening computed tomography. The tumors were located at upper trachea region in 4 cases, at the lower in 4 cases, and at main right bronchus in 1 case (upper tracheal region is defined as the sub vocal cord area to the lower end of the thyroid and lower tracheal region is defined as the lower end of thyroid to the bifurcation). The histopathological types were 5 (55.6%) adenoid cystic carcinomas (ACC), 2 (22.2%) mucoepidermoid carcinomas, and 2 (22.2%) squamous cell carcinomas. Five patients (55.6%) received radical surgeries and 2 patients (22.2%) who had distant metastasis received palliative surgeries. The remaining 2 (22.2%) patients received tracheal stenting. The postoperative adjuvant therapies included 2 cases with irradiation, and 1 case with chemotherapy. The 2 tracheal stenting cases received full dose irradiation therapy (including case with concurrent chemotherapy) and the 2 cases with palliative surgery also received adjuvant irradiation and chemotherapy, respectively. The overall survival rate was 55.6% at 5 years in all cases. The ACC group tended to have a better prognosis compared to that of the non-ACC group, having the 5-year survival rate was 80.0% vs 25.0%, respectively. In the ACC group, only 1 case (20.0%) died from ACC. The overall survival rate of the radical surgery group and the non-radical group was 60.0% vs 50.0% at 5 years, respectively. **Conclusion:** We found that PTC generally had a poor prognosis. Among the different types of PTC, ACC had a better prognosis than the other histopathological types. Complete resection achieved a better prognosis, especially in ACC.

Keywords: primary tracheal cancer, PTC, adenoid cystic carcinomas

P2.15-10 CLINICAL SIGNIFICANCE OF AGE AT DIAGNOSIS AMONG PATIENTS WITH THYMIC EPITHELIAL TUMOR

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Background: Thymic epithelial tumors (TET) originate in the thymus and include thymomas and thymic carcinomas. These tumors typically occur in adults with a median age of 50, and rare in children or adolescents. Few studies focusing on the effect of age on TET have been reported to date. Whether different age groups have homogeneous clinical features and survival outcomes remains unexplored. This study aimed to compare clinicopathologic characteristics and survival outcomes in different age groups using the Surveillance, Epidemiology, and End Results (SEER) database. **Method:** Information of 4431 TET patients was retrieved from the Surveilance, Epidemiology, and End Results (SEER) database. Demographic features, clinicopathologic characteristics and survival outcomes were compared between patients diagnosed at different age groups (0-18, 19-30, 31-40, 41-50, 51-60, 61-70, 71-80, 80+). **Result:** A total of 4431 patients were analyzed. Median age was 60-year-old. Twenty-eight (0.6%) patients were aged 1-18, 178 (4.0%) were aged 19-30, 381 (8.6%) were aged 31-40, 742 (16.7%) were aged 41-50, 971 (22.0%) were aged 51-60, 1108 (25.0%) were aged 61-70, 736 (16.6%) were aged 71-80 and 287 (6.5%) were aged 81-90. Gender, race, tumor histology and treatments were similar between different age groups. The 0-18 group was associated with a higher risk of distant metastasis. Compared to patients aged above 80, the hazard ratios of cancer specific survival (CSS) for patients aged 0-18, 19-30, 31-40, 41-50, 51-60, 61-70, 71-80 were 1.079, 0.739, 0.614, 0.621, 0.633, 0.673, and 0.861, respectively. Patients in the 31-40, the 41-50, the 51-60 and the 61-70 age groups had significantly better CSS compared with the 0-18 age group or the 71-80 group or the 81-90 group. From the subgroup analysis, we found that the 19-70 group had significant better CSS and overall survival (OS) than the above 70 group (CSS: p=0.000; OS: p=0.000). Multivariate survival analysis adjusted for gender, race, stage and histology showed that age was an independent prognostic factor for CSS. **Conclusion:** Age is a strong independent prognostic factor for survival in TET. Pediatric TET has a higher risk of distant metastasis and an inferior CSS. For the adults, patients older than 70-year-old were associated with a shorter CSS.

Keywords: thymic cancer, THYMOMA, age

P2.15-11 FAVORABLE LONG TERM SURVIVAL AFTER INITIALLY PALLIATIVE RESECTION FOR A GIANT PRIMARY RIB OSTEOSARCOMA WITH SEVERE MEDIASTINAL SHIFTING

K. Sinn, E. Gschwandtner, R. Hritcu, J.M. Matilla, K. Hötzenecker, G. Lang, S. Taghavi, W. Klepetko, M.A. Hoda, T. Klikovits

Medical University of Vienna, Vienna/Austria

Background: Osteosarcoma is the most common malignancy of the bone with high morbidity and mortality. Treatment of choice is chemotherapy (CHT) followed by surgery and adjuvant CHT. Primary rib osteosarcoma is a rare disease. We present a case of a young patient with a giant primary rib osteosarcoma undergoing palliative resection. **Method:** A 29-year-old woman presented with dyspnea and pain in the left chest wall in August 2012. Computed tomography (CT) showed a large lesion destructing the 3rdleft rib with extension to the left upper lobe. Biopsy revealed an osteoplastic osteosarcoma and staging examinations showed no distant metastases (DM). **Result:** CHT by the EURAMOS-1-protocol was started but was discontinued by the patient after 1 cycle due to side effects. 1.5 years later without any treatment or follow up, the patient was re-admitted with massive thoracic pain, severity of dyspnea and in a very limited general condition. CT showed a major tumor progression with severe mediastinal shift and total atelectasis of the left lung. Due to extreme large tumor size and lack of treatment alternatives, surgery in palliative intent was performed: clamshell incision, complete resection of the tumor including chest wall reconstruction. The postoperative course was challenging but she recovered well and was discharged after several months with no evidence of disease in combined positron-emission-tomography/CT. Thereafter, the patient again refused any further treatment and checkups. 4.5 years later she presented again with local recurrence in the left chest wall and in excellent overall condition without evidence for DM. Accordingly, a re-thoracotomy, partial resection of ribs 6-9, left diaphragm and pericardium and reconstruction was performed. The postoperative course was without complications and the surgery was well-tolerated. **Conclusion:** This case report shows an unexpected favorable outcome after resection in palliative intent for a giant primary rib osteosarcoma with severe mediastinal shifting. Currently, 7 years after diagnosis, the patient is free from disease.

Keywords: osteosarcoma, chest wall

P2.15-12 EPIDEMIOLOGY OF THYMIC EPITHELIAL TUMORS: 22-YEAR EXPERIENCE FROM A SINGLE-INSTITUTION

P. Rioja, S. Lozano, R. Ruiz, M. Galvez Nino, N. Valdivieso, M. Olivera, O. Cabero, M. Guillen, A. De La Guerra, E. Amorin, C. Barrionuevo, L. Mas

Instituto Nacional de Enfermedades Neoplasicas, Lima/Peru

Background: Thymic epithelial tumors (TETs) represents a heterogeneous group of rare neoplasms that represent, however, the most common entity of the anterior mediastinum. Epidemiological data and treatment options for these neoplasms are very limited. **Method:** Retrospective study of TET diagnosed at Instituto Nacional de Enfermedades Neoplasicas (INEN) in Lima, Peru, from 1996 to 2018. Clinicopathological data was retrieved from clinical files. All cases were reviewed by a pathologist and reclassified according to the 2004 WHO classification system. Staging was performed with the Masaoka-Koga Staging System. Treatment and follow-up data were also collected. Survival curves were constructed with the Kaplan-Meier method. **Result:** 84 patients were included. Median age at diagnosis was 55 years old (range 19 to 84) and 51.8% were female. Most patients (95.2%) were in good status performance (Zubrod 0-2) and 36.5% were smokers. The histological type corresponded to thymoma (T) in 63.9% of cases (n=53) and to thymic carcinoma (TC) in 36.1% of cases. T were of type A, AB, B1, B2 and B3 in 15.8%, 19.7%, 3.2%, 3.9% and 7.9% of cases, respectively. The proportion of advanced disease (Masaoka stage III-IV) was higher in TC (89.6%) than in T (51.1%). The most common treatment modality was systemic chemotherapy for advanced disease in 37.3%. With a median follow-up of 88.4 months, median overall survival (OS) was 81.6 months for T and 12.3 months for TC (p=0.01). Survival according to different histological types is shown in table 1.

Histological type	Median OS (months)
Thymoma A, AB, B1	102
Thymoma B2 – B3	16.7
Thymic carcinoma	12.3

Conclusion: The result of this study indicates a clear association between the WHO histological classification and Masaoka-Koga staging system with survival. We found a higher than expected proportion of T with advanced disease at diagnosis. The reasons behind this finding require further research. Being this a rare disease, collaboration is very important to foster knowledge and to promote prospective and randomized clinical trials focused on classification and treatment.

Keywords: WHO classification, Masaoka stage, thymic epithelial tumors

P2.15-13 THE ROLE OF ADJUVANT THERAPY FOR ATYPICAL BRONCHOPULMONARY CARCINOIDS: A POPULATION-BASED ANALYSIS

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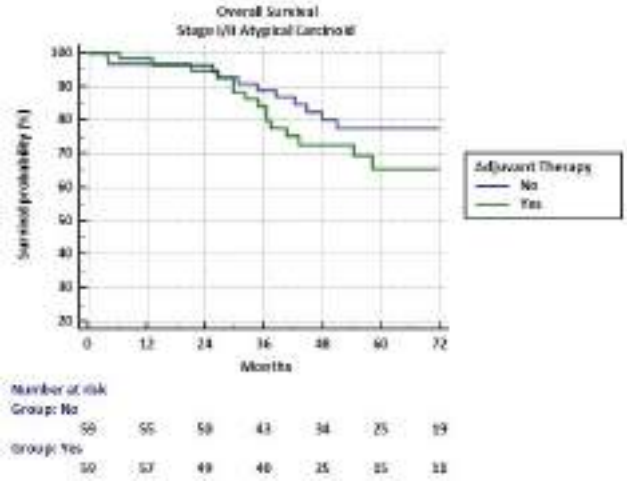
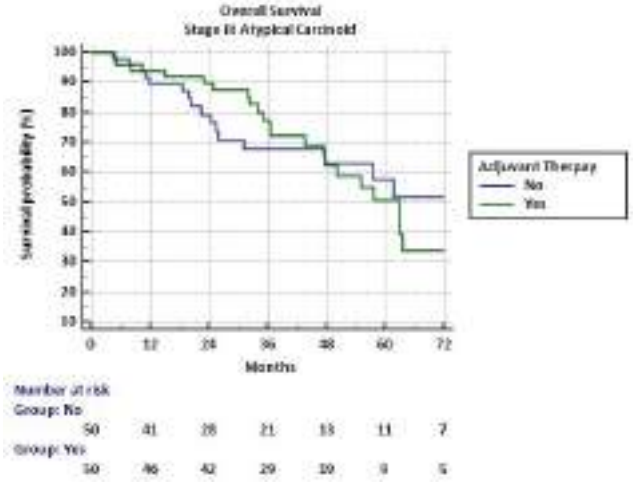
Background: Atypical bronchopulmonary carcinoid tumors are rare but carry high recurrence rates following resection. The role of adjuvant therapy remains unclear owing to a lack of high-volume data. To address this knowledge gap, we examined predictors of adjuvant therapy and effects on outcome. **Method:** We queried the National Cancer Database for patients with resected stage I-III atypical carcinoid. Adjuvant therapy was defined as chest radiation, chemotherapy, or a combination thereof. Multivariable logistic regression identified predictors of adjuvant therapy. Multivariable Cox regression evaluated predictors of survival. Propensity matching accounted for indication biases. **Result:** Overall, 533 stage I/II and 129 stage III patients were identified. Predictors for adjuvant therapy in stage I/II disease were stage II, positive margins, lymph node ratio (LNR) of 1-25%, and more remote year of treatment. Predictors for adjuvant therapy in stage III were female gender and LNR of 26-50%. Median overall survival in stage I/II and III was 116 months and 61 months, respectively. Predictors for survival in stage I/II were age, margins, comorbidity score, and LNR; factors for stage III disease were LNR and more remote year of treatment. Delivery of adjuvant therapy was not independently associated with survival in either stage I/II or III patients. Furthermore, propensity matched analysis did not reveal a benefit to adjuvant therapy.





Conclusion: This study shows no clear survival benefit with adjuvant radiotherapy and/or chemotherapy, even in stage III disease. Although this implies that adjuvant therapy should not be routinely delivered, individualized judgment is still recommended.

Keyword: atypical carcinoid, adjuvant treatment

P2.16 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.16-01 RISK FACTORS FOR SHORT-TERM POST-OPERATIVE EVENTS FOLLOWING LUNG CANCER RESECTION

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Background: Lung cancer represents 13% of all newly diagnosed US cancers and is the leading cause of all cancer deaths (25%). Reducing postoperative complications and improving quality of life following surgery remains central when providing treatment. We examined risk factors for short-term post-opeartive complications following lung cancer resection in patients treated at Mount Sinai, New York City. **Method:** Data was selected from the General Thoracic Surgery Database (2012-2018). Patients with a primary diagnosis of lung cancer who underwent a Lobectomy (n = 603) or a Wedge resection (n = 659) were included. Preoperative assessments of health, including the Zubrod Performance Score, % predicted FEV1, heart (congestive heart failure, coronary artery disease, peripheral vascular disease) lung (pulmonary hypertension, chronic obstructive pulmonary disease, and interstitial fibrosis) comorbidities, diabetes, and smoking status were measured for each patient. The primary outcome was the occurence of at least one post-operative event (pulmonary/cardiovascular/gastrointestinal/neurological complications, infections, and unexpected readmissions to the operating room or intensive care unit) during their hospital stay or within 30 days of their surgery; SAS v9.4 was used for statistical analyses. **Result:** There were 1262 patients (age 18-95 years); 60% were female, 64% were White, and 55% were Stage 1a / 1b. More patients underwent surgery with a Video-Assisted Thoracoscopic Surgery (VATS) approach (58%) rather than an Open approach (42%). The majority of patients was classified as past smokers (58%), while the remainder were never (27%) and current (15%) smokers. 17% of patients presented with at least one heart comorbidity, while 21% with at least one lung comorbidity. At multivariable analysis, female gender (ORadj 0.64, 95% CI: 0.49-0.96), Wedge resection (ORadj 0.64, 95% CI: 0.44-0.92 compared to Lobectomy), VATS (ORadj 0.54, 95% CI: 0.38-0.77 compared to an OPEN approach), and an increasing % predicted FEV1 were inversely associated with the occurence of a post-operative event. Increasing age (ORadj 1.03, 95% CI: 1.01-1.04), Zubrod performance score (ORadj 1.53, 95% CI: 1.21-1.93), duration of surgery in hours (ORadj 1.10, 95% CI: 1.01-1.21), and currently smoking (ORadj 1.97, 95% CI: 1.14-3.40) were associated with increased odds of a post-operative event. **Conclusion:** Significant risk factors exist for the occurence of a short-term post-operative event following lung cancer resection, which should be recognized to improve post-surgery quality of life. A VATS wedge resection should be utilized whenever appropriate to reduce the likelihood of post-operative complications.

Keywords: surgical approach, post-operative complications, Risk Factors

P2.16-02 RANDOMISING PATIENTS INTO TRIALS OF THORACIC CANCER SURGERY: AN ANALYSIS OF PATIENT AND CANCER TEAM BEHAVIOUR IN PRACTICE

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Background: Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) is a multicentre trial funded by Cancer Research UK. In Stage 1 participants were invited to consent for further evaluation within the PulMiCC protocol and if eligible were offered randomisation (Stage 2) to lung metastasectomy or continued active monitoring. Noting a decreasing rate of randomisation during 2016, the Data Monitoring Committee recommended that the reasons should be investigated. **Method:** The three most actively recruiting centres were approached and asked to provide reasons for patients in Stage 1 not being randomised and to provide data according to the fields in the first column of the table. We sought to discover who made the decision to not randomise and to establish what clinical management was then followed. If participants were deemed ineligible we asked for the reason. **Result:** Of 155 patient participants consented into Stage 1 of the trial, and after full information and counselling during the period of assessment, 41 elected to make their own decision. The split to have or not have metastasectomy was 22:19. When the clinicians made the decision 77/78 (99%) patients had metastasectomy. Full data are given in the table. Ten patients had other pathology, nine lung cancer and one carcinoid. The protocol placed no constraint on the number of metastases but one unit set its own limits at 2-4 deeming patients outside as not eligible for randomisation but as suitable for metastasectomy.

Reasons for not randomising a sample of 155 registered patients		
Patients elected to make their own decision	41	
Chose metastasectomy		22 (54%)
Chose to not have metasasectomy		19 (46%)
Clinical team overrode the trial protocol	78	
Metastasectomy		77(99%)
Non-operative management		1 (1%)
Primary lung neoplasia	10	
Deemed ineligible	18	
Local interpretation of the trial protocol		9
Undecided at time of data collection	8	
Total sample	155	

Conclusion: At trial closure, of 512 patients in Stage 1, 82% were not randomised resulting in an inconclusive result despite the efforts of many doctors and scientists and the participation of a large number of patients. In the sample of 155 drawn from the three most active centres, 78 patients deemed eligible had the decision made for them by the clinical team and of the 18 deemed ineligible, half of the reasons were not aligned with the written protocol. That means at least 56% of the patients were lost to randomisation by clinicians' decisions.The 41 patients who elected to make their own decision, to have or not have metastasectomy, did so in numbers which better reflected equipoise. The difficulty faced by clinicians in declaring uncertainty is well recognised. In PulMiCC this resulted in exclusion of many patients who had given their informed consent. Learning from this and similar experiences, later UK trials of thoracic oncology (MARS-2, VIOLETS) have recruited well after specific training in the QuinteT method for randomisation into surgical trials.

Keywords: Oligometastasectomy, Surgical oncology, Randomised trials

P2.16-03 IELCART QUALITY OF LIFE IN THE FIRST YEAR AFTER SURGERY FOR STAGE IA LUNG CANCER PATIENTS: PRELIMINARY RESULTS

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Background: To compare quality of life (QoL) after lobectomy (L) and sublobar resection (SLR) within the first postoperative year among patients undergoing video-assisted thoracoscopic surgery. **Method:** We used a prospective cohort of Stage I lung cancer patients from the Initiative for Early Lung Cancer Research on Treatment (IELCART). QoL used three validated instruments: SF-12 physical (PCS) and mental health (MCS), FACT-L lung cancer symptoms, and PHQ-4 for anxiety and depression. The QoL scores were measured before surgery, and within 4, 6, and 12 months after surgery. For each QoL measure, a piece-wise linear mixed effects model was used to estimate changes in average scores and test for differences between L and SLR patients within 2 months post-surgery and from 2 to 12 months. Social support was also assessed at baseline using the MOS survey. **Result:** Of the 160 patients, 58 (36.3%) had L and 102 (63.7%) SLR. After adjustment for demographics, BMI, pack-years of smoking, and comorbidities, mean QoL and social support scores at baseline did not differ between L and SLR patients. The post-operative rates of change are given in Table 1. L showed significant decreases in PCS (p = .01) and anxiety scores (p = .0001) within 2 months post-surgery and significant improvement from 2 to 12 months in PCS (p = .005) and FACT-L QoL scores (p = .01). SLR anxiety scores decreased (p = .004) within the first two months post-surgery; PCS did not change significantly within the first two months but improved significantly (p = .02) from 2 to 12 months. Other measures were stable across the year after surgery. No significant differences between L and SLR were detected in the post-operative rates of change.

Table 1: Adjusted trends in QoL measures

	Baseline difference			Rate (within 2 months)			Rate (2 - 12 months)		
PCS (SF-12)	**Estimate**	**SE**	**p value**	**Estimate**	**SE**	**p value**	**Estimate**	**SE**	**p value**
Lobectomy	45.08	1.55		-2.00	0.81	0.01	0.67	0.23	<0.01
Sublobar	46.37	1.35		-0.70	0.71	0.33	0.38	0.17	0.02
Lobectomy - Sublobar	-1.29	1.77	0.47	-1.30	1.08	0.23	0.29	0.28	0.31
MCS (SF-12)									
Lobectomy	52.60	1.46		0.59	0.74	0.43	0.08	0.21	0.69
Sublobar	51.24	1.27		-0.04	0.65	0.95	0.10	0.15	0.49
Lobectomy - Sublobar	1.36	1.65	0.41	0.63	0.99	0.53	-0.02	0.26	0.94
FACT-L									
Lobectomy	23.58	0.58		-0.40	0.31	0.19	0.21	0.08	0.01
Sublobar	23.78	0.50		0.08	0.26	0.76	0.10	0.06	0.09
Lobectomy - Sublobar	-0.20	0.66	0.76	0.48	0.4	0.24	0.11	0.10	0.29
Anxiety (PHQ4)									
Lobectomy	1.97	0.23		-0.51	0.13	<0.01	0.00	0.04	0.95
Sublobar	1.90	0.22		-0.33	0.11	<0.01	0.00	0.03	0.92
Lobectomy - Sublobar	0.07	0.28	0.80	-0.18	0.17	0.30	0.00	0.04	1.00
Depression (PHQ4)									
Lobectomy	0.79	0.22		0.10	0.11	0.35	-0.03	0.03	0.28
Sublobar	0.86	0.19		0.05	0.10	0.63	-0.02	0.02	0.31
Lobectomy - Sublobar	-0.07	0.24	0.78	0.06	0.15	0.69	-0.01	0.04	0.77
Social Support (MOS)									
Lobectomy	91.91	2.43							
Sublobar	90.88	2.10							
Lobectomy - Sublobar	1.03	2.69	0.70						

Conclusion: Mental health, anxiety, and depression scores either improved or remained stable. Decreases in physical health persisted 2 months postoperatively, but thereafter improved significantly. Implications for intervention include provision of preoperative counseling about anticipated changes in physical function after surgery, and post-op interventions aimed at improving physical function.

Keywords: Quality of life, Sublobar resection, lobectomy

P2.16-04 SINGLE-PORT VIDEO-ASSISTED THORACOSCOPIC SURGERY REDUCES PATIENT-REPORTED SYMPTOM BURDEN IN PATIENTS UNDERGOING LUNG RESECTION

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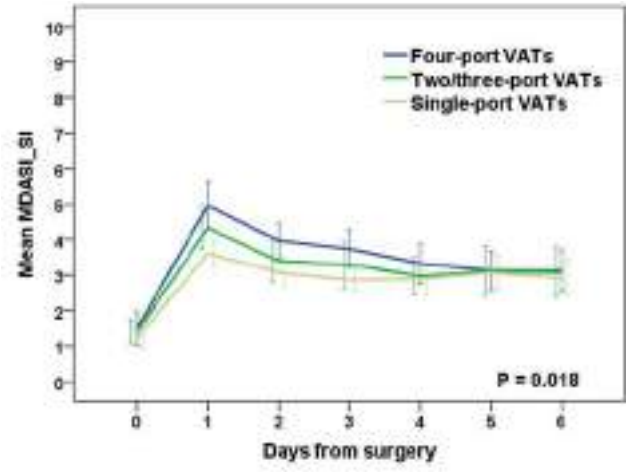
Background: Symptom relief has been considered one of the most important targets in recovery from a surgery. This study aimed to evaluate the advantages of single-port video-assisted thoracoscopic surgery (VATS) in reducing postoperative symptom burden, by comparison with multi-port VATS in patients undergoing lung resection. **Method:** Data were collected from an ongoing, real-world, multicenter, prospective, observational study initiated in November 2017 (NCT03341377). The MD Anderson Symptom Inventory for lung cancer (MDASI-LC) was administered to assess the severity of postoperative symptoms and their interference with daily functioning preoperatively and daily postoperatively until discharge. A symptom burden index (MDASI-SI) was generated by averaging the top 5 severe symptoms. MDASI-SI was compared between groups using the Wilcoxon rank sum test. The changes of symptoms over hospitalization were compared using mixed modeling. **Result:** Among 175 patients who underwent lung resection, 89 underwent single-port VATS, 30 two-port VATS, 13 three-port VATS, and 43 four-port VATS. We combined two- and three-port VATS patients due to the small sample size. The top 5 severe symptoms were pain, fatigue, coughing, disturbed sleep, and shortness of breath for all the patients. There were no significant differences between single-, two/three-, and four-port VATS in preoperative MDASI-SI. The median postoperative hospital stay was 6 days for each group. The MDASI-SI scores of single-port VATS (median=3.6; inter quartile range (IQR)=2.4) were significantly lower than those of two/three-port (median=4.6; IQR=2.8; P=0.043) and four-port VATS (median=5.1; IQR=3.3; P=0.0005) on postoperative day (POD) 1.

Compared to four-port VATS, patients who underwent single-port VATS experienced significantly lower symptom burden from POD 1 to POD 6 (estimate=-0.77; SE=0.28; *P*=0.005).



Conclusion: This study provided real-world evidence that the single-port VATS has a significant benefit of reducing symptom burden in patients undergoing lung resection during the early postoperative period. The long-term benefit and its impact on patient's quality of life, adjuvant therapy, and survival need to be investigated in further studies.

Keywords: Single-port VATS, Patient-reported symptom burden, Lung resection

P2.16-05 POPULATION-BASED ROS1 TESTING IN LUNG CANCER: CREATING OPPORTUNITY IN A PUBLICLY FUNDED SYSTEM

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[1]*University of Toronto, Toronto/Canada,* [2]*Tom Baker Cancer Centre, Alberta/Canada,* [3]*Princess Margaret Cancer Centre, Toronto/Canada*

Background: *ROS1* gene rearrangement is found in 1-2% of all non-small cell lung cancer (NSCLC) and is recommended as standard molecular diagnostic testing. This study models the most efficient *ROS1* testing strategy to maximize detection of true positive cases (TP) while minimizing costs and turnaround time (TAT). **Method:** A population-based *ROS1* testing model was developed from a Canadian (Ontario) public healthcare system perspective examining the use of immunohistochemistry (IHC) and next generation sequencing (NGS) versus fluorescence in situ hybridization (FISH, gold standard), reflex versus molecular or clinical selection (never smokers), and blood- versus tissue-based testing. Model inputs were derived from existing literature and expert opinion. Direct testing costs and TAT were obtained from the Ontario public perspective (University Health Network, Cancer Care Ontario). **Result:** The most cost-effective strategy for the outcomes of TAT and TP was reflex testing with IHC and subsequent FISH confirmation; this identified a high proportion of TP within a relatively short TAT. The most costly reflex strategy was NGS, with a greater proportion of missed TP (Table), and long TAT. Clinician selection of never smokers yielded the lowest proportion of TP. Population-based plasma ctDNA testing using commercial assays was the most costly strategy. One-way sensitivity analysis demonstrated that the TP outcome was most sensitive to the population prevalence of *ROS1*, while cost was most sensitive to the specificity of ROS1 IHC. **Conclusion:** Pathologist-initiated reflex testing using IHC with FISH confirmation provides the most cost-effective population-based testing strategy. Clinician-initiated testing significantly lengthens TAT. Selecting only never smokers for testing misses a larger proportion of TP patients who would benefit from targeted therapy despite potential cost savings.

	Strategy	Cost for 4000 cases (CAD)*	Longest TAT**	Proportion of TP
All comers - Reflex	FISH	1590×10^3	6.83	0.915
	IHC - FISH	662×10^3	10.23	0.878
	NGS	3790×10^3	19.64	0.769
Molecular	EGFR, ALK negative	1810×10^3	16.59	0.874
	EGFR, ALK, KRAS negative	3530×10^3	35.63	0.858
Clinician	EGFR, ALK negative	1810×10^3	30.59	0.874
	EGFR, ALK negative, never smokers	1480×10^3	28.71	0.705
	ctDNA	12200×10^3	19.91	0.815

*Excludes administrative costs and professional fees, and was determined based on the number of advanced NSCLC cases in Ontario in 2017

** Based on expected value of base case estimates

Keywords: ROS1, cost-effectiveness, Molecular Testing

POSTERS

P2.16-06 MOLECULAR FEATURES AND TREATMENT OUTCOME OF HER2 MUTATED ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS IN CHINA

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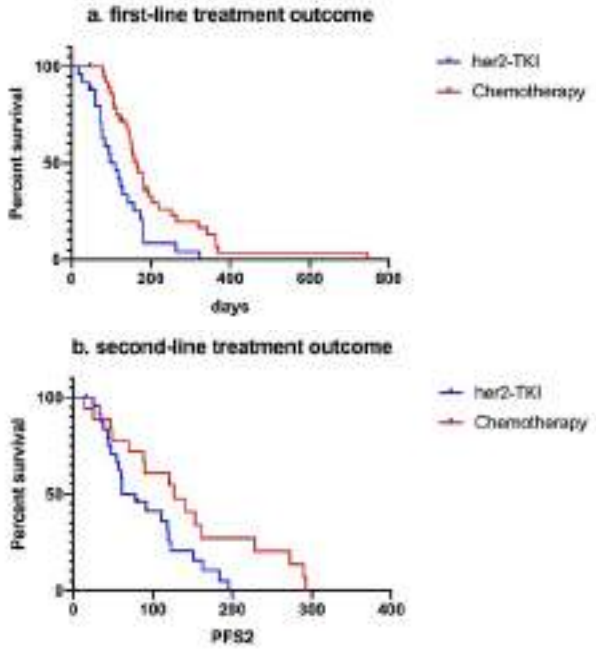
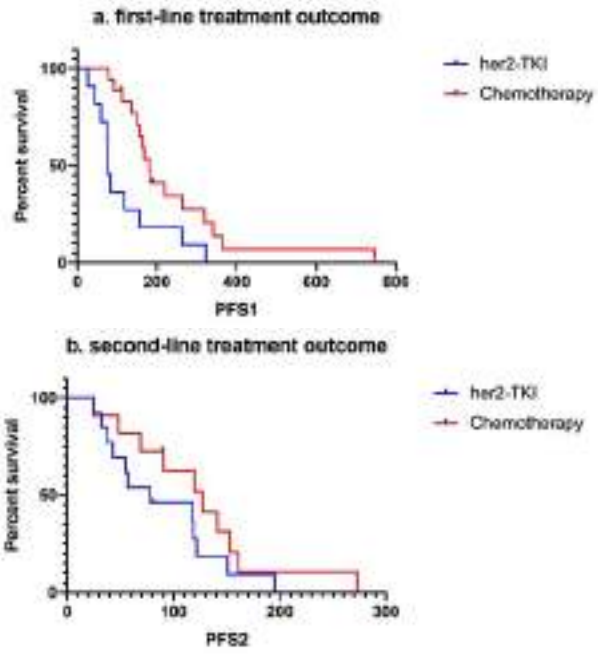
Background: HER2 mutations are found in 1-2% of lung adenocarcinoma patients. Chemotherapy remains the standard of care for patients harboring HER2 driver mutations, while many HER2 targeted tyrosine kinase inhibitors (TKIs) have been applied to them in practice in recent years. Studies comparing chemotherapy to HER2-TKIs was limited. This study was aimed to investigate molecular and clinical patterns of HER2 mutations in advanced non-small cell lung cancer (NSCLC), and compare the different outcomes between chemotherapy and HER2-TKIs. **Method:** Advanced or recurrent NSCLC patients with de novo HER2 mutations (N=75) were included in this study. Molecular information, clinical features, and treatment outcomes were retrospectively collected from a web-based patient registry and hospital chart review. **Result:** Between October 2012 and December 2018, 65 patients with in-frame insertion mutations, 8 with point mutations and 2 with gene amplification were found. The most common subtypes of insertion mutations were A775_G776insYVMA, G776delinsVC, and V777_G778insGSP. HER2 mutated patients were mostly young-aged, females, never or light smokers, and adenocarcinoma. For HER2 mutated advanced NSCLC, chemotherapy achieved better outcomes than HER2-TKIs (median PFS: 5.5 vs 3.7 months in first line setting and 4.2 vs 2.0 months in second line setting, *P*=0.001 and 0.031, respectively). Especially for the most common subtype, YVMA insertions, PFS was significantly longer in chemotherapy than HER2-TKIs both in first line (6.0 vs 2.6 months, *P*=0.008) and in second line (4.2 vs 2.6 months *P*<0.001).

Treatment response in HER2 mutated lung cancer patients as a whole



Treatment response in A775_G776insYVMA subtype



Conclusion: Compared to existed HER2-TKIs, chemotherapy might bring more benefit to HER2 mutated advanced lung cancer patients, especially the most common type of HER2 exon 20 insertions, A775_G776insYVMA subtype.

Keywords: HER2, molecular features, treatment outcome

P2.16-07 HOW TO MANAGE TOXICITIES OF EGFR-TKI FOR EXTREME ELDERLY LUNG CANCER PATIENTS: SUPPORTIVE CARE FOR PATIENTS AGED 85 AND OLDER

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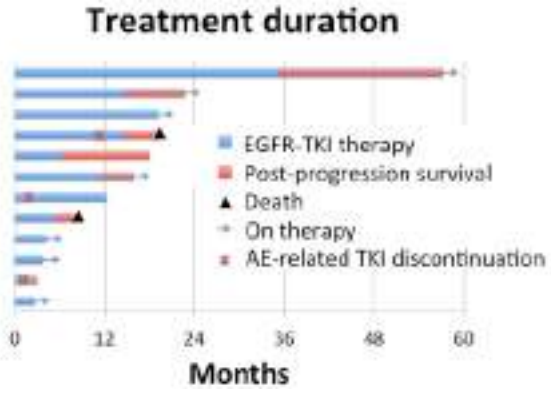
Background: In Japan, the population of extreme elderly individuals (85 years and older) was 5.75 million in 2018, and the number of elderly lung cancer patients is increasing. Recently, several elderly-specific trials showed that epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is effective and feasible for elderly patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC). Nevertheless, there have been few reports on the efficacy and safety of EGFR-TKI therapy in patients aged 85 years and older with *EGFR* mutation-positive advanced NSCLC. **Method:** We analyzed the efficacy and safety of EGFR-TKI therapy in patients with *EGFR* mutated NSCLC who were 85 years and older treated at our hospital, between 2014 and 2019. We assessed complications, prognosis, and supportive care needs. **Result:** The median age was 87 years (range, 85-93 years) at last checkup, and only one patient was male. The study population included 12 patients with ECOG performance status 0-1 and all patients had adenocarcinoma. Four patients (33%) were diagnosed with cognitive impairment. Nine patients received gefitinib therapy. Treatment-related deaths were not observed in our analysis. Median progression free survival, overall survival from recent TKI therapy was 11.3 months, and 16.0 months. The response rate and disease control rate were 17%, and 100%. The common adverse events were diarrhea (25%), skin toxicities (25%), and liver dysfunction (25%). One patient (8%) experienced grade 2 EGFR-TKI-related interstitial lung disease. The dose of EGFR-TKI was reduced in 5 patients (42%) and EGFR-TKI therapy was discontinued in 3 patients (25%) due to toxicities, digestive disorders and interstitial lung disease.



Conclusion: EGFR-TKI therapy is tolerable for extreme elderly patients with *EGFR* mutation-positive advanced NSCLC. Approximately half of the patients required a dose reduction or focused supportive care, but well tolerated and had similar efficacy compared to those of the younger. It is important for elderly patients to be treated with a personalized management plan and integrated supportive care.

Keywords: Extreme elderly patients, EGFR-TKI, Toxicity management

P2.16-08 CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH BRAF MUTATED NON-SMALL CELL LUNG CANCER

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Background: BRAF mutation is a driver oncogene identified in 0.5-2% of non-small cell lung cancer (NSCLC) patients in China, and clinical data are relatively inadequate. This study assessed the clinical characteristics, course of disease and treatment outcomes in patients with BRAF mutated NSCLC in a real-world setting. **Method:** Between Apr 1, 2017 and Feb 1, 2019, medical data of patients with NSCLC harboring BRAF mutation in our cancer center was retrospective collected. Patient characteristics and treatment outcomes were reviewed. Data cutoff was Apr 1, 2019. **Result:** A total of 36 patients were identified. BRAF V600E was the most common (31/36, 86.1%), other BRAF molecular subsets were observed in 5 (13.9%) cases including K601E, G469V, G596R and D594N. The majority of patients with BRAF mutation were female (20/36, 55.6%) and non-smokers (20/36, 55.6%), all of them were adenocarcinoma, and median age at diagnosis was 56 (range, 33-79). Twenty-seven patients were recurrent or metastatic NSCLC at data cutoff, most of whom received chemotherapy (16/27, 59.3%) as first-line therapy with median progression-free survival (PFS) of 9.8 months (95%CI 0.0, 21.5) and disease control rate (DCR) of 68.8% (11/16). Eight patients received anti-BRAF targeted therapy (including dabrafenib, trametinib and vemurafenib) in the first-line and showed superior efficacy than those received chemotherapy (median PFS, 15.9 months [95%CI, 4.5, 27.3] vs. 9.8 months [95%CI, 0.0, 21.5], P = 0.183; DCR, 100% vs. 68.8%, P = 0.130). As for distinct molecular subsets, most patients with V600E mutation were female (19/31, 61.3%) and non-smokers (19/31, 61.3%), while four of five (80.0%) patients with non-V600E mutation were male and smokers. All of the 3 patients in non-V600E mutations subgroup with recurrent or metastatic disease received chemotherapy in the first-line, and achieved 2 of SD, 1 of PD.

Table 1. Efficacy of first-line treatment strategies in patients with BRAF mutation.

Treatment strategies in first-line	Overall		V600E	
	DCR	PFS (95%CI)	DCR	PFS (95%CI)
Pemetrexed-contained chemotherapy	11/14, 78.6%	9.9 (0.0, 20.0)	8/11, 72.7%	12.5 (2.5, 22.5)
Paclitaxel-contained chemotherapy	1/3, 33.3%	1.5 (0.7, 2.3)	1/3, 33.3%	1.5 (0.7, 2.3)
Vemurafenib	6/6, 100%	15.4 (0.0, 36.2)	6/6, 100%	15.4 (0.0, 36.2)
Dabrafenib + Trametinib	2/2, 100%	NR	2/2, 100%	NR

DCR, disease control rate; PFS, progression-free survival; NR, not reached.

Conclusion: NSCLC with BRAF mutation was associated with specific characteristics, which were variable between molecular subsets. BRAF inhibitors should be considered firstly in treating patients with BRAF-mutated lung cancers. The prognosis value of non-V600E mutations and treatment selection needs more research.

Keywords: Non-Small Cell Lung Cancer, BRAF mutation

P2.16-09 REAL-WORLD BRIGATINIB USE IN NON-SMALL CELL LUNG CANCER PATIENTS WITH PRIOR USE OF CRIZOTINIB/OTHER ALK THERAPIES IN THE US

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Background: Anaplastic lymphoma kinase (ALK) gene rearrangements occur in 3 to 8% of non-small cell lung cancer (NSCLC) cases. Targeted therapy options for ALK+ NSCLC patients have increased recently and are associated with improved survival. This study aimed to describe the real-world use of brigatinib, particularly after crizotinib and other ALK-tyrosine kinase inhibitors (TKI), where most brigatinib patients were found in this study. **Method:** Adult (≥18 years) patients with ≥ 1 claim for brigatinib (index claim) after crizotinib were identified between 01-Jan-2011 and 30-Jun-2018 from IQVIA's US-based Longitudinal Patient-Centric Pharmacy Claims Database. Patients had ≥ 6 months of observation before crizotinib and were continuously followed post-index for use of brigatinib and until discontinuation (≥ 90-day gap in brigatinib therapy, switch to another ALK-TKI therapy, or the end of follow-up of brigatinib). Brigatinib on-treatment rates at 6- and 12-months post-index were estimated using Kaplan-Meier analysis in subgroups with > 50 patients. **Result:** The final sample consisted of 92 post-crizotinib brigatinib patients, most of whom were treated with crizotinib and ≥ 1 second generation (2G) ALK-TKI inhibitor (n=72); twenty patients received crizotinib only prior to brigatinib. Among the 72 patients treated with crizotinib and ≥ 1 2G ALK-TKI median (range) age at brigatinib initiation was 58.1 (30-85) years; 68.1% of the sample was female and most had third party insurance (51.4%). Mean (SD) post-index follow-up time was 6.7 (4.2) months. Sixty patients (56.9%) received crizotinib and alectinib (± ceritinib), while twelve (16.7%) received only crizotinib and ceritinib prior to brigatinib. Median brigatinib treatment duration was 8.3 months in patients with prior crizotinib and ≥ 1 2G ALK-TKI (n=72) ; 64.8% and 49.3% of these patients were still on brigatinib 6- and 12- months after initiation. In the subgroup of patients with crizotinib and alectinib ± (ceritinib) prior to brigatinib (n=60), median duration of brigatinib treatment was also 8.3 months; 66.6% and 48.1% were still on brigatinib 6- and 12-months after initiation. **Conclusion:** This US-based real-world study provides early insight into the use of recently approved brigatinib in NCSLC in the post crizotinib setting. These results indicate that use of brigatinib may be associated with potential clinical benefit with patients staying on therapy for a significant duration of time post a 2G ALK-TKI inhibitor. The duration of brigatinib in earlier lines remains to be investigated in future studies when larger sample sizes are available.

Keywords: Non-Small Cell Lung Cancer, ALK-TKI, brigatinib

P2.16-10 ADVANCES IN DIAGNOSIS AND TREATMENT OF NON-SMALL CELL LUNG CANCER ARE TRANSLATING INTO REAL-WORLD SURVIVAL GAINS IN THE UNITED STATES

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Background: The last two decades have been notable for advances in the histologic and molecular classification of non-small cell lung cancer (NSCLC) as well as the introduction of new cytotoxic agents, targeted therapies and immunotherapy into the routine care of metastatic NSCLC based on clinical trial results. We sought to evaluate temporal trends in overall survival (OS) among unselected patients with metastatic NSCLC in the United States (US). **Method:** We utilized the Surveillance, Epidemiology, and End Results (SEER) 9 registries in identifying patients with new diagnoses of stage IV NSCLC. Staging was based on the American Joint Committee on Cancer (AJCC) 3rd and 6th edition staging guidelines for the periods 1986-2003 and 2004-2015, respectively. We calculated median OS over successive 5 year intervals (1986-1990; 1991-1995; 1996-2000; 2001-2005; 2006-2010; 2011-2015) according to the year of initial diagnosis for the entire cohort as well as by subgroups defined by age (20-44 years[y]; 45-64y; 65-74y; 75-84y; ≥85y); gender (male; female); race/ethnicity (Whites; Blacks; Hispanics; Others); region (northeast; south; midwest; west); and histology (adenocarcinoma[AC]; squamous cell carcinoma[SCC]; others). Univariate analysis was performed with Kaplan-Meier analysis and log-rank tests. Independent associations between OS and time periods were examined with a multivariate Cox proportional hazard model that adjusted for the effects of age, gender, race, region, histology, as well as the interaction of time with these covariates. **Result:** There were 113,518 cases of newly diagnosed stage IV NSCLC. Median OS increased from 4 months (m) in 1986-1995 to 7m in 2011-2015. Median OS improved for all age-groups and by subcategories of gender, race/ethnicity, region, and histology. Multivariate analysis demonstrated a progressive decrease in mortality since the 2000s, relative to those diagnosed in 1986-1990 with the following adjusted hazard ratios (aHR) and respective confidence intervals (CI): 1991-1995: 1.09 (95%CI: 0.93, 1.29; p=0.129); 1996-2000: 0.95 (95%CI: 0.81, 1.12; p=0.561); 2000-2005: 0.83 (95%CI: 0.71, 0.97; p=0.017); 2006-2010: 0.79 (95%CI: 0.67, 0.93; p=0.005); 2011-2015: 0.57 (95%CI: 0.48, 0.68; p<0.001). Although all subcategories of patients had improved OS over time, females had a relative improvement in OS over males in 2011-2015 compared to 1986-1990 (aHR: 0.90; 95%CI: 0.85, 0.95; p<0.001). Those aged ≥85y had OS that was comparatively worse than those aged 20-44y in 2011-2015 relative to 1986-1990 (aHR: 1.31; 95%CI: 1.04, 1.65; p=0.023). Additionally, those with SCC had worse OS than those with AC in 2011-2015 relative to 1986-1990 (aHR: 1.13; 95%CI: 1.06, 1.21; p<0.001). There were no relative differences in OS over time by race/ethnicity or region. **Conclusion:** There has been a near doubling in median OS for patients diagnosed with stage IV NSCLC in the US over the 30-year period spanning 1986-2015. These findings suggest that advances in the diagnostic classification and treatment of NSCLC resulting from clinical trial participation are translating into real-world survival gains particularly for those with AC. However, patients with SCC and the most elderly patients have benefited less proportionately underscoring the need for further characterization of SCC with the development of targeted therapies and inclusion of the most elderly in cancer clinical trials.

Keywords: SEER, NSCLC, lung cancer survival

P2.16-11 ADVANCE-1: DEVELOPMENT AND FEASIBILITY TESTING OF A BENCHMARKING APPROACH FOR QUALITY IMPROVEMENT IN LUNG CANCER CARE

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Background: Benchmarking is successfully utilized in industry to improve working process and productivity. In its original sense benchmarking is a systematic process for comparing performances, functions or processes of organisations against the best in the world. However, the majority of research within lung cancer is focused on prevention, diagnosis and treatment rather than examining infrastructure or processes of managing lung cancer patients. ADVANCE-1 is a European Respiratory Society (ERS) funded pilot study with the aim of creating a benchmarking tool that can easily document and reflect the structure and process within a lung cancer centre and its associated registry and how these processes impact on the pathway of a patient through the individual centres. **Method:** The ADVANCE-1 study group was constituted by the two ERS fellowship-holders and senior lung cancer specialists from the two participating lung cancer services in the Beatson West of Scotland Cancer Centre, Glasgow, Scotland, and the Lungenklinik Heckeshorn in the Helios Klinikum Emil von Behring, Berlin, Germany. We created the study design with direct cooperation of the German Benchmarking Centre as well as the University of Glasgow. Final results were externally reviewed by the German Society for Quality Management in Health Care. **Result:** Two benchmarking tools were created; the first for documentation of the service provided at each centre, the underlying cancer registry and a test of the robustness and comprehensiveness of information and data collecting resources available at each centre. Secondly; a patient pathway tool to reflect the journey of a patient through each of the relevant centres. Patient satisfaction surveys and staff satisfaction surveys were also created. Prospective testing of these benchmarking tools in Glasgow and Berlin will allow a comparison between the two centres in order to

ascertain best practice and learning from each centre in a so called 'collaborative' benchmarking approach. **Conclusion:** This unique study has created a benchmarking tool that can easily document the service of a lung cancer centre and the pathway of a patient through that service. With comparison and learning from each other using this tool we aim to improve the patient care and journey through a lung cancer service.

Keywords: benchmarking, service, Quality Improvement

P2.16-12 TREATMENT UPTAKE AND OUTCOMES OF ELDERLY STAGE III NSCLC PATIENTS: A 15-YEAR RETROSPECTIVE REAL-WORLD STUDY

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Background: Incidence of non-small cell lung cancer (NSCLC) is highly correlated with age; the age-specific incidence rate of NSCLC in individuals ≥ 75 is nearly double that of patients < 70. Further, nearly one-third of patients diagnosed with NSCLC present with locally advanced (Stage III) disease. This represents an anatomically heterogeneous, frequently non-resectable tumour for which contemporary practice guidelines, based on two decades of clinical trials, recommend concurrent chemoradiotherapy (cCRT) to maximize both local tumor control and survival. Underrepresentation of elderly patients in clinical trials requires the use of real-world populations to assess whether current recommendations and trial-derived survival outcomes are also applicable to this significant and growing age group. **Method:** A 15-year population-based retrospective analysis of patients with *de novo* Stage III (AJCC 7th edition) NSCLC diagnosed between 1999-2014 was conducted. Demographic, clinical characteristics, treatment and outcome data were extracted from the institutional Glans-Look Lung Cancer Database. We defined elderly patients as those ≥ 75 years at diagnosis, and investigated the treatment intent, type, uptake and outcomes among elderly and non-elderly patients. **Result:** We identified 1040 patients with a Stage III diagnosis. 333 (32%) were elderly. Treatment patterns differed significantly between elderly patients and non-elderly patients: elderly patients were less significantly likely to receive any form of active treatment (82% vs. 58%), particularly curative-intent treatment (41% vs. 14%), and no elderly patients underwent surgical resection. Median overall survival (mOS) favoured non-elderly patients (13.2 vs. 9.7 months, log-rank p <0.001.) Among elderly patients, receipt of curative-intent treatment was associated with significant improvement in mOS (17.4 months vs. 9.3 months for no active treatment/observation, vs. 8.5 months for palliative-intent treatment, p < 0.001). When receiving curative-intent treatment, specifically cCRT, survival outcomes of elderly patients were not significantly different from those of younger patients (24.5 vs. 21.3 months, p=0.81), and had comparable 5-year survival rates (15.9% and 12.2% respectively). **Conclusion:** This real-world population reveals that elderly patients are less likely to receive any, and particularly, curative-intent treatment for their NSCLC diagnosis when compared with a younger cohort. When deemed suitable for a curative-intent regiment of cCRT, elderly patients show comparable outcomes to younger cohorts. This finding reinforces the current guideline recommendations that cCRT is associated with best outcome for non-resectable, locally-advanced NSCLC, even among elderly patients. Further, it supports the critical need for more tolerable and effective treatments for this presentation of disease to improve feasibility of curative-intent treatment for all, but in particular, elderly patients.

Keywords: locally advanced NSCLC, treatment uptake, Outcomes of elderly patients

P2.16-13 RISK FACTORS OF RADIATION PNEUMONITIS IN LUNG CANCER PATIENTS WITH SUBCLINICAL INTERSTITIAL LUNG DISEASE AFTER THORACIC RADIOTHERAPY

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Background: Previous studies reported that patients with subclinical interstitial lung disease were more susceptible to developing radiation pneumonitis after thoracic stereotactic body radiotherapy or thoracic radiation therapy. The present study aimed to evaluate the incidence and risk factors of radiation pneumonitis after thoracic radiation therapy in lung cancer patients with subclinical interstitial lung disease. **Method:** Patients with subclinical interstitial lung disease between January 2016 and December 2017, who were treated with thoracic intensity-modulated radiation therapy in our institutions, were prospectively analyzed. The diagnosis of subclinical interstitial lung disease was based on the pretreatment high-resolution computed tomography imaging, such as honeycombing, subpleural reticular opacities, ground-glass opacity, and traction bronchiectasis. Statistical analysis was performed using SPSS software 22.0 for Mac. Univariate and multivariate analyses were used to assess the correlation of clinical factors, dose-volume histogram-based dosimetric parameters,and imaging characteristics of preexisting subclinical interstitial lung disease with radiation pneumonitis. A P value < 0.05 was considered statistically significant. **Result:** A total of 87 consecutive patients with subclinical interstitial lung disease were prospectively analyzed. The median follow-up time was 14.1 months. RP was observed in 19 (21.8%), 27 (31.0%), 10 (11.5%), 3 (3.4%), and 5 (5.7%) patients with grades 1, 2, 3, 4 and 5 RP, respectively. The location of tumors and mean lung dose were significantly associated with ≥grade 2 RP in univariate analysis (*P*=0.043, *P*=0.024, respectively). Patients who received gemcitabine in the past and the involvement of subclinical interstitial lung disease ≥ 25% of the lung volume were significantly associated with ≥grade 3 radiation pneumonitis in univariate analysis (*P*=0.031, *P*=0.037, respectively). Patients who received gemcitabine in the past and the involvement of subclinical interstitial lung disease ≥ 25% of the lung volume were significantly associated with ≥grade 3 RP in multivariate analysis (*P*=0.046,*P*=0.017, respectively). **Conclusion:** Subclinical interstitial lung disease is associated with an increased risk of radiation pneumonitis. Patients who received gemcitabine in the past and the involvement of subclinical interstitial lung disease ≥ 25% of the lung volume are associated with an increased risk of ≥grade 3 radiation pneumonitis.

Keywords: interstitial lung disease, Lung cancer, Radiation pneumonitis

P2.16-14 SURVIVAL RATES IN NON-SMALL CELL LUNG CANCER PATIENTS IN THE BRAZILIAN PRIVATE HEALTH SYSTEM: A COHORT STUDY

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Background: Lung cancer is the leading cause of cancer-related mortality in Brazil. Non-small cell lung cancer (NSCLC) is the most prevalent subtype and is associated with high rates of mortality. Despite being diagnosed in late phases, few studies have addressed the survival rates of such disease in the Brazilian private health system. **Method:** An exploratory cohort study based on administrative database claims that included patients with advanced NSCLC diagnosed between 2011 to 2016. The inclusion criteria were defined as having lung cancer diagnosis (ICD-10 code 34 with stage III and IV) and compatible histologic subtype for NSCLC, such as adenocarcinoma, squamous cell, non-squamous cell and others. Non-parametric statistics (Kaplan Meier method, product limit estimator) was used to perform survival analyses, considering diagnosis as index date. **Result:** A total of 5,016 patients were included in this study. At time of diagnosis, most patients had stage IV disease (67%) and were 60 to 69 years old (33.7%). Patients took 31 days on average to receive diagnosis after being attended by a health service. The clinical oncologist was the first professional to

attend the patient in 44% of cases. The average time to start the treatment was 35 days and where patients received chemotherapy (32%) or chemotherapy plus radiotherapy (21%). The median survival rate for stage III NSCLC was 7 months; while for stage IV, 50% of the population was alive in 8 months. **Conclusion:** This study suggests a high percentage of patients diagnosed with stage IV disease. The survival rates were very low, comparable to the public healthcare system where the patient doesn't have access to all medications approved by ANVISA, Brazilian Regulatory Agency, (median overall survival of 8 to 12 months). The results show an opportunity to improve care in private healthcare system.

Keywords: Brazil, private healthcare system, Non small cell lung cancer

P2.16-15 SURVIVAL AND CLINICAL IMMUNOTHERAPY OUTCOMES IN HISPANIC PATIENTS VS NON-HISPANIC WHITE PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: The number of Hispanic (HISP) patients (pts) enrolled in immunotherapy (IMMUNO) trials is minimal or non-existent in non-small cell lung cancer (NSCLC). It's well known that HISP pts with NSCLC have not only a different genomic profile than Non-Hispanic Whites (NHW)- like higher expression of EGFR mutations- but also better outcomes than NHW ("Hispanic Paradox"); thus the need to validate outcomes in HISP pts treated with IMMUNO. **Method:** We present data in 436 NSCLC pts treated with IMMUNO at 5 large institutions (3 in the US, 2 in Latin America). The agents evaluated include: nivolumab, pembrolizumab and atezolizumab. 256 pts were HISP and 180 pts were NHW. Most of the pts were treated with single agent therapy as second line or beyond while a small group of pts were treated as first line. The primary endpoints of the study were: response rate (ORR), progression free survival (PFS) and overall survival (OS). Secondary endpoints were disease control rate (DCR), PD-L1 expression and others. **Result:** The results are consolidated in the table below.

	Hispanics (n=256)	NHW (n=180)	p value
Sex (males)	52%	45%	0.2059
ORR			
First Line	35%	30%	0.6590
Second Line	18%	19%	0.3236
Adeno	22%	24%	0.6714
SQCC	24%	23%	1.0000
PDL1 (+)	29%	32%	0.4839
PDL1 (-)	5%	17%	0.3040
Disease Control Rate: ORR+SD (DCR)			
Adeno	68%	67%	0.8989
SQCC	67%	46%	0.0777
Median PFS	4m	4m	0.7509
Median OS	22m	22m	0.2004

There were no statistical significant differences among HISP and NHW pts regarding ORR, DCR, PFS, OS, and responses according to PD-L1 status. **Conclusion:** No significant differences were found in the clinical outcomes between these 2 ethnic groups despite the "Hispanic Paradox" and expected genomic differences; however pts with actionable mutations were excluded as they usually do not get IMMUNO as first or second line; an approach that might change after IMPOWER 150. This is the largest comparison of NSCLC immunotherapy outcomes in HISP vs NHW pts. These results are comparable to the ones seen in Checkmate and Keynote studies. As expected, higher response rates were seen in first line therapy and pts with PD-L1 (+) status. Further comparisons will be better addressed by a larger prospective study.

Keywords: Hispanics, Immunotherapy, NSCLC

P2.16-16 CALF CIRCUMFERENCE IS ASSOCIATED WITH POSTOPERATIVE OUTCOMES IN LUNG CANCER PATIENTS WHO UNDERWENT SURGERY

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Background: Sarcopenia has gained considerable attention as a poor prognostic factor in lung cancer after surgical resection. Calf circumference (CC) is an easy-to-measure, non-invasive clinical indicator that reflects body muscle mass as well as subcutaneous fat. For this property, many studies have reported that CC is capable of screening sarcopenia, aside from the assessment of nutritional status. In this study, we investigated the association between CC and postoperative outcomes in lung cancer patients. **Method:** Between 2007 and 2016, 873 lung cancer patients underwent surgery in our institution. Patients who received induction therapy (n=33), with a prior history of the disease that could affect the diameter of lower limb (n=5), and with missing data (n=17) were excluded in advance, leaving 818 patients for this retrospective analysis. CC was measured prior to surgery in the occasion of hospital admission. We chose 34 cm for men and 33 cm for women as the CC cutoff value for predicting low muscle mass, following the previous report in Japan (Kawakami R et al. Geriatr Gerontol Int.). The patient characteristics, operative factors, and surgical outcomes were examined to compare the groups. The Kaplan-Meier method was used to estimate long-term survival. **Result:** The mean age of all patients was 67.9 years. There were 473 men and 345 women, and each of their average CC was 34.4 cm and 32.0 cm. In the smaller CC (s-CC) group (n=427), the average age and the female proportion were significantly higher, whereas BMI, %VC, %FEV1 and %DLco, in addition to the proportion of the other cancer history were significantly lower (P<0.01 each) compared with the other group (n=391). As for operative factors, there were no significant differences in surgical approach, type of resection, operation time and intraoperative bleeding, except that the ratio of systematic hilar and mediastinal lymph node dissection was lower (P<0.01) in the s-CC group. Though overall postoperative complications were equivalent (27.2% vs. 23.0%), complications grade 3 or higher were more frequent in the s-CC group (10.5% vs. 5.9%, P=0.02). The 5-year DFS (65.1% vs. 77.9%, P=0.01) and OS (77.9% vs. 81.7%, P=0.03) were significantly poorer in the s-CC group. **Conclusion:** The smaller CC was associated with severe postoperative complications and poor DFS and OS in patients with resected lung cancer. CC was useful for assessing sarcopenia and therefore predicting postoperative outcomes.

Keywords: Lung cancer, surgery, sarcopenia

P2.16-17 REAL-WORLD TRENDS IN SYSTEMIC THERAPY FOR NONSQUAMOUS EGFR/ALK-NEGATIVE ADVANCED NSCLC (ANSCLC) IN THE US, 2011–2018

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Background: Systemic anticancer therapy (SACT) options for aNSCLC continue to increase each year with approvals of more effective therapies that improve long-term outcomes, as seen with immunotherapies (IO). We aimed to examine real-world trends in SACT distribution and sequence from first- to second-line (1L-2L) for EGFR/ALK-negative nonsquamous aNSCLC from 2011-2018 at US community oncology practices. **Method:** This study used the nationwide Flatiron Health de-identified, EHR-derived database (cutoff: 31Jan2019). Eligible patients were adults with aNSCLC, nonsquamous histology with known EGFR/ALK-negative status, who initiated 1L SACT from Jan2011-Jun2018. SACT regimens were assigned to mutually exclusive classes in hierarchical order, from highest to lowest: (1) PD1/PD-L1 inhibitor (anti-PD1/L1)-based, (2) EGFR/ALK TKI-based, (3) platinum-based chemotherapy (PBC) combination with vascular endothelial growth factor inhibitor (PBC+VEGF), (4) PBC only, (5) single agent chemotherapy, (6) others. 2L regimens were examined for patients initiating 1L SACT only through 2017 to enable sufficient follow-up. Results were stratified by year and by pre-IO/post-IO years of 1L initiation, defined as 2011-2014/2015-2018, respectively, based on earliest IO approval for 2L therapy in Mar2015. **Result:** For 1L, in the pre-IO period, most patients were prescribed PBC (53%) or PBC+VEGF (30%), and post-

IO, most were prescribed PBC (43%), anti-PD1/L1 (25%), or PBC+VEGF (23%). Among patients prescribed 1L therapy, the percentages who received 2L therapy were 50%-62% post-1L PBC; 56%-62% post-1L PBC+VEGF; and 28%-38% post-1L anti-PD1/L1 (table). A substantial percentage (25%) of those initiating 1L anti-PD1/L1 in 2017 were still on therapy at cutoff.

SACT prescribing for EGFR/ALK-negative nonsquamous aNSCLC by 1L initiation year and including three most common 2L regimens overall

1L Regimen	2011 (n=566)	2012 (n=1205)	2013 (n=1621)	2014 (n=2081)	2015 (n=2542)	2016 (n=2712)	2017 (n=2806)	2018(½) (n=1267)
PBC, n(%)	287(51)	602(50)	837(52)	1145(55)	1280(50)	1352(50)	1002(36)	378(30)
Still on 1L[a]	2%	3%	3%	5%	3%	4%	6%	--
Rec'd 2L[a]	62%	61%	52%	50%	55%	55%	55%	--
Anti-PD1/L1[b]	1%	1%	4%	10%	50%	69%	76%	--
Single[b]	42%	42%	44%	41%	18%	9%	8%	--
PBC[b]	24%	27%	22%	19%	17%	11%	9%	--
PBC+VEGF, n(%)	170(30)	375(31)	507(31)	608(29)	827(33)	747(28)	411(15)	118(9)
Still on 1L	2%	2%	3%	4%	3%	5%	4%	--
Rec'd 2L	59%	58%	58%	56%	62%	62%	58%	--
Anti-PD1/L1	2%	3%	5%	18%	57%	73%	81%	--
Single	39%	42%	41%	30%	13%	8%	3%	--
PBC+VEGF	29%	29%	27%	25%	19%	11%	10%	--
Anti-PD1/L1, n(%)[c]	0	0	0	6(0)	84(3)	329(12)	1220(44)	691(55)
Still on 1L	--	--	--	--	10%	14%	25%	--
Rec'd 2L	--	--	--	--	38%	32%	28%	--
PBC+VEGF	--	--	--	--	22%	27%	25%	--
Anti-PD1/L1	--	--	--	--	9%	20%	26%	--
Single	--	--	--	--	25%	27%	19%	--
Single, n(%)	54(10)	110(9)	127(8)	178(9)	169(7)	116(4)	73(3)	22(2)
EGFR/ALK, n(%)	22(4)	69(6)	92(6)	86(4)	98(4)	91(3)	55(2)	19(2)
Other, n(%)	33(6)	49(4)	58(4)	58(3)	84(3)	77(3)	45(2)	39(3)

[a]Patients still on 1L or prescribed 2L represent percentages of patients initially prescribed 1L.
[b]Percentages for 2L SACT regimens represent percentages of patients prescribed 2L.
[c]Anti-PD1/L1 regimens included anti-PD1/L1 monotherapy and combination therapy with PBC.

Conclusion: Changing trends in real-world prescribing of 1L-2L SACT for EGFR/ALK-negative nonsquamous aNSCLC from Jan2011-Jun2018 include decreasing use of PBC in 1L and 2L, decreasing use of PBC+VEGF in 1L, and, increasing use of PD1/PD-L1 inhibitors in 1L and 2L. Slightly more than one-half of patients with nonsquamous aNSCLC prescribed 1L PBC are subsequently treated with 2L therapy.

Keywords: nonsquamous NSCLC, real-world therapy trends, Immunotherapy

P2.16-18 OPIOID-INDUCED CONSTIPATION IN PATIENTS WITH CANCER PAIN IN JAPAN (OIC-J STUDY): A POST-HOC ANALYSIS OF LUNG CANCER PATIENTS

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Background: Opioid-Induced Constipation (OIC) is a common side effect of opioid analgesic therapy. OIC-J study was a multicenter, prospective, observational study of cancer patients who started opioid therapy in Japan (UMIN000025864). The aim of this post-hoc analysis was to clarify the OIC burden focusing on lung cancer patients. **Method:** This post-hoc analysis was conducted by using a lung cancer patient's data from OIC-J study. The incidence of OIC was determined by ROME IV diagnostic criteria based on the record of patient diary for 2 weeks, physician's assessment, spontaneous bowel movement (SBM; <3 SBM/week), Bowel Function Index (BFI; score >28.8) and Patient's assessment. The change in the Patient Assessment of Constipation-Symptoms (PAC-SYM) score and the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) score in 2 weeks after starting opioids were compared between OIC patients and non-OIC patients determined by ROME IV diagnostic criteria. **Result:** 67 lung cancer patients from 212 in total cancer patients who were registered in OIC-J study were included in this analysis. The incidence of OIC was 48.0% (ROME IV diagnostic criteria), 59.1 % (physician's assessment), 39.1% (SBM) and 53.0% (BFI), respectively. The incidence of OIC by patient's assessment was 43.5% in 2 weeks after starting opioids (40.3% at a week after staring opioids). The change in PAC-SYM and PAC QOL score in OIC-patients compared to non-OIC patients were 0.399 vs -0.122 (p=0.0031) and 0.214 vs -0.016 (p=0.0540), respectively. **Conclusion:** The OIC can occur quickly after the initiation of opioid therapy in lung cancer patients and can have an impact on patient's QOL. These results suggest that an OIC management focusing on a quality and patient's feeling of bowel movement in early stage in opioid analgesic therapy is important for lung cancer patients.

Keywords: OIC-J, opioid-induced constipation, cancer pain

P2.16-19 REAL WORLD DATA IN NON-SMALL CELL LUNG CANCER WITH ACTIVATING EGFR MUTATION - A MULTICENTER OBSERVATIONAL STUDY

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Background: Osimertinib demonstrated durable responses in patients with advanced non-small cell lung cancer (NSCLC) harboring major epidermal growth factor receptor (EGFR) mutations (EGFRm+) and T790M resistance mutation (T790M+) in global trials, and approved in March 2016 in Japan. The best treatment strategy of EGFR tyrosine kinase inhibitors (TKIs), especially osimertinib, cytotoxic drugs, and immune checkpoint inhibitors (ICIs) is unknown. **Method:** To evaluate treatment selection with special attention to osimertinib, medical records of the patients with advanced EGFRm+ NSCLC who were under treatments at May 2016 or started a new treatment after May 2016 were collected. **Result:** A total of 543 patients were collected. Median age 69 years (range: 35 to 90); female 67%; never smokers 60%; adenocarcinoma 99%; major EGFR mutations 94%; interstitial lung diseases (ILD) 5%. The first line regimen was started between September 2002 and August 2018. The median total number of regimens was 2 (range: 1 to 13). EGFR-TKIs were administered to all patients, and were rechallenged in 56%; 42% received platinum combination regimens. The median overall survival and the median duration of EGFR-TKI treatments were 85 and 40 months, respectively. Re-biopsy was performed 1 to 6 times for 296 patients, T790M was detected in 47% of them. Osimertinib were used in 167 patients including 7 patients in whom an 1st EGFR-TKI was switched to osimertinib without PD. The median treatment line of osimertinib was 3 (range: 1 to 10), the response rate and the disease control rate of osimetinib was 44% and 71%, respectively, and the median time to treatment failure (TTF) was 13 months while 52% were censored. Osimertinib-induced ILD developed in 4 patients, and one patient died. Sixty-two patients received once or twice ICI treatments: nivolumab, pembrolizumab, and atezolizumab were administered to 38, 19 and 7 patients, respectively. The ICIs-induced ILD developed in 1 patient with nivolumab. The median TTF of ICIs was 2.3 months (range: 0 to 29), the response rate and the disease control rate were 14% and 53%, respectively, and 9% could continue ICI for one year or more. **Conclusion:** Re-biopsy was performed in 55%, and T790M was detected in 47%. In T790M+ including de novo T790M+ patients, osimertinib was used in 94%. Although this analysis has some limitations especially in patient selection, long-term survivors received platinum combination regimens, other cytotoxic drugs, and ICIs in addition to EGFR-TKIs.

Keywords: EGFR mutation, Non-Small Cell Lung Cancer, Osimertinib

P2.16-20 BIG DATA AND SURVIVAL PREDICTORS IN LUNG CANCER PATIENTS

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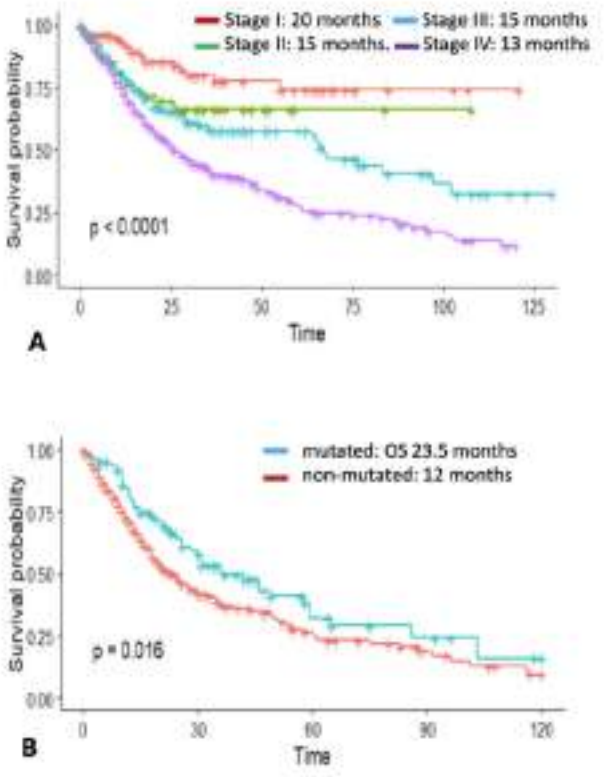
Background: Lung cancer is the most common and fatal one (18% of all cancer deaths). Parameters which imply better survival are still unknown. The objective of this project is to turn the large amount of data from each patient into exploitable information. **Method:** Between 2008-2019, 935 non-small cell lung cancer patients from our hospital were enrolled in an observational study. Unstructured data was obtained from the patient Electronic Health Records. Politecnica University from Madrid made the information analysis using Big Data and machine learning techniques. **Result:** A total of 251.730 documents have been analyzed from 935 patients, 54% in stage IV. EGFR/ALK mutation was found in 9%, showing better OS than non-mutated (23.5 months vs 12 months, log-rank p=0.016). Survival curves are shown in figure 1. In a multivariate analysis (table 1), independent predictors of mortality were male sex, squamous histology and PS status. Additionally, independent predictors of survival were receiving immunotherapy, surgery treatment or developing endocrine toxicities. **Conclusion:** Big data is a very useful tool to exploit a large amount of lung cancer data, increasing knowledge about these disease and allowing the development of survival predictive models.

This work was supported by the EU H2020 programme, under grant agreement Nº 727658 (Project iASiS).

MULTIVARIATE ANALYSIS (N=935)			
	OR	95% CI	P Value
MALE (N = 661)	1.46	1.5-2.03	<.03
SQUAMOUS	1.85	1.35-2.52	<.001
PS 1 *	1.65	1.23-2.23	<.001
PS 2 *	2.33	1.45-3.76	<.001
PS 3 *	2.53	1.04-6.11	.004
IMMUNOTHERAPY	0.5	0.32-0.85	.009
SURGERY	0.7	0.52-0.97	0.03
ENDOCRINE TOXICITIES SECONDARY TO TREATMENTS**	0.5	0.41-0.85	.005

*PS: Performance status: compared to PS 0
** Endocrine toxicities: Hypo/hyperthyroidism and adrenal insufficiency.



Keywords: mutations, Big data, predictive survival models

POSTERS

P2.16-21 EFFECTS OF MOLECULAR MARKERS ON RESPONSES, RELAPSES, AND SURVIVAL IN LUNG CANCER PATIENTS WITH HIV

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Background: Patients with HIV are aging due to potent combination antiretroviral therapy (ART) and the incidence of lung cancer has increased. Limited research has been performed on the relationship between HIV and lung cancer prognosis and recurrence. Based on previous data and our clinical experience, patients with HIV and lung cancer have worse prognosis1 potentially due to social and behavioral risk factors, unfavorable molecular markers and differences in treatment patterns. **Method:** We identified patients with HIV and lung cancer between January 1, 2001 and December 31, 2015 using Northwestern Medicine (NM) Electronic Data Warehouse (EDW). Lung cancer cases were verified and treatment/outcome information was extracted by chart review. We then compared the effects of molecular markers on treatment responses, relapses, and survival in lung cancer patients with HIV infection. Incidence and prognosis were compared to historical, non-HIV lung cancer controls. **Result:** We included 36 individuals with HIV and lung cancer in this analysis. The median age at diagnosis was 55 years, 75.0% (27/36) were male, 94.0% (34/36) smokers. Histology: Small Cell – 1 (2.8%), Squamous cell – 10 (27.8%), Adenocarcinoma – 21 (58.3%), Other NSCLC – 2 (5.6%) Unreported – 2 (5.6%). Molecular: EGFR – 2 (5.6%), ROS1 – 0 (0%), ALK – 3 (8.3%), KRAS – 1 (2.8%), PDL1 – 2 (5.6%), Not Reported – 6 (16.7%). Stage at Diagnosis: Stage I – 3 (8.3%), Stage II – 6 (16.7%), Stage III – 2 (5.6%), Stage IV – 21 (58.3%), unreported – 4 (11.1%) Median survival – 2 years for all patients. EGFR – 1 year, ALK – 5.5 years, KRAS – 1 year, PDL1 – 1 year **Conclusion:** In prior research, patients with HIV and lung cancer appear to have decreased survival with reported overall survival of 7 months compared to 25 months for historical controls irrespective of stage and stage appropriate treatment for lung cancer2. In our study cohort, patients appeared to be treated similar to non-HIV controls, and the overall survival is fairly consistent with historic non-HIV controls, but smoking incidence (34/36; 94%) was higher than in non-HIV patients with lung cancer (85%). The prevalence of ALK translocation (3/36; 8%) was higher than typically observed among those without HIV (3-5%) and occurred exclusively in smokers. Typically, ALK translocation occurs in non-smokers. HIV patients treated with ALK inhibitors appeared to respond to similarly to non-HIV patients with NSCLC based on historic clinical data. Increased mortality in HIV, lung cancer patients is likely multifactorial, including concerns for lack of aggressive anti-cancer therapy delivered in this population. Our findings suggest that identifying driver mutations and molecular marker mutations may improve clinical practice for treatment of HIV-associated lung cancer. More prospective study is needed in this population.

Keywords: HIV, molecular markers, median survival

P2.16-22 PREDICTIVE ANALYTIC OF SURVIVAL USING A NEURAL NETWORK IN A REAL WORLD COHORT OF ADVANCED NON SMALL CELL LUNG CANCER PATIENTS

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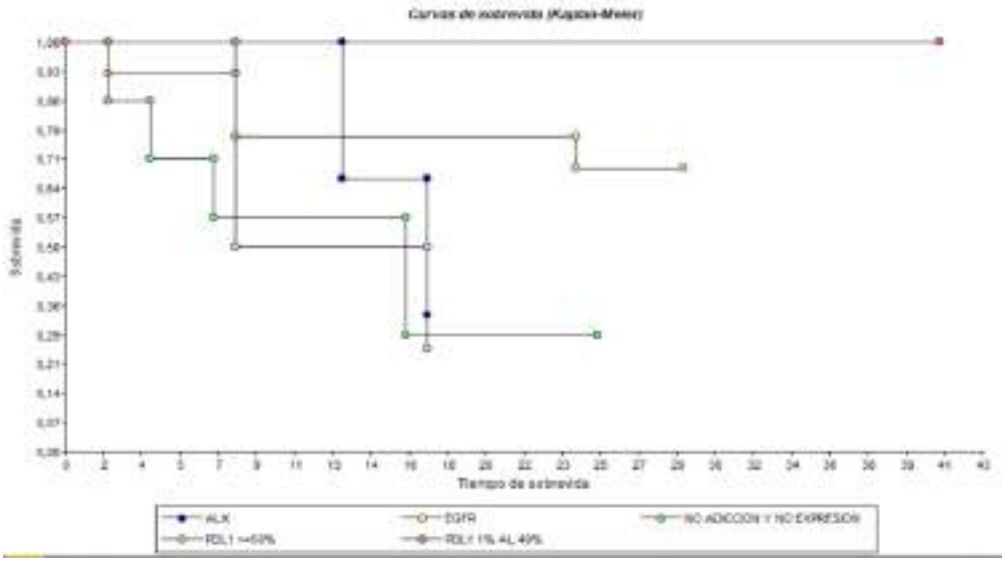
Background: When talking about a probabilistic neural network a new concept on survival is introduced. Using advanced statistics, different characteristics amongst patients such as oncogenic driver mutation, smoking status or age can be correlated to calculate the probability of survival in each individual and even for each attending institution. **Method:** We built a neural network model that allowed us to estimate the probability of mortality according to the variables: Oncogenic addiction (EGFR mutation and ALK rearrangements), expression of PDL-1, age, gender and exposure to cigarette. These variables were obtained from a cohort of patients with advanced non-small cell lung carcinoma who received treatment in our institution during the last 3 years. **Result:** Thirty-one patients were included in the model. The accuracy of the neural network was 78.57% for the patients that died and 82.35% for the patients still alive. It was possible to calculate the probability of overall survival and the probability of dying in relation to age, exposure to cigarette, gender, oncogenic addiction and PDL-1 expression for each person and for the whole cohort. Individual results and global results (Kaplan Meier) are shown in table and graphic.

Gender	Age (years)	Exposure to cigarette	Mutation/PDL-1	Probability of overall survival	Probability of dying
M	21	No	PDL1: 1% AL 49%	1.2%	98.8%
F	28	No	EGFR mut	19.1%	80.9%
F	40	No	EGFR mut	13.8%	86.2%
F	41	No	PDL1 1% AL 49%	8.3%	91.7%
F	44	No	EGFR mut	7.8%	92.2%
F	48	No	EGFR mut	5.1%	94.9%
M	49	Si	PDL1 >=50%	14.2%	85.8%
F	50	Si	EGFR mut	47.8%	52.2%
M	52	Si	EGFR mut	5.6%	94.4%
F	53	No	EGFR mut	3.5%	96.5%
F	53	Si	EGFR mut	41.5%	58.5%
F	54	No	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	4.5%	95.5%
F	54	No	ALK mut	8.3%	91.7%
F	58	Si	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	16.8%	83.2%
F	60	Si	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	19.3%	80.7%
M	60	Si	ALK mut	7.7%	92.3%
M	62	No	PDL1 >=50%	0.8%	99.2%
M	63	Si	ALK mut	8.6%	91.4%
M	69	Si	PDL1 1% AL 49%	2.8%	97.2%
F	73	Si	EGFR mut	9.2%	90.8%
M	75	Si	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	4.9%	95.1%
M	75	Si	PDL1 >=50%	47.7%	52.3%
F	76	Si	EGFR mut	8.7%	91.3%
M	77	Si	PDL1 >=50%	47.9%	52.1%
M	78	No	EGFR mut	0.6%	99.4%
M	79	Si	PDL1 1% AL 49%	1.8%	98.2%
M	85	Si	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	6.2%	93.8%
F	75	No	EGFR mut	1.3%	98.7%
F	62	Si	EGFR mut	17.7%	82.3%
M	53	No	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	5.3%	94.7%
M	56	Si	NO ONCOGENIC ADDICTION – NO PDL1 EXPRESSION	7.8%	92.2%



Conclusion: The minimum data sample required to produce the model was used (n=31), thus it would not be correct to talk about global conclusions. However, this is a representative model of a proof of concept related to predictive analytics related to probability of survival in a real world setting using a neural network that worked on an individual basis according to clinical and biological characteristics. Results for the entire cohort are also available. Using a greater amount of data will increase the accuracy of the neural network to predict survival and other outcomes in an individual and even institutional basis that will improve data analytics in real oncologic settings.

Keyword: Non Small Cell Lung Cancer, Neural Network, Predictive Analytics

POSTERS

P2.16-23 RATES OF SUPPORT AND CARE OFFERINGS AMONG PATIENTS IN AN ADVOCACY ORGANIZATION SPONSORED LUNG CANCER PATIENT REGISTRY

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Background: We conducted a survey of lung cancer patients and caregivers in the United States in 2015 and 2016 that identified gaps in access to supportive care and patient education. An additional survey of patients and caregivers in 2016 revealed low rates of molecular testing among lung cancer patients despite being recommended by clinical guidelines. In order to gauge how much progress has been made in addressing these gaps, we looked at self-reported rates among participants in a lung cancer patient registry founded by a patient advocacy organization, the GO2 Foundation for Lung Cancer. **Method:** The Lung Cancer Registry, supported by the GO2 Foundation for Lung Cancer, and partners The American Lung Association and The International Association for Lung Cancer, collects self-reported data from lung cancer patients and caregivers through an online interface on a variety of topics related to patients' lung cancer diagnoses and care experiences. For this study, we analyzed data collected from 939 registry participants between November 2016 to December 2018 on supportive care, assistance, and molecular testing offerings to patients. **Result:** The majority of registry participants reported that their doctors had discussed future treatment options beyond their current line of therapy with them (72%) and that care navigation help had been offered to them by a nurse navigator or care coordinator (60%). Additionally, most participants (88%) reported their clinic had provided educational materials related to their diagnosis or treatment. High rates of molecular testing were also reported among registry participants (76%). Testing most commonly occurred at initial diagnosis. **Conclusion:** Registry participants were offered navigation and patient education resources at high rates. Additionally, molecular testing was offered at high rates occurring early in care. This suggests that significant progress has been made by the lung cancer community in the United States to address previously identified gaps in certain aspects of support and care. However, registry participants represent a highly educated, technology-enabled population, indicating that gaps may still exist and should be looked at further in other demographics such as in rural and lower socio-economic areas where lung cancer is common.

Keywords: Molecular Testing, Lung cancer, patient navigation

P2.16-24 PROGNOSTIC VALUE OF RDW, NLR AND CYFRA 21-1 IN OVERALL SURVIVAL OF PATIENTS WITH METASTATIC NSCLC

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Background: Lung cancer remains as the main cause of death in many regions around the world. Unfortunately, most cases are diagnosed as advanced disease that determinates dismal outcomes. There is a lack of biomarkers in clinical practice and also high mortality rates not related to cancer. CYFRA 21-1 is an important biomarker related to burden of disease; neutrophils-to-lymphocyte ratio (NLR) and red blood call distribution width (RDW) represent systemic inflammatory biomarkers indirectly related to immune response, and nutritional components, which are critical factors that can increase the risk of death not related to cancer. Our aim was to evaluate the prognosis value of CYFRA 21-1, NLR, RDW and components of nutritional status (albumin, creatinine, and hemoglobin) in overall survival (OS) of metastatic NSCLC patients treated at a private institution (Oncosalud - AUNA). **Method:** We analyzed data of 87 patients with metastatic NSCLC treated at Oncosalud-AUNA 2011 - 2014 (Lima - Peru). The clinical-pathological data were collected from digital medical records. The laboratory data (hemoglobin, albumin, RDW-CV, creatinine, neutrophil, lymphocyte, and monocyte) and CYFRA 21.1 were collected from blood routine tests. Optimal cutoff value of NLR (<3.6 and >3.6), LMR (<4.7 and >4.7), RDW-CV (<15% and >15%) and CYFRA 21.2 (<3.3 and >3.3) were determinate using the maximally selected rank statistics. OS was determinate using Kaplan-Meier method and survival curves comparison were performed using log-rank or Breslow test. Cox model was used to estimate the effect of nutritional components and tumoral biomarkers on overall survival. **Result:** The median age was 68 years (range: 40-84) and 50.6% of cases were women. The 26.4% presented with 2-4 ECOG scale, the most frequent site of metastasis were bone (36%) and brain (22%), and the most common histology was adenocarcinoma (84%). Hemoglobin was low in 16% and 28.7% had abnormal albumin, 44.8% elevated RDW-CV, 24.1% abnormal creatinine, 47.1% elevated NLR, and 72.4% high CYFRA 21-1 value. The 88.5% of patients received chemotherapy and 11.5% had TKI as first-line treatment. The median follow-up was 60 months (95%CI: 44.4-74.6), median survival was 13.2 months (95%CI: 9.8 - 16.7), two and 5-years survival rate were 30.8% and 17.1%, respectively. In univariate analysis, only ³2 ECOG scale (p = 0.062), RDW-CV >15 (p = 0.011), NLR >3.6 (p = 0.019) and CYFRA 21.1 >3.3 ng/mL (p = 0.003) were associated with poor survival. We did not found significant differences with age, sex, Hb, albumin, and LMR. In the Cox model, low values of Hb (HR: 2.1, 95%CI: 1.01-4.5), high values of RDW-CV (HR: 2.6, 95% CI: 1.3 - 5.2), NLR (HR: 1.8, 95% CI: 1.1 – 3.2) and CYFRA21.2 (HR: 2.3, 95% CI: 1.1 - 4.6) were associated with poor OS. **Conclusion:** Overall survival for our patients was similar to reports from other series. Patients with elevated RDW, NLR and CYFRA 21.2 have poor prognostic in our cohort.

Keyword: Metastatic NSCLC, RDW, NLR, CYFRA 21.1, Overall Survival

P2.16-25 EPIDEMIOLOGY OF ADVANCED LUNG CANCER IN PERU

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Background: Epidemiology and survival data of lung cancer is scarce in Latin America. This information is essential to understand the regional burden that cancer represents and to design and implement targeted interventions for cancer control. Similarly to what happens in the rest of the world, most of our lung cancer patients present with advanced disease. **Method:** Retrospective analysis of metastatic lung cancer cases diagnosed at Instituto Nacional de Enfermedades Neoplasicas (INEN) Lima-Peru between 2010 to 2014 were reviewed. Data was manually curated from clinical files. **Result:** 993 patients were included, corresponding to 85% of total lung cancer cases diagnosed within the same time period. Median age at diagnosis was 63 years old (range 20-91y) and 55% were females. 25% of patients had history of exposure to biomass fumes from cooking inside the house and 20% of patients were smokers. The histologic type was adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma and large cell carcinoma in 89.2%, 9.8%, 0.8% and 0.2% of the cases, respectively. The adenocarcinoma/squamous cell carcinoma ratio was 9/1. With a median follow-up of 78 months, median overall survival (OS) was 7 months. Median OS for adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma was 7, 6, and 5 months, respectively. **Conclusion:** The epidemiological profile of lung cancer in Peruvian patients is unique as it is characterized by a younger age at presentation, a preponderance of females over males and a strikingly high frequency of adenocarcinomas. This may be in concordance with the low prevalence of tobacco smoking and the high prevalence of EGFR mutations previously reported for our population as well as with special exogenous exposures. The low survival could be partially attributed to the lack of access to targeted therapy during those years. The molecular characterization of this cohort of patients is ongoing.

Keywords: Advanced lung cancer, NSCLC, epidemiology

P2.16-26 OPPORTUNITY OF WBRT IN EGFR-MUTATED LUNG ADENOCARCINOMA PATIENTS WITH MULTIPLE BRAIN METASTASES: A RETROSPECTIVE STUDY BASED ON DS-GPA

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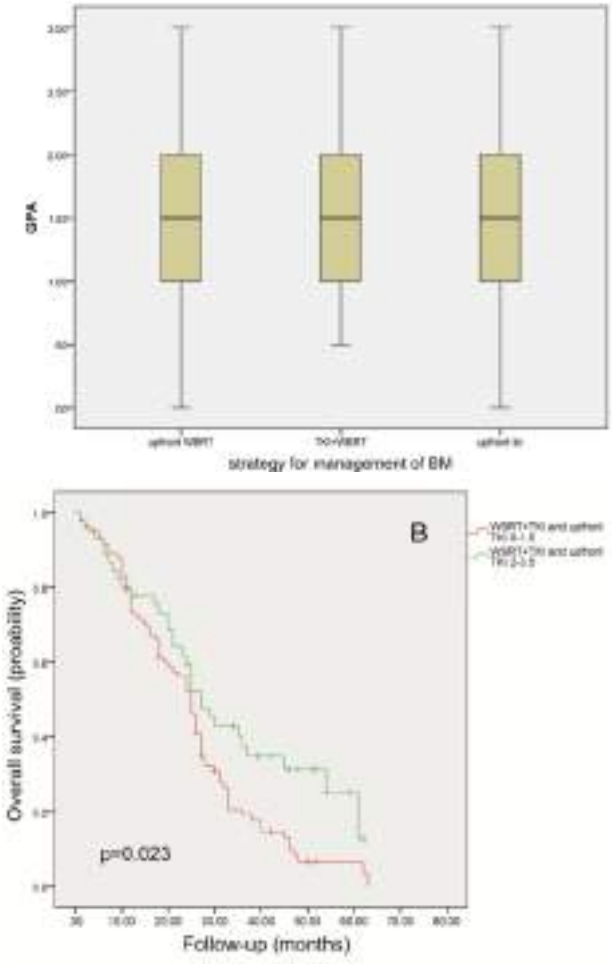
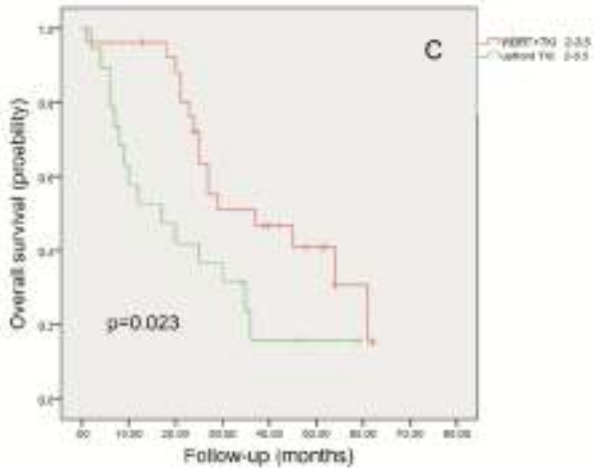
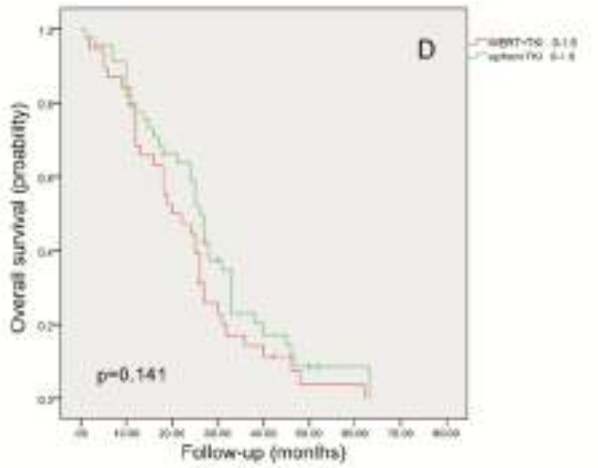
Background: Whole-brain radiotherapy (WBRT) and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are effective treatment options for multiple brain metastases (BM) in patients with EGFR-mutant adenocarcinoma. This study evaluated the optimal treatment sequence between EGFR-TKI and WBRT in patients with EGFR mutation adenocarcinoma and multiple BM **Method:** A total of 195 patients with EGFR-mutant adenocarcinoma with multiple BM were enrolled in the study. Patients were treated with EGFR-TKI for over 4 weeks after WBRT,received EGFR-TKI concurrently in phase with WBRT or within 4 weeks after WBRTor treated with WBRT during intracranial progression after EGFR-TKI initiation. Overall survival (OS) and disease-specific Graded Prognostic Assessment (DS-GPA) was measured. **Result:** For the entire cohort, the median OS was 27 months (95% CI, 24.6 to 29.4). GPA-based subdivided patients upfront WBRT of GPA, 0 to 1.5 (median: 30 months; n=36; 18%); upfront WBRT of GPA, 2.0 to 3.5 (median:48 months; n=31; 16%); EGFR-TKI concurrently with WBRT of GPA, 0 to 1.5 (median:20 months; n=38; 19%); EGFR-TKI concurrently with WBRT of GPA 2.0 to 3.5 (median:37 months; n=26; 13%); upfront EGFR-TKI of GPA 0 to 1.5 (median:26 months; n=45; 23%); and upfront EGFR-TKI of GPA, 2.0 to 3.5 (median:17 months; n=19; 10%).The prognosis of patients in different GPA groups differed significantly (p<0.0001). The data by these parameters and the results showed no imbalance with respect to the number of patients on GPA scores (T=1.786,p=0.076).In groups at EGFR-TKI concurrently with WBRT and upfront EGFR-TKI, patients with GPA score 2-3.5 demonstrated a significantly longer OS than those at score 0-1.5 (P=0.023), patients with EGFR-TKI concurrently with WBRT is longer than those with upfront EGFR-TKI in subgroup at GPA score 2-3.5(P=0.023).There was no difference in the OS at 0-1.5 score level between the EGFR-TKI concurrently with WBRT group and the upfront EGFR-TKI group (P=0.141).







Conclusion: For EGFR-mutated lung adenocarcinoma patients with multiple BM,the use of upfront WBRT achieved a significantly longer OS in high DS-GPA scores groups.

Keywords: whole brain radiation therapy (WBRT), brain metastases (BM), disease-specific Graded Prognostic Assessment (DS-GPA)

P2.16-27 LONGITUDINAL SKELETAL MUSCLE CHANGES IN PATIENTS WITH ADVANCED SQUAMOUS CELL LUNG CANCER

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Background: Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass. Skeletal muscle depletion is prevalent in lung cancer patients and is associated with poor prognosis. This study analyzed the changes in skeletal muscle mass until the end of life in patients with advanced squamous cell lung cancer (SQCLC). **Method:** This retrospective study consisted of 70 consecutive patients who underwent palliative chemotherapy for SQCLC and died between September 2010 and March 2015. A cross-sectional area of muscle at the level of the first lumbar vertebra (L1) was measured using computed tomography scans. An artificial intelligence algorithm was developed and used for serial assessment of muscle area. Sarcopenia was defined as a L1 skeletal muscle index of ≤ 46 cm2/m2 for men and ≤ 29 cm2/m2 for women. Median interval between last scans and deaths was 1.3 months (95% CI, 0.9 to 1.7). **Result:** The median age was 69 years and 82% of patients were male. Sarcopenia was present in 58 patients (76%) at baseline. Median overall survival was 8.7 months (95% CI, 5.9 to 11.5). All patients experienced net muscle loss over the disease trajectory. Mean percentage loss of skeletal muscle between the first and last scans were 16.5±11.0%; mean decrease of muscle area was 17.28±13.00 cm2 (p < 0.001) at a rate of 2.64±2.36 cm2/month. Skeletal muscle loss was accelerated over time. Patients lost an average of 1.64±1.02 cm2, 2.00±1.52 cm2, 2.91±2.69 cm2, and 4.82±4.59 cm2 skeletal muscle per month during the last 12, 9, 6, and 3 months, respectively (p < 0.001). Patients losing skeletal muscle at ≥ 3.24 cm2/month (upper tertile) had shorter overall survival

compared with patients who lost muscle at slower rate (median, 5.7 vs. 12.0 months; p < 0.001). **Conclusion:** Patients with advanced SQCLC lose significant amount of skeletal muscle until death. The rate of muscle mass reduction is faster at the end of life. Patients who lose muscle at the higher rate have shorter survival time.

Keywords: cancer cachexia, muscle, Lung cancer

P2.16-28 RETROSPECTIVE ANALYSIS OF PATIENTS WITH PREVIOUS EXTRATHORACIC MALIGNANCIES AFTER RESECTION OF NON-SMALL CELL LUNG CANCER

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Background: The number of patients with previous malignancies has increased because survival time is prolonged in various malignancies. Therefore, opportunities to consider surgical indications for non-small cell lung cancer (NSCLC) patients with previous malignancies are increasing. The aim of the study is to compare the backgrounds and prognosis of NSCLC patients who had the history of previous extrathoracic malignancies with no other cancer history. **Method:** Our institutional database of patients after curative resection of NSCLC from 2006 to 2013 was reviewed. Patients with synchronous or metachronous multiple lung cancer were excluded. Clinicopathological features of these patients and information about survival and recurrence were collected from the electronic medical record. Overall survival (OS) and recurrence-free probability (RFP) were estimated using the Kaplan-Meier method. **Result:** In a total of 249 patients, 49 (19.7%) had previous extrathoracic malignancies. The number of previous extrathoracic malignancies was 1 in 44 patients, 2 in 3 patients and 3 in 1 patient. Sixteen patients had colorectal cancers among previous extrathoracic malignancies, 10 patients had gastric cancers and 5 had hematopoietic neoplasms. If patients with previous extrathoracic malignancies were compared to those without, the median age was 69.5 vs. 65.5 (p=0.015), male sex was 71.4% vs. 66.5% (p=0.506), average of Brinkman index was 914.2 vs. 709.7 (p=0.127) and average of serum level of carcinoembryonic antigen was 5.4 ng/mL vs. 7.5 ng/mL (p=0.506). Pathologically, stage 0 and I NSCLC account for 73.5% of patients with previous extrathoracic malignancies and 66.0% of those without it (p=0.311). The 5-year OS was 70.3% vs. 79.1% (p=0.422) and the 5-year RFP was 58.9% vs. 67.7% (p=0.223). **Conclusion:** Patients with previous extrathoracic malignancies are significantly older than those without previous extrathoracic malignancies. Patients with previous extrathoracic malignancies had relatively earlier stage NSCLC. The OS and RFP also tended to be worse in patients with previous extrathoracic malignancies. Further study is needed to consider surgical indication for NSCLC with previous extrathoracic malignancies.

Keywords: Non small cell lung cancer, prognosis, extrathoracic malignancies

P2.16-29 LUNG CANCER IN LLEIDA: AN EPIDEMIOLOGIC STUDY

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Background: According to GLOBOCAN, in 2018 lung cancer was associated with the greatest incidence and mortality attributable to cancer worldwide: 27.9 cases/100,000 habitants and 23.5 cases/100,000 habitants, respectively. In Spain, lung cancer is the fourth most frequent cancer but the first cause of cancer mortality in the country. We have undertaken this study to compare the epidemiologic data for lung cancer in our Spanish provincial population with those worldwide and nationwide **Method:** This was an observational, retrospective study. It included all patients with lung cancer in the Lleida province of Catalonia, Spain in a period of 6 years, from January 2011 to December 2016. Data taken from electronic medical records included variables such as sex, age of diagnosis, smoking history, histology, stage, and oncologic treatments, among others. Incidence, prevalence, survival and mortality rates were determined, as well as the main clinical characteristics of the cohort **Result:** Seven hundred eighty-two patients with a diagnosis of lung cancer between January 2011 and December 2016 were included. Median follow-up was 11.7 months. Men comprised 78.6% of the cohort. The median age at diagnosis was 66.6 years. More than half of the patients (53.2%) smoked at the time of diagnosis. The majority were adenocarcinomas (44.1%), with 33.2% squamous cell carcinomas, and 12.1% small cell carcinomas. EGFR testing was performed in 300 patients. 18.7% were positive for a mutation, of which 69.7% were exon 19 insertions. At diagnosis, 52.3% of cases were stage IV, 25.3% stage III, 7.3% stage II, and 14.5% stage I. The average annual incidence rate was 37 cases/100,000 habitants. The median overall survival (OS) was 12.3 months (95% CI: 10.7-13.8). The OS at 1 year was 50.8% (95% CI: 47.3-54.3) and at 5 years was 13.7% (95% CI: 10.2-17.2). The estimated mortality rates were 49.2% in the first year and 86.3% at 5 years **Conclusion:** In the Lleida province of Spain, the incidence and mortality associated with lung cancer are greater than global rates but lower than those of Spain as a whole. Lung cancer survival at 5 years is greater than countrywide statistics. The heathier lifestyle and rural geography may favor the lower incidence of lung cancer in Lleida compared with the rest of Spain

Keywords: Lung cancer, epidemiology, spain

P2.16-30 REAL WORLD DATA OF TARGETED THERAPY VERSUS CHEMOTHERAPY MAINTENANCE AMONG PATIENTS WITH III-IV CLINICAL STAGE LUNG CANCER AT ONCOSALUD – AUNA

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Background: Lung cancer is still a prevalent and fatal neoplasm in developing countries where newer therapies usually had issues about economic toxicity and real clinical benefit in terms of overall survival. In the last decades, chemotherapy maintenance has occupy an important role in the treatment, as well as targeted therapies (tirosin kinase inhibitors and bevacizumab) in the frontline treatment. Our aim was to evaluate the survival impact of targeted therapy in advanced lung cancer at a private Peruvian institution (Oncosalud – AUNA). **Method:** We analyzed retrospectively data of two cohort of patients with advanced NSCLC (III-IV clinical stage) treated at Oncosalud-AUNA during the period 2008 - 2013 (Lima, Peru). The clinical-pathological data were collected from digital medical records. After a clinical response obtained with a standard regimen based on chemotherapy (≥ stable disease), all patients were distributed in two groups. Group 1 received only maintenance chemotherapy and group 2 had maintenance with targeted therapy, either erlotinib or bevacizumab. OS was determinate using Kaplan-Meier method and survival curves comparison were performed using log-rank or Breslow test. Cox model was used for multivariate analysis. **Result:** During the study period 58 cases were included, 30 and 28 cases were distributed in group 1 and 2, respectively. The median age was 65 years (range: 44-85) and male:female ratio was 1:1, less than 16% had ≥2 ECOG scale, and about two thirds were diagnosed as CS IV. No statistically difference was found between both two groups. More than 60% of patients received at least six cycles platins based chemotherapy, only five cases reached complete response (8%), partial response was 47% and stable disease 45%. In the group 2, 46% received combined treatment based on bevacizumab and 54% erlotinib as maintenance therapy. Progression rates were 87 and 86% in groups 1 and 2, respectively. The median follow-up was 3 years, median PFS were 10 months for group 1 and 17 months for group 2, and 2-years PFS rates were 17 versus 30%, respectively (p=0.008). Median OS were longer in the group with targeted therapy (3.7 versus 1.4 years, p=0.014). In multivariate analysis the use of targeted therapy (PFS: HR:0.47, 95% CI[0.26,0.85], p=0.013 and OS: HR:0.36, 95% CI[0.18, 0.74], p=0.005) and age <60 years (PFS: HR:0.41, 95% CI[0.19,0.9], p=0.027 and OS: HR:0.30, 95% CI[0.12, 0.73], p=0.008) were associated to better outcomes. **Conclusion:** An important clinical benefit in terms of survival was obtained with the addition of targeted therapy to the standard of care in the treatment of lung cancer in our cohort.

Keyword: Advanced lung cancer, targeted therapy, Overall Survival

P2.16-31 IMMUNOTHERAPY IN THE REGIONAL SETTING: REAL WORLD EXPERIENCE OF OUTCOME AND TOXICITY

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Background: Immune checkpoint inhibitors (ICI) have revolutionised the management of lung cancer. These agents have an established role in metastatic non small cell lung cancer (NSCLC) and inoperable NSCLC. Recent studies demonstrate benefit of ICI in first line treatment of metastatic NSCLC. Ongoing studies are exploring the role of ICI in early stage lung cancer and small cell lung cancer. ICI possess a distinct adverse effect profile which differs from cytotoxic chemotherapy. We explore the implications of ICI for patients with NSCLC in a regional setting. **Method:** The medical records of all patients with NSCLC who were treated with an immune checkpoint inhibitor at our cancer centre were examined. Information regarding patient demographics, tumour histology, PDL1 staining, performance status, smoking status and sites of metastasis were obtained. We calculated rates of clinical outcomes including progression free survival and objective response rates. We also examined rates of adverse effects and need for emergency department presentation, hospitalisation and treatment with steroids. **Result:** Forty-five patients with lung cancer who were treated with ICI between 2016 and 2018 were identified. 70% were male. The average age was 70 years. 30 (67%) received nivolumab, 8 (18%) received atezolizumab, 4 (9%) received durvalumab and 3 (6%) received pembrolizumab. 31 (69%) had adenocarcinoma histology. Only 4 patients (9%) had PDL1 stain testing performed; 3 were PDL1 high (greater than 50%) and 1 was PDL1 negative. 13% of patients had brain metastases and 16% had liver metastases. Of the 41 patients with metastatic disease, 10 patients obtained a partial response. The objective response rate was 22%. Median progression free survival was 5.8 months. Median overall survival was 11.6 months. 37 patients (82%) had an adverse effect of any grade and 7 (16%) had a grade 3 or greater adverse effect. The most common adverse effect was fatigue (62% any grade, 6% grade 3 or greater). 36% of patients required steroid treatment. 12 patients (27%) died within 30 days of receiving ICI. **Conclusion:** Treatment of cancer patients in regional settings carry unique challenges which need to be overcome in order to ensure equitable health outcomes. We report the experience of an individual regional cancer centre. Results are comparable to other published reports and demonstrate safe treatment of lung cancer patients in a regional setting.

Keywords: toxicity, Immunotherapy, regional

P2.16-32 BEST SUPPORTIVE CARE FOR EXTREME ELDERLY LUNG CANCER PATIENTS

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Background: In Japan, the population of extreme elderly individuals (85 years and older) was about 5.8 million in 2018, and the number of extreme elderly lung cancer patients is increasing. Because of their environmental conditions, they often received the best supportive care (BSC) without chemotherapy or definitive therapy. **Method:** We conducted an IRB-approved retrospective analysis of 34 lung cancer patients aged 85 years and older, who were treated at our institute from 2014 to 2017, and assessed their backgrounds and prognosis. **Result:**

Table: Cox proportional hazard analysis of overall survival.

Variable	Hazard.ratio (95% C.I)	p.value
PS = 0-2	0.11 (0.04-0.34)	<0.01
Without cognitive-function disorder	0.35 (0.14-0.89)	0.027
Without metastasis	0.22 (0.07-0.68)	<0.01
Good nutrition (serum albumin ≧ 3.5 g/dL)	0.09 (0.02-0.41)	<0.01
Low plasma CRP(CRP ≦ 10mg/L)	0.27 (0.08-0.92)	0.036

The median age was 89 years (range, 85-96 years), and 22 patients were male. Among the patients considered, 11 had adenocarcinoma (3 harboring EGFR mutation), 8 had squamous cell carcinoma, 5 had NSCLC-NOS, 3 had SCLC, and 7 had an unknown cancer type. Fifteen patients were assigned an ECOG good PS of 0-2, and 19 patients a poor PS of 3-4. The main reasons for receiving BSC alone were poor PS (44%), own will (38%) and cognitive-function disorder (18%). In 10 patients, cancer did not metastasize and 15 patients were transferred to the nursing facility. The median overall survival was 5.6 months. According to univariate analysis (Cox proportional analysis), absence of metastatic disease [hazard ratio: 0.22, 95% confidence interval [C.I.]: 0.07-0.68], PS 0-2 [hazard ratio: 0.11, 95% C.I.: 0.04-0.34], good cognitive function [hazard ratio: 0.35, 95% C.I.: 0.14-0.89], good nutrition (serum albumin ≥ 3.5 g/dL) [hazard ratio: 0.09, 95% C.I.: 0.02-0.41] and plasma C reactive protein(CRP) ≤ 10 mg/L [hazard ratio: 0.27, 95% C.I.: 0.08-0.92] were associated with significantly longer overall survival. Median overall survival of patients with and without metastasis were 1.8 months and 19.7 months, respectively. Patients without metastasis tended to have good PS and had lesser hypoalbuminemia. Most of the patients without metastasis received BSC alone, of their own will. **Conclusion:** In extreme elderly lung cancer patients, BSC alone had often been selected for reasons other than the disease condition. It is important to construct a palliative treatment strategy based on medical and social characteristics of extreme elderly individuals.

Keywords: extreme elderly lung cancer patients, Best supportive care, Prognostic factor

P2.16-33 WHAT INFLUENCES PATIENT DECISION-MAKING ABOUT LUNG-CANCER TREATMENT? A DISCRETE CHOICE EXPERIMENT

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Background: Despite major advances in radiotherapy, surgery remains the treatment of choice for patients with stage I non-small cell lung cancer. We sought to investigate what influenced preferences for surgery or SABR among cancer patients. **Method:** Using a discrete choice experiment (DCE) survey, we asked cancer patients to choose between lung cancer treatment options described by: type of treatment, chance of being cancer free for 12 months, chance of experiencing life threatening complications, chance of ongoing complications, impact on usual activities, who recommended treatment, whether treatment is usual care and out-of-pocket (OOP) costs. Each respondent completed nine choice questions. Choices were analysed using latent class analysis. **Result:** A total of 204 responses were received (57% female). Of these, 20 reported a diagnosis of lung cancer; the rest had been diagnosed with other cancers, including 53 with melanoma. Overall, the chance of being without cancer was considered the most important attribute and costs the least. The latent class analysis identified three groups: Group 1 (21%) was focussed on costs and the doctor's recommendation; Group 2 (60%) focused on the intervention (with a preference for surgery over radiotherapy), efficacy, side effects, functioning, doctor's recommendation and the highest level of OOP costs; Group 3 members (19%) were focused on the doctor's recommendation only. Women are more likely to be in Group 1 relative to 3, and those with higher educational attainment are more likely to be in Group 2 than 3. A more substantive analysis showed further differences between groups in terms of their tumour status, gender, educational attainment and health-care card status. **Conclusion:** The results of this study show that a doctor's recommendation is a vital factor in patients' decision-making. The importance of this finding is emphasised by the fact that Group 2, representing 60% of respondents, preferred surgery over radiotherapy. Advocates of radiotherapy as a curative intervention for lung cancer need to educate doctors as well as patients about its potential side-effects, benefits and costs.

Keywords: Patient preference, Decision-making, radiotherapy

P2.16-34 IS PROPHYLACTIC CRANIAL IRRADIATION USEFUL IN REAL WORLD?

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Background: Small cell lung cancer (SCLC) is the most aggressive lung cancer subtype. Just one third of patients are diagnosed as limited stage (LS), in which the goal is to perform a radical treatment. However, the majority will develop metastasis, being in central nervous system (CNS) one of the most frequent. In patients with LS, after systemic treatment, prophylactic cranial irradiation (PCI) should be considered. Nevertheless, the effectiveness of PCI has been a controversial issue in terms of overall survival (OS). **Method:** A cohort of 81 patients diagnosed of localized SCLC were retrospectively analyzed in our center over a 10-year period (January 2008-December 2017). Brain imagen was done before chemo-radiotherapy (CRT) and repeated before PCI. Baseline demographics characteristics and brain metastases rate incidence were described. **Result:** From 81 patients, 48 received PCI and 33 did not. Complete baseline characteristics from both groups are shown in *table 1.* No differences were found in performance status at diagnosis between groups . From those who did not receive PCI, 8 (26%) had developed brain metastases after CRT and before PCI. Brain metastases incidence rate in PCI subgroup was 9/100 people per year vs 35/100 people per year in those who did not receive PCI, in whom 54.5% had brain or systemic progression before PCI planning. Progression free survival in both subgroups was 13.5 months and OS was 21.2 months.

	PCI realized	No PCI realized
NUMBER OF PATIENTS	48	33
SEX	29 male; 19 female	22 male; 11 female
AGE AT DIAGNOSED	62 year (IQR 58-68)	67 (IQR 57-77)
STAGE TNM 8TH	≤ IIIA: 25 IIB ó IIC: 23	≤ IIA: 17 IIB ó IIC: 16
CNS METASTASES DEVELOPMENT YES/NO	14 vs 34	15 vs 18
PERCENTAGE OF CNS PROGRESSION	29% (14/48) p 0,13	45% (15/33) p 0,13
CNS METASTASES BEFORE PCI	0	8
METASTASES DEVELOPMENT INCIDENCE RATE	9/100 people-year	35/100 people-year

Conclusion: In our series, PCI had a significant effect in decreasing brain metastases. This study also confirms the requirement of brain imaging to confirm lack of brain metastases after initial CRT and before PCI.

Keywords: PCI, SCLC, Brain metastases

P2.16-35 FACTORS ASSOCIATED WITH PROLONGED POSTOPERATIVE HOSPITAL STAY IN PATIENTS UNDERGOING LUNG CANCER SURGERY

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Background: It is important to focus on the risk factors associated with prolonged postoperative hospital stay (PHS) as they can significantly increase medical costs. The study aimed to identify independent risk factors of prolonged PHS in patients who underwent lung cancer surgery. **Method:** Data were collected from an ongoing, real-world, multicenter, prospective, observational study (NCT03341377). Inclusion criteria were age 18 years and older, no cognitive impairment and ability to understand the study requirements, pathological primary lung cancer diagnosis, and scheduled surgical procedure. Prolonged PHS was defined as hospitalization for more than 7 days after a lung cancer surgery. Logistic regression was used to identify risk factors of prolonged PHS. **Result:** A total of 192 patients (117 males and 75 females) who underwent lung cancer surgery were included. The median PHS was 7 days (range, 2–46 days). Among 192 patients, 64 (33.3%) had prolonged PHS. Among those with PHS, 73.4% were males and patients with a smoking history accounted for 60.9%, Charlson Comorbidity Index scores of >1 for 57.8%, tumor located in the upper lobe for 64.1%, open surgery for 57.8%, lobectomy for 64.1%, systematic lymphadenectomy for 57.8%, and tumor stage ≥II accounted for 59.4%. The overall in-hospital complication rate was 25%. The most common complication was prolonged air leak. The multivariate analysis revealed that the surgical approach (open vs. video-assisted thoracoscopic surgery) (OR 2.65, 95% CI 1.05-6.67; P=0.039) and in-hospital complications (no vs. yes) (OR 0.15, 95% CI 0.06-0.35; P<0.001) were independent risk factors of prolonged PHS.

Table 1 Correlation between patient characteristics and prolonged PHS

Variables	Total (n = 192)	Prolonged PHS (n = 64)	Normal PHS (n = 128)	P value
Gender				0.012[a]
Male	117	47	70	
Female	75	17	58	
Age				0.005[a]
≤ 63 years old	136	37	99	
> 63 years old	56	27	29	
BMI				0.053[a]
≤ 23.9	129	49	80	
> 23.9	63	15	48	
Smoking history				0.001[a]
Yes	85	39	46	
No	107	25	82	
Drinking history				0.021[a]
Yes	60	27	33	
No	132	37	95	
Neoadjuvant therapy				0.341[a]
Yes	7	4	3	
No	185	60	125	
ASA classification				0.126[a]
≤ I	96	27	69	
> I	96	37	59	
CCI score				0.001[a]
≤ I	106	25	81	
> I	86	39	47	
Tumor location				0.400[a]
Upper	110	41	69	
Middle	19	5	14	
Lower	63	18	45	
Surgical approach				0.000[a]
VATS	134	27	107	
Open	58	37	21	
Resection type				0.000[a]
Sublobectomy	34	5	29	
Lobectomy	129	41	88	
Extended resection	29	18	11	
Lymphadenectomy type				0.005[a]
Systematic	84	37	47	
Non-systematic	108	27	81	

Table 1 Correlation between patient characteristics and prolonged PHS

Variables	Total (n = 192)	Prolonged PHS (n = 64)	Normal PHS (n = 128)	P value
Chest tube drainage				0.074[a]
One tube	119	34	85	
Two tube	73	30	43	
Operative time				0.147[a]
≤ 120 minutes	79	31	48	
> 120 minutes	113	33	80	
Histological type				0.000[a]
Adenocarcinoma	137	35	102	
Others	55	29	26	
pTNM stage				0.001[a]
I	101	26	75	
II	33	10	23	
III	43	25	18	
IV	15	3	12	
In-hospital complication				0.000[a]
Yes	48	33	15	
No	144	31	113	

[a], by $\chi 2$ test; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; PHS, postoperative hospital stay; TNM, tumor node metastasis; VATS, video-assisted thoracoscopic surgery.

Conclusion: Prolonged PHS is still very common in the real world. Open surgery and in-hospital complications were the two main reasons of prolonged PHS in patients who underwent lung cancer surgery. Further studies with a larger sample size are warranted to confirm our results.

Keywords: Risk Factors, lung cancer surgery, Postoperative hospital stay

P2.16-36 PATTERNS OF CARE IN A PROSPECTIVE CLINICAL COHORT OF PATIENTS WITH LUNG CANCER - PRELIMINARY ANALYSES FROM THE ENRICH PROGRAM

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Background: Lung cancer accounts for 9% of all cancer diagnoses, is the most common cause of cancer related death, and is the leading cause of morbidity and burden of disease in NSW and across Australia. The outlook for patients with lung cancer remains poor with only a 15% overall five year survival rate. For patients diagnosed with advanced stage disease, five year survival is less than 5%. There is an urgent need to identify and reduce unwarranted clinical variation that may contribute to morbidity and burden of disease, and to improve quality of care, and thereby ensure best possible outcomes, for the lung cancer population. Sydney Catalyst is addressing this need through the Embedding Research (and Evidence) in Cancer Healthcare 'EnRICH' program, a program of translational research in lung cancer which aims to: describe the natural history of and patterns of care for lung cancer; identify current gaps in evidence and practice for clinical quality improvement; and create a platform for researchers across the T1-T3 translational research spectrum to develop and initiate clinical research and intervention studies to address gaps. The EnRICH dataset currently includes comprehensive patient, diagnostic, treatment and outcome data (including patient reported outcomes) for more than 600 consecutive patients with lung cancer (non-small cell and small cell, any histological type, any clinical/pathological stage) treated in metropolitan and regional hospitals across three Local Health Districts in NSW, Australia. By mid-2020, the EnRICH dataset will include data for more than 1000 patients. **Method:** This preliminary analysis will provide descriptive data on the first 500 consecutive patients in the EnRICH cohort and, specifically, will describe patterns of care stratified by patient and disease characteristics. Patterns of care will be mapped to evidence-based quality indicators to identify clinical variation. **Result:** Data collection is complete for 420 patients. Remaining data collection and analyses will be complete for 500 consecutive patients by 19 July 2019. Data presented will include: Descriptive data Patient characteristics: age; sex; CALD status; comorbidities, symptoms, performance status Risk factors: smoking history; family history of lung cancer; occupational exposure; clinical history of lung disease; previous malignancy Disease characteristics: histological type and sub-stype; pathological stage; clinical stage; genetic mutations Quality indicators Diagnosis - proportion with: clinical stage; pathological stage; appropriate analysis of predictive markers; time from diagnosis to treatment Treatment - proportion: with performance status assessment; reviewed by MDT; undergoing resection, chemotherapy, targeted-therapy, immunotherapy, radiotherapy; receiving no active anti-cancer treatment Referral - proportion: of current smokers with documented smoking cessation counselling; of stage IV patients referred to palliative care; referred to supportive care services; referred to/enrolled in clinical trials OutcomesClinical outcomes: major complications (Clavien-Dindo/CTCAE grade ≥3); hospitalisations; survival Patient reported outcomes: Global health status/QoL; social functioning; physical functioning; role functioning; emotional functioning; cognitive functioning; social functioning; symptoms; distress **Conclusion:** Data from EnRICH for the first 500 consecutive patients treated for lung cancer across a wide geographical area in NSW, Australia will map routine patterns of care, and identify unwarranted clinical variation to be addressed by quality improvement interventions to achieve best possible patient outcomes.

Keywords: Quality Improvement, Patterns of care, Clinical variation

P2.16-37 IMPACT OF BRAIN METASTASES ON HEALTHCARE UTILISATION AND COSTS IN PATIENTS WITH NSCLC TREATED WITH EGFR-TKIS

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Background: NSCLC with brain metastases is difficult to treat and associated with poor survival. The impact of brain metastases compared with other metastases on healthcare utilisation and costs among patients treated with EGFR-TKIs is not well known. **Method:** Newly-diagnosed adult patients with metastatic NSCLC initiating approved first-/second-generation EGFR-TKI treatment (within 90 days of diagnosis) were identified retrospectively from IBM Watson Health MarketScan® healthcare claims databases from 2013–2017. Patients were divided into mutually-exclusive cohorts based on evidence of brain or non-brain metastasis (BM or NBM). Demographics, clinical characteristics and healthcare expenses were captured at baseline. Healthcare utilisation and cost were analysed during the variable-length follow-up period. Costs were standardised to 2017 US$ and reported as per-patient-per-month (PPPM). Generalised linear models were used to assess the impact of brain metastases, adjusting for baseline demographics, comorbidities, healthcare expenses and length of follow-up. **Result:** Overall, 222 BM and 280 NBM patients were included. BM patients were, on average, younger than NBM patients (59.9 vs 65.7; p<0.05); both cohorts included mostly female patients and had an average of 14 months follow-up. Among all patients, first EGFR-TKI treatment was 82.3% erlotinib, 16.3% afatinib and 1.4% gefitinib; 10 patients treated with osimertinib were excluded. Seizures (9.0% vs 1.1%), headaches (17.6% vs 10.0%) and altered mental status (11.3% vs 5.7%) were more common in the BM vs NBM cohort (p<0.05). NSCLC-related healthcare utilisation was >2-fold higher in BM patients receiving radiation treatment in the inpatient (15.3% vs 6.8%; p<0.05) and outpatient (87.8% vs 37.5%; p<0.05) settings. PPPM radiation costs were also higher among BM patients in the inpatient ($796 vs $464, p=0.172) and outpatient ($2477 vs $762, p<0.05) settings. All-cause inpatient admissions were more common among the BM vs NBM cohort (67.1% vs 57.1%; p<0.05). While all patients had evidence of outpatient services, the PPPM number of outpatient visits was greater among the BM vs NBM cohort (p<0.05) for both NSCLC-related (5.1 vs 4.2) and all-cause (6.4 vs 5.7) healthcare utilisation. Adjusted NSCLC-related and all-cause PPPM costs were 1.2 times higher among BM patients (+$5674 and +$6393, respectively; p<0.05); age was also a significant predictor in both models (p<0.05). **Conclusion:** Healthcare utilisation, hospital admission rates and costs, especially those attributable to radiation treatment, were higher among patients with BM compared with NBM. Future research should assess if central nervous system (CNS)-active EGFR-TKIs have the potential to reduce healthcare utilisation and costs associated with brain metastases.

Keywords: Brain metastases, NSCLC, Outcomes

P2.16-38 EFFICACY AND SAFETY OF TARGET THERAPY AND IMMUNOTHERAPY IN ADVANCED NSCLC IN ELDERLY: A SYSTEMATIC REVIEW OF REAL WORLD STUDIES

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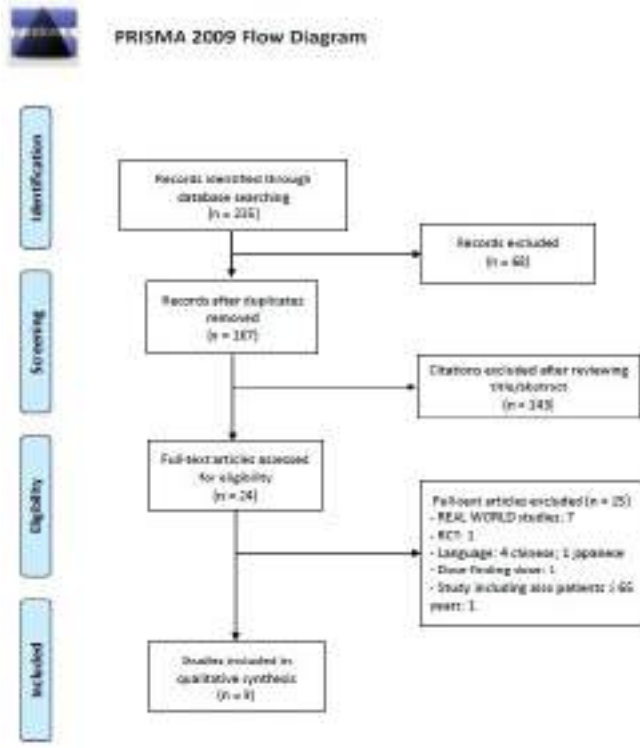
Background: Despite notable advances, treatment of advanced non small cell lung cancer (NSCLC) in the elderly remains a challenge.Target therapy and immunotherapy outcomes have been demonstrated in several randomized controlled trials (RCT), however real world setting may closely mirrors everyday clinical practice in elderly population, characterized by poor performance status, significant comorbidities, concomitant treatments, limited adherence and compliance. Systematic review was conducted to examine the published real-world studies evaluating efficacy and safety of target therapy and immunotherapy in elderly patients with advanced NSCLC. These real-world data were compared to those obtained in

the phase II and III randomized controlled trials. **Method:** Following PRISMA guidelines, in February 2019 we searched the MEDLINE, Web of Science, and Scopus databases in English language.Titles and abstracts were reviewed by 2 independent reviewers (FT; FV); disagreements were resolved by a third. All identified full papers were assessed independently by three researchers (FT, FV, and AV). Included studies were required to be RWS, and evaluate target therapy or immunotherapy in advanced NSCLC elderly patients. The Newcastle Ottawa Scale (NOS) was used for quality assessment of studies included in the systematic review. **Result:** We found 235 studies through the database, 167 remained after duplicate removal and 24 full-text articles were assessed for eligibility (Figure 1). The systematic search of the literature identified 9 studies meeting the selection criteria to analyse in qualitative synthesis.These studies included a total of 1882 elderly patients mainly treated with first-generation EGFR tyrosine-kinase inhibitors (5 studies), osimertinib only in one study. Bevacizumab in association with chemotherapy was evaluated in two studied. Immunotherapy data was available only in one study. Clinical characteristics of each study population are analyzed. The first relevant aspect is the lack of data on Multidimensional Geriatric Assessment and Charlson Comorbidity Index, that should represent main instruments in clinical practice to personalize therapeutic approach. Heterogeneity of first-generation EGFR TKI efficacy among the studies could be influenced by genetic differences among ethnic groups. In general, the results showed that PFS of patients with advanced NSCLC treated with first-generation EGFR TKI in the real world setting were consistent with those observed in clinical trials, while an inferior survival was recorded. Collected toxicity data were limited.



Conclusion: RWS represent a broad picture of the activity and tolerability of new drugs and can provide interesting observations and research ideas in several settings, particularly in elderly patients, integrating and defining data of the RCTs.

Keyword: elderly patients, real-world studies, non small cell lung cancer

P2.16-39 THE ASSOCIATION BETWEEN DIETARY PROTEIN INTAKE AND THE RISK OF LUNG CANCER: A META-ANALYSIS

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Background: Dietary protein intake had been explored whether had some effective on lung cancer risk, however, the results were not consistent. This meta-analysis aimed to find exact relationship between them. **Method:** Databases of PubMed, Embase, and Web of Science were retrieved up to January 1, 2019. Summarized odds ratio (OR) with corresponding 95% confidence intervals (CI) were calculated. Publication bias and sensitivity analysis were assessed. **Result:** Seven articles with 8 independently studies (4 population-based case-control studies (PBCC) and 4 hospital-based case-control studies (HBCC)) involving 2990 cases and 7142 participants were used in this paper. The overall analysis suggested that dietary protein intake had no significant association on lung cancer risk (Summarized OR= 0.951, 95%CI= 0.798-1.134, *I2*= 53.0%, *P* for heterogeneity= 0.037). However, when we explored the association between lung cancer risk and geographic location, we found an inverse association among Asian populations (Summarized OR= 0.880, 95%CI= 0.840-0.922), instead of North American populations or European populations. **Conclusion:** Findings from this meta-analysis indicated that higher intake of protein may be associated with decreased of lung cancer risk among Asian populations, instead of other populations. As some limitations listed in our study, more studies are warranted to further confirm the association between them.

Keywords: Protein intake, Lung cancer, Meta-analysis

P2.16-40 ACKNOWLEDGING SOCIAL AND ECONOMIC INEQUITIES EXPERIENCED BY CANADA'S INUIT: IMPLICATIONS FOR DIAGNOSIS AND TREATMENT OF LUNG CANCER

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Background: The Inuit living in Canada's north have the highest rates of lung cancer in the world. Barriers to care are numerous and exist at all phases of the lung cancer journey. Beginning with difficulty in accessing the diagnostic phase of care through to treatment at a tertiary cancer centre located over 2000 km away and little to no palliative care available locally, this population experiences obstacles at each step of their lung cancer journey. The Inuit in Canada's arctic experience dramatically higher rates of social and economic inequity than the rest of Canada with only one hospital serving a land mass similar to the size of Mexico, access to or from many communities is by air only. This means that diagnosis and treatment for lung cancer is provided thousands of kilometres away from family, community and culture, often for months at a time. Along with geographic barriers to care, Inuit peoples also have a historical mistrust of government and mainstream health care services owing to past encounters with colonization and marginalization. A lack of awareness of Inuit specific culture from health care providers (i.e. discrimination) further compounds this lack of trust. These end result of these traumas contribute to the significant health disparities experienced by the Inuit as compared to other Canadians and may in part explain why approximately 30% of Inuit diagnosed with lung cancer between 2000-2010 did not access cancer care. To better meet the needs of this population, TOHCC hired an Indigenous Nurse Navigator in 2016 with a goal to provide culturally safe care for Inuit patients and their families. Collaborative relationships have been built with key stakeholders in Inuit communities through consistent efforts which in turn have garnered awareness of Inuit specific issues within TOHCC and the surrounding city. **Method:** In depth semi-structured interviews with Inuit patients, caregivers and community leaders. The Indigenous nurse navigator will interview participants either in person or by video during April and May 2019. **Result:** The results of these interviews will be presented at the 2019 World Lung Cancer Conference in Barcelona. **Conclusion:** There is still much work to do in breaking down barriers to accessing care at all phases of the lung cancer journey for the Inuit of Canada's North. This presentation offers the opportunity to hear directly from a marginalized community who potentially have the greatest lung cancer needs of any population in the world.

Keywords: Indigenous, Inequity

P2.16-41 PEMBROLIZUMAB FOR PREVIOUSLY TREATED, PD-L1–EXPRESSING ADVANCED NSCLC: REAL-WORLD TIME ON TREATMENT AND OVERALL SURVIVAL

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Background: Information from real-world clinical settings remains limited regarding outcomes of pembrolizumab therapy for advanced NSCLC. Our aim was to examine real-world time on treatment (rwToT) and overall survival (OS) for patients prescribed pembrolizumab monotherapy for previously treated, PD-L1–expressing advanced NSCLC, thus clinically similar to patients in the KEYNOTE-10 (KN010) trial. **Method:** This retrospective study used Flatiron Health's nationally representative EHR-derived database to identify adult patients with histologically confirmed advanced NSCLC and PD-L1 tumor proportion score (TPS) ≥1% previously treated with platinum-containing chemotherapy (and appropriate TKI if nonsquamous NSCLC with EGFR/ALK aberration). Eligible patients initiated pembrolizumab monotherapy from January 1, 2016, to May 31, 2018; those with <6 months of follow-up were excluded. Kaplan-Meier (KM) rwToT and OS were calculated. **Result:** Median follow-up was 15.6 months (range 6.0–32.8 months). Of 281 eligible patients (56% male), median age was 68 years; 36% had squamous NSCLC; 10% brain metastases; and 57%, 18%, and 25% ECOG performance status 0–1, ≥2, and unknown, respectively. Baseline characteristics were similar across PD-L1 TPS distributions. The table summarizes rwTOT and OS by PD-L1 TPS categories.

rwToT and OS in months (mo)

Data cutoff Nov 30, 2018	TPS ≥1% n=281	TPS ≥50% n=182	TPS 1–49% n=82
Discontinued, n (%)	189 (67)	120 (66)	56 (68)
KM rwToT, median (95% CI)	5.0 (3.9–6.2)	5.8 (4.4–7.2)	3.9 (2.1–6.2)
12-mo restricted mean (rMean) rwToT (95% CI)	6.1 (5.6–6.7)	6.5 (5.8–7.2)	5.4 (4.4–6.5)
24-mo extrapolated rMean rwToT (95% CI)	9.2 (6.4–12.1) [Gompertz]	9.9 (6.5–13.4) [Gompertz]	8.0 (7.2–9.4) [LogLogist]
12-mo on-treatment rate, % (95% CI)	31.0 (25.3–36.9)	33.9 (26.7–41.3)	26.6 (16.5–37.8)
18-mo on-treatment rate, % (95% CI)	25.9 (19.9–32.3)	27.3 (20.0–35.1)	26.6 (16.5–37.8)
OS events, n (%)	140 (50)	86 (47)	43 (52)
OS, median (95% CI)	13.5 (10.3–16.2)	15.6 (13.0–23.6)	9.7 (7.0–14.9)
12-mo survival, % (95% CI)	53.6 (47.2–59.6)	58.0 (50.0–65.1)	46.2 (33.8–57.7)

Conclusion: Real-world patients treated with pembrolizumab monotherapy after platinum-containing chemotherapy for PD-L1–expressing advanced NSCLC experienced rwToT and OS benefits similar to findings in a clinical trial setting, validating KN010 findings and approved indication in second line.

Keywords: Pembrolizumab, overall survival, real-world time on treatment

P2.16-42 THE USE OF A SMARTPHONE APPLICATION IMPROVES POSTOPERATIVE OUTCOMES IN PATIENTS UNDERGOING LUNG CANCER RESECTION

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Background: For early stages of lung cancer, complete surgical resection with curative intent for patients who are surgical candidates remains the most effective treatment. However, thoracic surgery procedures are related to postoperative pulmonary complications which increase the morbidity and mortality. Preoperative pulmonary rehabilitation programs improve postoperative outcomes. This study aims to evaluate the role of a smartphone application to improve pulmonary rehabilitation in a group patients scheduled for lung cancer resection. **Method:** A Smartphone application containing peri-operative medical advice (stop smoking, mouth health, early mobilization and pain control) and ten chest physical exercises (aerobic exercise, inspiratory muscle strength and secretion mobilization technique) was created. This prospective and no randomized study was developed between January 2017 and December 2018. All patients scheduled for surgery were asked to participate. A group of 68 patients used and interacted with the software before and after the surgery. The control group (114 patients) received classical information and education by the Department of Physical Medicine and Rehabilitation. Clinical-pathological variables, incidence of postoperative pulmonary complications, duration of chest drainage, length of hospital stay and 30 days mortality rate were recorded and analyzed. **Result:** Postoperative pulmonary complications were developed 17.6% in the intervention group and 33.3% in the control group (P=0.02). The length of hospital stay was shorter in the intervention group (median 3±4.09d vs. 5±6.87d P=0.001). No differences were found in duration of chest drainage or 30 day mortality compared with control group. **Conclusion:** This new technological resource created by thoracic surgeons demonstrates that preoperative rehabilitation program and patient education improve postoperative outcomes in patients undergoing lung cancer resection, decreasing the incidence of postoperative pulmonary complications and length of hospital stay.

Keywords: Chest Physical Therapy, Postoperative Pulmonary Complications, Smartphone Application

P2.16-43 IMMUNOTHERAPY IN ELDERLIES. REAL WORLD DATA

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Background: Because of its tolerability immunotherapy is suitable for unfit patients. Elderly patients are under-represented in clinical trials due to the association between aging and a significant prevalence of comorbid diseases. We analyzed our elderly patients treated with immunotherapy and tried to find any impact on overall survival (OS) from other non-comorbidity factors. **Method:** 24 NSCLC patients older than 70 years received immunotherapy after previous treatment at our hospital from September 2015 and July 2018 according to pharmacy records. Data was collected from medical records. Retrospective observational study whose primary end point was to analyze safety and efficacy in elderly patients was made. Secondary endpoint was to find if toxicity had any impact in OS. **Result:** 23 were men. 17 were former smokers, 6 still smoking. 10 were adenocarcinoma, 12 squamous cell carcinoma, 2 NOS. 7 were stage III, 17 stage IV. 14 had at least one metastatic organ. 2 had liver while 2 had brain metastases. Median number of previous lines was 1 (range=1-4). Best response to any previous treatment

was stable disease (SD) 37.5% (n=9); partial response (PR) 37.5% (n=9). All received Nivolumab. Best response to immunotherapy was PR 8.3% (n=2) with SD 37.5% (n=9); unfortunately, 9 were not valuable. Median number of cycles was 9 (range=1-55). 20 (83.3%) were PS<=1 before immunotherapy while 11 (45.8%) still PS<=1 after. Median overall survival (OS) was 10 months (95%CI 1.33-18.66). Median progression free survival (PFS) was 4 months (95%CI 0.65-7.39). Compared with under 70 years old patients -at our center- OS was not statistically longer in older patients (median OS: 22 vs 10months). OS was higher in those with any grade of toxicity (mean OS: 23 months vs 8 p<0.05); in those with less previous lines (median OS: 17 months in <=1 vs 3 months in more p<0.05); in PS<=1 before immunotherapy (median OS: 17 months vs 2 p<0.05) and in PS<=1 after immunotherapy (mean OS: 22 months vs 7 p<0.05). 37.5% (n=9) had any grade of immune-related toxicity (77.8% <=grade 2). Hypothyroidism was the most common toxicity. 41.7% (n=10) needed corticosteroids to control toxicity. Immunotherapy stopping reasons were progression 16 (66.7%) and related G3-4 toxicity in three out of four cases while the other one was due to persistent grade 2 toxicity. There were no deaths due to immune related toxicities. 29.2% (n=7) received treatment after progressionbeing all of them PS1 after immunotherapy. Best response to treatment after immunotherapy was SD 60% (n=3), PR 40% (n= 2) -in those that could be analysed- with 100% disease control rate. 13 (54.2%) patients died at cut-off. **Conclusion:** Although it is a small number of patients, as in other published studies, it suggests that elderly patients behave to immunotherapy as younger counterparts do.In the analysis made in our center in population under 70 years old, immunotherapy median number of cycles, toxicity frequency, and cause of treatment stop were similar in both populations and there were no statistically differences in OS.Any grade of toxicity was related with higher OS.Elderly people must be considered for immunotherapy treatment just like young patients.

Keywords: Immunotherapy in elder population, Real world data, Immunotherapy in pretreated patients

P2.16-44 REAL-WORLD TREATMENT PATTERNS AND OUTCOMES IN ALK+ NSCLC PATIENTS RECEIVING IMMUNO-ONCOLOGY THERAPY IN THE UNITED STATES

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Background: Cancer immunotherapies are new treatment options in advanced non-small cell lung cancer (NSCLC). Evidence of immuno-oncology (IO) therapy efficacy in tumors with activating mutations, such as anaplastic lymphoma kinase (*ALK*) rearrangements, is lacking. This retrospective study describes the characteristics of ALK+ NSCLC patients treated with IO therapy and assesses treatment outcomes in these patients (time to treatment discontinuation, real-world progression-free survival [rwPFS]). **Method:** The Flatiron Health Electronic Health Record (EHR)–derived database (Jan 2011–Jun 2018) was used to identify patients with advanced ALK+ NSCLC who had received IO therapies (nivolumab, pembrolizumab, atezolizumab, durvalumab). Discontinuation of IO therapy was defined as switch to an ALK TKI or chemotherapy or addition of chemotherapy (for IO monotherapy), death, gap between IO administrations >120 days, or gap between last IO therapy administration and last follow-up date of >120 days. rwPFS was estimated as the time from treatment initiation to progression (abstracted from clinician notes and radiology reports) or death. Time to discontinuation and rwPFS were analyzed using Kaplan-Meier methods. **Result:** Of 593 ALK+ NSCLC patients with follow-up between 2015–2018, 83 (14%) patients were treated with IO therapy. Mean age was 60.3 years, with 65.1% of patients diagnosed at stage IV, and 61.4% patients receiving nivolumab. Of the 83 IO-treated patients, 50.6% received IO therapy before first ALK TKI, and 38.6% were treated with IO therapy after ≥2 ALK TKIs. Median (95% CI) time to discontinuation of IO therapy was 2.17 mo (1.41–3.32) and rwPFS was 2.34 mo (1.55–3.09). **Conclusion:** We identified ALK+ NSCLC patients who received IO therapy, half of whom were treated post-ALK TKI. Time to discontinuation of IO therapy was short, and real-world effectiveness (rwPFS) was limited. These results point to IO therapy's relative futility in ALK+ NSCLC patients. Compared to IO therapy, several approved ALK inhibitors have shown better effectiveness in both first and later lines of therapy. However, the optimal sequencing of ALK inhibitors with other therapies, including chemotherapy and IO therapy, remains unclear.

Keywords: immuno-oncology, Outcomes, Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer

P2.17 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.17-01 ANALYSIS OF CLINICAL FEATURES AND PROGNOSIS OF NON-SMALL CELL LUNG CANCER EXCEEDING 30 MM DEPENDING ON THE GROUND GLASS OPACITY (GGO) RATIO

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Background: The ground glass opacity (GGO) ratio is associated with the prognosis of small (<30 mm) non-small cell lung cancer (NSCLC). However, the clinical features, especially the GGO ratio, and prognosis of NSCLC exceeding 30 mm are not well known. Therefore, this study aimed to determine the characteristics of patients with NSCLC exceeding 30 mm and analyze the clinical significance of the GGO ratio on prognosis. **Method:** Totally, 271 patients with NSCLC tumors exceeding 30 mm on preoperative computed tomography scans and who underwent complete resection at our institution between January 2007 and December 2017 were included. The patients were divided into three groups based on the GGO ratio: pure solid tumors, GGO ratio 0–40%, and GGO ratio ≥40%. The cut-off value of 40% was determined based on the recurrence rate for each GGO ratio group. Clinical feature and prognosis of each group were analyzed. **Result:** Of the included patients, 147 (54%) had pure solid nodule, 67 (25%) had nodules with a GGO ratio 0–40%, and 57 (21%) had nodules with a GGO ratio ≥40%. Among the patients with a GGO ratio ≥40%, 10 underwent limited resection (segmentectomy in 9 patients and wedge resection in 1); no patients experienced recurrence. Among the 147 patients with pure solid nodules, 47 (32%) experienced recurrence. Among the 67 and 57 patients with GGO ratio 0–40% and GGO ratio ≥40%, 16 (24%) and 2 (4%), respectively, experienced recurrence. The 3-year recurrence-free survival (RFS) rate was significantly shorter in patients with pure solid nodules (60.5%) than in patients with GGO ratio 0–40% (74.0%; p=0.010) and GGO ratio ≥40% (93.6%; p<0.001). Moreover, RFS was significantly shorter in patients with GGO ratio 0–40% than in patients with GGO ratio ≥40% (p=0.009). Similar results were observed for overall survival (OS). The 3-year OS rate was significantly shorter in patients with pure solid nodules (79.1%) than in patients with GGO ratio 0–40% (88.2%; p=0.046) and GGO ratio ≥40% (95.6%; p<0.001). Moreover, OS was shorter in patients with GGO ratio 0–40% than in patients with GGO ratio ≥40% with marginal significance (p=0.052). **Conclusion:** A pure solid nodule was a major component among NSCLC tumors exceeding 30 mm. Among such patients, as the GGO ratio decreased, the recurrence rate increased. A GGO ratio of 40% is the appropriate cut-off value, and patients with GGO ratio ≥40% have better prognosis compared to patients with GGO ratio <40% or pure solid nodules. The prognosis of patients with GGO ratio ≥40% who undergo limited resection may be similar to that of patients undergoing lobectomy, the standard operation procedure.

Keywords: GGO ratio, NSCLC exceeding 30mm

P2.17-02 SURVIVAL IN PERFORMANCE STATUS 3 NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING RADICAL RADIOTHERAPY

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Background: International guidelines currently recommend radical radiotherapy for non-small cell lung cancer (NSCLC) patients with ECOG performance status (PS)0-2. Despite a paucity of evidence for treating poorer PS patients, modern advances have allowed patients with PS3 to be offered radical radiotherapy. **Method:** PS0-3 NSCLC patients receiving radical radiotherapy at The Christie Hospital, UK between August 2016-October 2017 were retrospectively identified from hospital electronic patient records. Survival was calculated from date of first oncology review to November 2018. Baseline and treatment characteristics for PS3 patients were recorded including adult comorbidity evaluation (ACE)-27 score, pulmonary function, radiation dose volume parameters and radiotherapy regimen (i.e stereotactic ablative radiotherapy (SABR) vs standard radiotherapy (50-55Gy/20 fractions)). **Result:** 504 patients were identified: 440(87%) PS0-2 and 64(13%) PS3. Six PS3 patients withdrew themselves; four before treatment and two after one fraction. Of 58/64(91%) PS3 patients completing radiotherapy, 43(74%), 4(7%), 10(17%) and 1(2%) were Stage I, II, III and IV at diagnosis, respectively. ACE-27 score was 0, 1, 2 and 3 in 3(5%), 8(14%), 16(28%) and 31(53%) patients, respectively. 31(53%) received SABR and 27(47%) standard radiotherapy. On intention-to-treat analysis, there was no significant difference in survival over 18 months in PS3 patients compared to PS0-2; p=0.858 (Fig.1). There was no significant difference in survival among PS3 patients completing radiotherapy when stratifying by stage(I vs II vs III) (p=0.343), ACE-27 score(1 vs 2 vs 3)(p=0.266), or radiotherapy regimen(p=0.655). Lung function tests(FEV1, FVC) and radiotherapy dose volume parameters(PTV, V5, V10,V20) failed to predict survival of PS3 patients at 6, 12 and 18 months.

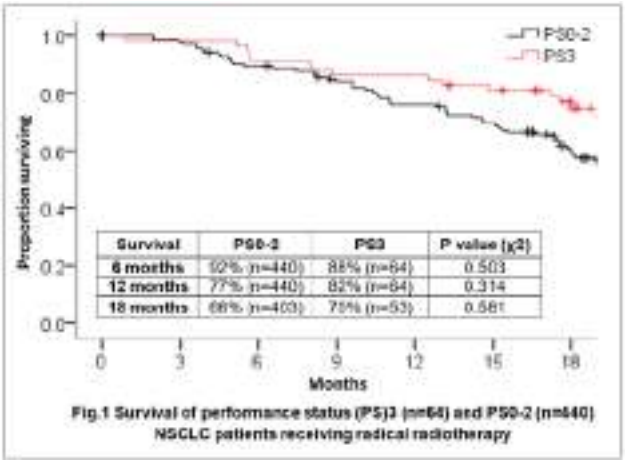

Fig.1 Survival of performance status (PS)3 (n=64) and PS0-2 (n=440) NSCLC patients receiving radical radiotherapy

Conclusion: This study demonstrates that PS3 patients receiving radical radiotherapy had a similar 18-month survival compared to PS0-2 patients and baseline and treatment characteristics did not predict overall survival in PS3 patients. This suggests more PS3 patients could be considered for radical radiotherapy and further studies with larger cohorts are recommended.

Keywords: Non-Small Cell Lung Cancer, radical radiotherapy, performance status

P2.17-03 SURGICAL OUTCOMES OF REPEATED ANATOMICAL PULMONARY RESECTION FOR THE IPSILATERAL SECOND LUNG CANCERS

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Background: The opportunity of pulmonary resection for metachronous second lung cancers is increasing as an effective surgical strategy for properly selected patients in the course of postoperative follow-up after thoracic surgery for the first lung cancer. However, the surgical indication is controversial regarding the repeated pulmonary resection for the ipsilateral second lung cancer. **Method:** Among surgically resected 3316 non-small cell lung cancer (NSCLC) from 2008 to 2018, ipsilaterally detected 104 metachronous second lung cancers (3.6%) was retrospectively reviewed with regard to the surgical outcomes and clinicopathological characteristics. In this study, re-anatomical resection was defined as a repeated anatomical surgery for ipsilateral secondary NSCLC after major lung resection for primary NSCLC. Overall survival (OS) was estimated using the Kaplan-Meier method. Survival outcomes were evaluated using Cox proportional hazard model. A difference was considered statistically significant when the p-value was less than 0.20 in the univariable, and 0.05 in the multivariable models. **Result:** Of all, 61 (67%) were male with an average age of 67y at the second surgery. Pathological-stage I disease was found in 65 (63%). Histologically, adenocarcinoma was frequent in 80 (77%) cases. Seventy-seven (74%) was diagnosed as second primary. The 3y-OS after the second lung resection was 80.1%. Multivariate analysis revealed that radiological pure-solid tumor, pack-year smoking were the independent prognosticators of the OS (p=0.045, 0.001). Operative procedures were not associated with the survival outcomes (re-anatomical: 81.8%, others: 78.2%, p=0.816), however, re-anatomical resection was an independently significant predictor of the postoperative morbidity after the second surgery (p=0.035). Therefore, we focused on the 58 cases that underwent re-anatomical resection. Among them, postoperative morbidity (G3 or more in the CTCAE 4.0) was found in 20 (35%). A multivariable analysis revealed tumor size and postoperative morbidity were the independently significant prognosticators (p=0.003, 0.026). The 3y-OS of tumor less than 20mm was excellent (91.9% vs. 66.6%, p=0.008). Furthermore, we classified them into 2 groups based on the operative modes, i.e., completion pneumonectomy (CP; n=26) and the other re-anatomical resections to avoid CP (non-CP; n=32). The details of non-CP were ipsilateral secondary lobectomy/segmentectomy after the primary lobectomy/segmentectomy in 28 and completion lobectomy after the primary segmentectomy in 4, respectively. Among them, right side operation was more frequent in the non-CP (54% vs. 84%, p=0.011), while intra-pericardial procedure was employed more in the CP (85% vs. 47%, p=0.005). In contrast, the oncological outcomes (3y-OS; 75.8% vs. 87.1%, p=0.881), technical aspects including operative time (242min vs. 234min, p=0.802), bleeding amount (334ml vs. 242ml, p=0.521), blood transfusion (15% vs. 19%, p=0.736), arterial reconstruction (19% vs. 28%, p=0.431), or postoperative morbidity (27% vs. 41%, p=0.275) was similar between CP and non-CP. **Conclusion:** Re-anatomical pulmonary resections for the ipsilateral second lung cancers are oncologically feasible but predictive for the postoperative morbidity. In particular, non-CP could be effective strategy to avoid CP for lung preservation, however, this procedure is technically challenging as well as CP, and strict caution would be warranted for the perioperative management. While oncological outcome of small-sized lung cancer is fully favorable even in case that repeated anatomical resection would be needed.

Keywords: second lung cancer, repeated anatomical pulmonary resection, surgical outcome

P2.17-04 ROLE OF LYMPHADENECTOMY IN THORACOSCOPIC LOBECTOMY FOR NON-SMALL CELL LUNG CANCER

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Background: The adequacy of lymphadenctomy in video-assisted thoracoscopic surgery (VATS) for the patients with non-small cell lung cancer (NSCLC) has been questioned. This study aims to identify the role of lymphadenectomy during VATS lobectomy for NSCLC. **Method:** To include different level of lymphadenectomy proficiency and heterogeneous lymphadenectomy policy, we included all consecutive surgical cases from April 2005 to June 2013, irrespective of surgeon's experience, lymph node sampling or dissection, and solid or subsolid nodule. Patients who underwent VATS lobectomy and who were followed up for more than 5 years were included in this study. The relationship between long-term survival and the number of removed lymph nodes was analyzed. **Result:** During the study period, a total of 2,502 patients underwent curative surgical resection of NSCLC and VATS lobectomy was performed in 1,055 patients (42.2%). The median length of postoperative hospital stay was 5 days and 30-day and 90-day all-cause mortality rates were

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0.3% and 0.9%, respectively. Pathological stage I, II, III and IV were 79.0%, 10.6%, 8.7%, and 1.7% and the median number of removed lymph nodes was 24. The 5-year overall and recurrence-free survival rates were 83.9% and 78.5 %, respectively. Recurrences were developed in 233 patients (22.1%) and the most common pattern was distant metastasis (n=153, 14.5%). The number of removed lymph nodes, year of operation, age, tumor size, pathologic stage, histology, and radiologic features were the significant prognostic factor for recurrence-free survival in multivariate analysis. More than 10 lymph node removal was associated with improved recurrence-free survival and the effect lasted until 40. However, the number of removed lymph nodes were not a significant risk factor for overall survival (table). **Conclusion:** The number of removed lymph nodes was closely related with recurrence-free survival after VATS lobectomy. Proper lymphadenectomy should be performed in VATS lobectomy like as open lobectomy.

Keywords: Non-Small Cell Lung Cancer, VATS, lymphadenctomy

P2.17-05 FEASIBILITY STUDY OF ADJUVANT CHEMOTHERAPY WITH CARBOPLATIN AND NAB-PACLITAXEL FOR COMPLETELY RESECTED NSCLC

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Background: Cisplatin-based regimen is the standard adjuvant chemotherapy for patients with completely resected stage II or III non-small cell lung cancer (NSCLC). However, the patients unfit for cisplatin-based chemotherapy due to old age or renal impairment recently increased. This phase II study was conducted to evaluate the tolerability and efficacy of carboplatin and nab-paclitaxel as adjuvant chemotherapy. **Method:** Patients with completely resected stage II to IIIA NSCLC enrolled. Eligible patients received postoperative adjuvant chemotherapy with 4 cycles carboplatin (area under the curve=5, on day1) and nab-paclitaxel (100 mg/m2, on days 1, 8 and 15) administered every 4 weeks. The primary endpoint was to evaluate the completion rate of 4 cycles of chemotherapy. We assumed completion rate of 50% would be the lower limit. **Result:** From Jan 1, 2014 to Jan 31, 2019, 21 patients were enrolled, but two patients were excluded. Two patients of them are on protocol chemotherapy at data cutoff point. Median age of the 17 patients was 73 years (ranging from 53 to 80 years). Four of 17 patients (23.5%) were at stage IIA, 3 (17.6%) were at stage IIB, and 10 (58.8%) were at stage IIIA. Eleven (64.7%) had adenocarcinoma and 6 (35.3%) had squamous cell carcinoma. The most reasons of unfit for cisplatin regimen were old age (≥70 years old, n=14) and renal impairment (n=7). Ten of 17 patients (58.8 (32.9-81.6) %) completed four cycles of regimen. The reasons for discontinuation of the chemotherapy were febrile neutropenia (n=2), neutropenia (n=1), empyema (n=1), drug-induced pneumonitis (n=1), renal failure (n=1), and patient refusal due to fatigue (n=1). Three of 10 patients who completed four cycles needed dose reduction due to grade 4 neutropenia. Nab-paclitaxel on day 15 was omitted in 39 of 49 cycles (79.6%) because of grade 3 or 4 neutropenia. The most common grade 3 or 4 adverse event was neutropenia (n=14, 82.4%), followed by anemia (n=3, 17.6%). Febrile neutropenia, grade 3 pneumonitis, grade 1 peripheral sensory neuropathy were observed in 11.8%, 5.9%, 35.3% of the 17 patients respectively. The median time to disease recurrence was 24.4 (10.8-37.5) months. **Conclusion:** Carboplatin and nab-paclitaxel as adjuvant chemotherapy for NSCLC unfit for cisplatin was not tolerable. Dose reduction should be considered in further study of adjuvant chemotherapy.

Keywords: adjuvant chemotherapy, carboplatin, feasibility study

P2.17-06 ANALYSIS OF LEFT ATRIAL BLOOD FLOW USING 4D FLOW MRI IN THE PATIENT WHO SUFFERED FROM CEREBRAL INFARCTION AFTER LEFT UPPER LOBECTOMY

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Background: Cerebral infarction is one of the complication after left upper lobectomy, and it may be caused by thrombus in left atrial. However, the mechanism of incidence of cerebral infarction has not been elucidated. In order to elucidate it, we performed the blood flow analysis of left atrium including the stump of the left upper pulmonary vein, by 4D flow MRI, which is recently very useful for blood flow analysis. **Method:** We examine blood flow by 4D flow MRI in 3 patients with cerebral infarction after left upper lobectomy. **Result:** Case1: A 76-year-old woman underwent left upper lobectomy for lung adenocarcinoma (cT1aN0M0 stageIA1). She had atrial fibrillation and took edoxaban, oral anticoagulant medicine. Three days after the surgery, she made cerebral infarction in MRI. By chest CT a thrombus was found near the left upper pulmonary vein stump. Case 2: A 42-year-old woman underwent left upper lobectomy due to lung cancer (cT1aN0M0 stageIA1). She had Cushing syndrome. One month after the surgery, she was diagnosed as cerebral infarction in MRI. There was no evidence of incidence of thrombus by chest CT. Case 3: A 77-year-old woman underwent left upper lobectomy for lung adenocarcinoma (cT3N0M0 stageIIB). Five months after the surgery, she was diagnosed as cerebral infarction in MRI. CT showed thrombus in the left atrial appendage. We performed blood flow analysis in left atrium for the three patients by 4D flow MRI. It showed a decrease in blood flow near the left superior pulmonary vein stump and left atrium around the stump in all patients. **Conclusion:** We performed blood flow analysis of left atrium by 4D flow MRI, and it was able to visualize the blood flow after left upper lobectomy. The analysis showed the reduction of blood flow not only in the left superior pulmonary vein stump but also in the left atrium. These results suggest that blood flow stagnation may induce the thrombus formation in left atrium, and cause cerebral infarctions. In future, we will compare the blood flow before and after surgery and simulate the blood flow in left atrium. We hope to select patients at high risk for stroke before left upper lobectomy using flow analysis.

Keywords: left upper lobectomy, thrombus, 4D flow MRI

P2.17-07 ROLE OF ADJUVANT CHEMOTHERAPY AFTER SUBLOBAR RESECTION IN STAGE I NSCLC

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Background: Adjuvant chemotherapy (AC) has been associated with improved survival for several subsets of surgically managed NSCLC (e.g. nodal metastases, tumors >4cm). The surgical practice of removing less than the entire lobe ("sublobar resection") has been associated with increased risk of NSCLC recurrence, yet the impact of AC in this subset is unknown. Stage I NSCLC patients managed by sublobar resection (SR) in the National Cancer Data Base (NCDB) were studied to evaluate SR as a potential indication for AC. **Method:** The NCDB was queried for completely resected (R0) stage I NSCLC patients who underwent multi-agent AC after SR (wedge resection or segmentectomy) between 2004 & 2014. Survival was calculated from 30 days after surgery to minimize immortal time bias. Multivariable Cox proportional hazards models adjusting for patient, tumor (including visceral pleura invasion (VPI) and lympho-vascular invasion (LVI)) and treatment characteristics were created and stratified by size (0-1 cm, 1.1-2 cm, 2.1-3 cm and 3.1-4 cm). **Result:** Of the 12,063 patients identified, 584 (4.84%) received multi-agent AC. AC patients tended to be younger (median age 66 vs 71 years, p<0.001), privately insured (35.13% vs 23.05%, p<0.001), and with high risk pathological features (VPI: 6.47% vs 4.55%, p<0.001, LVI: 10.32% vs 5.70%, p<0.001, high grade: 47.15% vs 34.50%, p<0.001). In patients with tumors measuring ≤3 cm, AC was not significantly associated with a mortality reduction (Table 1). In patients with tumors measuring 3.1-4 cm (N=1,172), AC (N=145, 12.37%) was associated with a lower mortality (HR 0.65, 95% CI 0.48 to 0.87, p=0.003) (Figure 1).

Tumor size	Total N	AC N (%)	Mortality hazard AC vs no AC		
			HR	95% CI	*P*
0-1 cm	1629	52 (3.19)	1.43	0.93 to 2.21	0.11
1.1-2 cm	6113	214 (3.50)	1.10	0.87 to 1.36	0.45
2.1-3 cm	3149	173 (5.49)	1.12	0.89 to 1.42	0.35
3.1-4 cm	1172	145 (12.37)	0.65	0.48 to 0.87	0.003

Table 1. Impact of AC in patients with stage I NSCLC undergoing SR

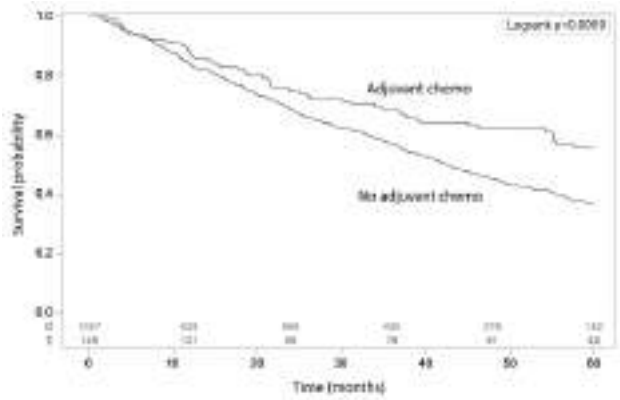

Figure 1. Kaplan-Meier survival curves for patients with 3.1-4 cm stage I NSCLC undergoing SR

Conclusion: The administration of AC was associated with superior survival in stage I NSCLC patients who underwent SR, but only those with tumors 3.1-4 cm. Additional study to validate SR as an indication for AC in stage I NSCLC patients is indicated.

Keywords: NSCLC, Sublobar resection, adjuvant chemotherapy

P2.17-08 ETHANOL RELEASE HEAT-GENERATING POLYMER FOR FOCAL THERAPY OF SMALL LUNG CANCERS UNDER OPEN MRI

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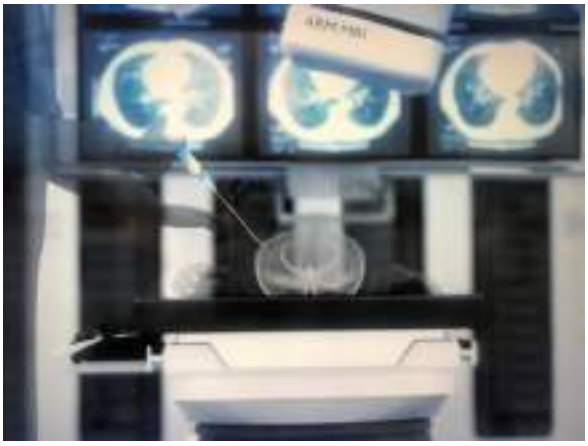
Background: Recently, the lung cancer lesions of small GGO lesions are increasingly found. Such an elderly person who found a small cancer lesion reveals low durability for surgery and sometimes has many medical complications around chronic diseases. **Method:** therapy of micro lung cancers under open MRI and developed medical devices. We have synthesized low viscosity silicon material which absorb a trace amount of water, generates heats and indurate in a few minutes. We have adjusted the concentration of titanium catalyzer, and a fine image can be visualized under CT imaging equipment and 0.3T open MRI. In animal experiments, rat lungs are divided in 10-micron unit CT imaging, the indurated conditions of thermosetting resin in the lungs was analyzed as 3D DICOM image data and 0.3T MRI DICOM images of Hitachi Corporation. We have developed non-artifact metallic needle as a biopsy needle under open MRI circumstance.



Result: It was confirmed that the indurated resin was hardened three-dimensionally without cracks, the surrounding cells were damaged, the resin can be detected with CT. The micro resin can be detected with 0.3T Open MRI. **Conclusion:** We have succeeded in synthesizing "Ethanol Release Heat-Generating Polymer" for focal therapy of micro lung cancers and archiving non-artifact medical devises under MRI. The idea of this research is Japanese patent JP6447858. This work was PCT patent pending JP2017/025044 in US and China and supported by JSPS KAKENHI Grant Number JP15K15517 and 18H05377.

Keywords: focal therapy, MRI visible, Polymer

P2.17-09 PREOPERATIVE RISK FACTORS OF POTENTIAL FAILURE FOR LOBE-SPECIFIC NODAL DISSECTION IN CLINICAL EARLY STAGE (I-IIA) NON-SMALL CELL LUNG CANCER

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Background: Clinical early stage (I-IIA) non-small cell lung cancer (NSCLC) is treated with pulmonary resection and systematic nodal dissection (SND) or lobe-specific nodal dissection. The aim of this study was to identify the preoperative risk factors for potential failure of lobe-specific nodal dissection in clinical early stage NSCLC. **Method:** A retrospective review was carried out on patients who underwent pulmonary lobectomy and SND for clinical early stage (I-IIA) NSCLC. Patients with computed tomography and positron emission tomography were included, whereas patients with invasive mediastinal staging and right middle lobe tumor were excluded. Lobe-specific nodal dissection failure was defined as unexpected metastasis at inferior mediastinal nodes (stations 7, 8, and 9) for both upper lobe tumors and at superior mediastinal nodes (stations 2R and 4R for right upper lobe tumors and stations 4L, 5 and 6 for left upper lobe tumors) for both lower lobe tumors. The incidence of pN2 disease following the tumor location and the factors for the failure of lobe-specific nodal dissection were analyzed. **Result:** From July 2005 to May 2017, 2130 patients were included in this study. Overall, 12.5% (266/2130) of the patients had pN2 disease. Among them, 33.2% (78/266) of pN2 patients showed potential failure of lobe-specific nodal dissection. Lobe-specific nodal dissection failure was shown in 49 of 764 (6.4%), 21 of 468 (4.5%), 2 of 534 (0.4%), and 6 of 364 (1.6%) cases in right upper lobe, right lower lobe, left upper lobe and left lower lobe, respectively. At multivariable analysis, female (OR: 1.86; 95% CI 1.14-3.03; p = 0.012), right upper lobe tumor (OR: 20.98; 95% CI 5.05-87.08; p < 0.001), right lower lobe tumor (OR:14.81; CI 3.43-63.97; p < 0.001), higher SUVmax (≥ 4.75) (OR: 5.51; 95% CI 3.18-9.55; p < 0.001), and adenocarcinoma histology (OR: 8.89; 95% CI 2.11-37.42; p = 0.003) were significant risk factors for the failure of lobe-specific nodal dissection **Conclusion:** Lobe specific nodal dissection revealed a considerable failure rate in clinical early stage NSCLC. Lobe-specific SND should be performed cautiously in clinical early stage NSCLC, especially in patients with female sex, right sided tumor, higher SUVmax (≥ 4.75) and adenocarcinoma histology.

Keywords: NSCLC, pathologic N2 disease, Lymph Node Dissection

P2.17-10 EFFECTS OF THE OMEGA-6/OMEGA-3 RATIO ON POSTOPERATIVE COMPLICATIONS AFTER LUNG RESECTION: PRELIMINARY RESULTS

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Background: In the last 3 decades, the intake of omega-6 (*n*-6) fatty acids has increased while the intake of omega-3 (*n*-3) has decreased, leading to an increase in the *n*-6/*n*-3 ratio, which is now 20:1. This ratio has been postulated as an inflammatory marker of carcinogenesis, implicated in the development of multiple chronic diseases, and associated with postoperative complications due to the proinflammatory effects of omega 6. Consequently, the preoperative

assessment of nutritional markers, together with immunonutrition, represent a promising target to improve outcomes in patients with lung cancer who are candidates for surgical resection. The aim of this study was to assess the effect of the *n*-6/*n*-3 ratio on postoperative complications in patients undergoing radical-intent surgery for lung cancer. **Method:** Prospective cohort study of 38 patients diagnosed with lung cancer treated with radical surgery between October 2017 and May 2018. The *n*-6/*n*-3 ratio was determined immediately prior to surgery with the patient under anesthesia. **Result:** Of the 38 surgically-treated patients, 29 were men (76%) and 9 women (24%). Mean patient age was 62 ±10 years. Twelve (32%) patients were active smokers at the time of surgery. The most common histological subtype was adenocarcinoma (60%) and most patients underwent lobectomy (68%). The mean body mass index (BMI) was 27 ±5 and the mean preoperative prognostic nutritional index (PNI) score was 48±7. The mean *n*-6/*n*-3 ratio was 20 ±6. The most common complications were prolonged air leak (> 5 days) in 11 patients (29%) and respiratory failure in 6 patients (16%). Patients with prolonged air leak had a significantly higher *n*-6/*n*-3 ratio than patients without prolonged air leak (25 ±3 vs. 18 ±6, respectively; p=0.02). Patients with an *n*-6/*n*-3 ratio > 20 were significantly more likely (p=0.002) to present prolonged air leak. Neither BMI nor PNI were significant predictors of air leak duration. **Conclusion:** These preliminary findings indicate that patients with a higher *n*-6/*n*-3 ratio—that is, those with a greater proinflammatory status—were more likely to present prolonged air leak than those with a lower inflammatory status. Based on these encouraging results, we propose to continue with this line of research to better understand the effects and prognostic value of immunonutritional status on the clinical course of patients after lung cancer surgery.

Keywords: omega, Lung cancer, Nutrition

P2.17-11 EVALUATING PD-L1 AS A PROGNOSTIC BIOMARKER IN SURGICALLY RESECTABLE NON-SMALL CELL LUNG CANCER

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Background: Identifying biomarkers that can predict which early stage non-small cell lung cancers (NSCLCs) are likely to recur following surgical resection is critical to improving survival outcomes. Programmed Cell Death Ligand-1 (PD-L1) is an immune regulatory protein expressed on tumor cells that inhibits T effector response against tumors. Therefore, high PDL-1 expression on tumor cells may enable evasion of the anti-tumor response and be associated with worst outcomes. We conducted a meta-analysis to determine if PDL-1 expression is associated with survival in surgically resected early stage NSCLCs. **Method:** PubMed was searched to identify eligible studies comparing survival of surgically resected stage I-III NSCLC patients according to PD-L1 tumor expression. Included studies were grouped according to measurement criteria of PDL-1 expression: 1%, 5%, 50% cutoffs or as a continuous variable expressed as H-score. The latter is calculated from the percentage of cells expressing PDL1 multiplied by the intensity of staining. Meta-analysis was performed using a linear mixed-effects model to determine overall survival (OS). I2 was used as a measure of heterogeneity across studies. **Result:** Of the 519 articles queried, 31 articles met eligibility criteria, accounting for 6,713 patients. Nine studies (n=2,407) used H score, where higher PD-L1 expression was associated with worse OS (hazard ratio [HR]meta: 1.68, 95% confidence interval [CI]: 1.17-2.41, I2= 15.45%). Five studies used a 1% cutoff (n=1,073), 14 studies reported using a 5% value (n=2,310) and 6 studies (n=1,572) used a 50% cutoff for evaluating high vs. low PD-L1 expression. PD-L1 expression was not statistically significantly associated with survival according to these cutoffs and there was high inter-study heterogeneity (HRmeta: 1.47, 95% CI 0.89-2.41; I2= 17.57%; HRmeta: 1.09, 95% CI 0.79-1.52; I2= 35.49%; HRmeta: 1.21, 95% CI 0.61-2.40; I2= 58.26% for 1%, 5%, 50%, respectively). **Conclusion:** Higher PD-L1 expression in early stage NSCLCs as measured by H scores was associated with worse post-surgical survival. The measurement of PD-L1 expression as a continuous variable (i.e. H score) may provide more accuracy for predicting survival outcomes over percentage cutoffs. Future research is needed to validate PD-L1 expression as a predictive biomarker of survival for early-stage NSCLCs undergoing surgical resection.

Keywords: PD-L1, Biomarker, NSCLC

P2.17-12 ROBOTIC ASSISTED SEGMENTECTOMY - INTRAVENOUS VS INTRABRONCHIAL FLUORESCENCE THORACOSCOPY TO IDENTIFY THE INTERSEGMENTAL PLANE

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Background: Increasingly earlier detection of small lung cancers may permit the possibility of anatomical sublobar resection. Robotic assisted thoracic surgery (RATS) facilitates complex segmentectomy but identification of the intersegmental boundary remains a drawback to minimally invasive techniques. We have employed two contrasting methods using either intravenous (IV) or intrabronchial (IB) indocyanine green (ICG) and compared the efficacy. **Method:** The location of the lesion was identified on CT reconstruction. Patients were allocated to either method by surgeon preference. IV ICG was injected during RATS after division of the target segmental artery. A novel aerosolized IB technique (by fibreoptic bronchoscopy) was used to inject the target segmental bronchus before RATS. All operations were performed using the Da Vinci Xi robot (*Intuitive Surgical, Sunnyvale, CA, USA*) and near infrared thoracoscopy (Firefly®). IV ICG was administered in 18 patients and IB ICG was given in 13 patients. The intersegmental plane was identified by the fluorescence demarcation line, which was then divided using the robotic stapler. **Result:** On univariate analysis, there were no intergroup differences between IV and IB in the patient demographics (median age 70.5 years vs 71 years), number of staple firings (8 vs 10, p>0.05), success in identifying the intersegmental plane (94 vs 100% respectively, p>0.05), postoperative air leak duration (2 vs 3 days, p >0.05), or TNM staging of tumours (T1 64% vs 86% respectively, p>0.05). The total anaesthetic time (230 vs 290 mins, p<0.05) and the operative duration (171.5 vs 193.5 mins, p<0.05) were significantly less in the IV ICG group. In IB ICG, more than half of the segmentectomies involved the apical segment of either lower lobe (5 R S6, 1 L S6; 3 L S1-3, 2L S4-5), whereas in IV ICG more complex segmentectomies were performed (2 R S1-2, 2 R S6, 2 R S7-10; 2 L S1-2, 5 L S1-3, 2 L S4-5, 1 L S7-10, 1 L S7-8). There was no mortality nor major complications in either group. One case was converted to thoracotomy due to extensive adhesions in the IV ICG group. In the same group, there was one R1 resection due to parietal pleura involvement.

Comparison between IV and IB ICG in RATS segmentectomies

Total number of patients	IV ICG (n=18)	IB IVG (n=13)
Excluded patients	1 case converted to thoracotomy	1 wedge resection (frozen section negative) 1 lobectomy (abnormal anatomy)
Patient age (median,range)	70.5 (35-84)	71 (50-89)
Sex (M/F)	11/7	7/6
Target segments (R/L)	R S1-2 2 R S6 2 R S7-10 2 L S1-2 2 L S1-3 5 L S4-5 2 L S7-10 1 L S7-8 1	R S6 5 L S1-3 3 L S4-5 2 L S6 1
Operative duration (median, range)	171.5 mins (111-228)	193.5 mins (178-275)
No of staple firings (median, range)	8 (2-14)	10 (7-15)
Success in identifying the intersegmental plane (%)	16/17 (94%)	11/11 (100%)
Major complications	0	0
Conversion to VATS or open	1(adhesions)	0
Tumour clearance (%)	R0 16/17 (94%)	R0 11/11 (100%)
NSCLC (%) T-status in NSCLC (%)	NSCLC 14/17 (82%) T1 9/14 (64%)	NSCLC 7/11 (63%) T1 6/7 (86%)

Conclusion: In RATS segmentectomy, identification of the intersegmental plane is facilitated by the intraoperative use of ICG. Both IV and IB routes are feasible with comparable results. As the IV route appears to reduce the use of theatre time, a future randomized comparison is suggested.

Keywords: robotic segmentectomy, fluorescence thoracoscopy, intersegmental plane

P2.17-13 THORACOSCORE FAILS TO PREDICT IN-HOSPITAL MORTALITY FOLLOWING ELECTIVE SURGERY IN A BRAZILIAN LUNG CANCER COHORT

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Background: According to SEER database only 40% of patients with lung cancer present localized or regional disease at diagnosis. The cornerstone of treatment of potentially resectable lung cancer is surgical removal of the tumor and it is important to estimate the loss of lung function after resection. The risk of in-hospital death can be estimated by some a scores system such as Thoracoscore. The aim of this study is to evaluate the applicability of this risk assessment model for in-hospital mortality in a Brazilian cohort of patients submitted to surgical resection. **Method:** This is a prospective analysis of patients who underwent lung resection for lung cancer in two thoracic surgery centers in Brazil between January 2015 to December 2018. Patients were included if they were 18yo or older, had a histologically proven diagnosis of lung cancer. Tumor staging was done according the seventh edition of the AJCC classification. Data on prognostic factors such as histology, gender, performance status, comorbidities and type of treatment were collected. Thoracoscore was calculated based on the following variables: age, sex, American Society of Anaesthesiologists' class (ASA), performance status classification, dyspnea score, priority of surgery, procedure class, diagnosis group and comorbidities score. A receiver operating characteristic analysis determined the ability of the thoracoscore to predict in-hospital mortality and it would be considered acceptable if AUC > 0.7; significance test for AUC was performed using Chi-square test. Proportion of events was compared between groups according to the Cochran-Armitage linear trend test to evaluate the calibration of Thoracoscore. All P-values were 2-sided. Results were considered significant if $p < 0.05$. Statistical analyses were performed using SAS version 9.4. **Result:** 166 patients were included in the study. Median age was 62 years, 48,8% were male, 57.8% had adenocarcinoma, 71.7% had one or two comorbidities, 40.3%, 36.1%, 19.2% and 3.6% were respectively clinical stage I, II, III and IV, 71% and 13.3% underwent respectively lobectomy/bilobectomy and pneumectomy, 79.5% were ASA ≤2, 100% had ECOG ≤2, elective surgery and dyspnea score ≤2. The observed in-hospital mortality was 13 patients (7.8%). We attributed our mortality to high rate of stage III lung cancer patients and we also included stage IV patients who underwent to palliative surgery. Mean thoracoscore was 3.92 (SD ± 1.41) and the mean predicted in-hospital mortality using thoracoscore was 1.81%. The AUC for thoracoscore was 0.579. When this area was compared with the area of 0.50 (absent discrimination), no significant difference was observed ($p = 0.3642$). Thoracoscore was divided into three risk groups: low (0–3), moderate (3.1–5) and high (≥5.1). The score was not able to differentiate the mortality among the groups ($p = 0.30$). **Conclusion:** Our results corroborate the non-validation of Thoracoescore in a Brazilian population of patients with lung cancer. Additional studies are needed for the development of more accurate mortality risk scores in this population.

Keywords: Lung cancer, mortality risk, surgery

P2.17-14 IMPAIRED IMMUNE DEFENSE IN TUMOR MICRO-ENVIRONMENT IS ASSOCIATED WITH RISK OF RECURRENCE IN EARLY STAGE LUNG ADENOCARCINOMA

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Background: Despite curative surgery with or without chemotherapy, 27-76% of surgically resected early stage lung cancer will unfortunately develop recurrence which is often fatal. Platinum-based adjuvant chemotherapy in NSCLC improves cure rates in only 5% of patients at the cost of significant toxicities. Developing biomarkers to select high risk patients and strategies to reduce recurrence in early stage lung cancer are critical. **Method:** Thirty surgically resected primary lung adenocarcinomas from 16 patients with lung cancer recurrence and 14 patients without recurrence in 4 years were included in this study. Among these 30 patients, 27 have either stage I or II. RNA sequencing (694 genes and 14 key immuno-oncology (IO) pathways) was determined using nanoString technology and RNA from primary tumors from recurrent versus non-recurrent patients. **Result:** Chemokines including CCL18, CCL23, CXCL1, CXCL2, CCL26 and chemokine receptors CXCR2, CX3CR1 and TNFRSF10C were significantly decreased in tumors from patients who had recurrence versus those from patients without recurrence. By contrast, genes related to cancer associated fibroblasts in the stromal microenvironment such as LRRC15 and genes involved in release of cancer cell antigens were significantly increased in adenocarcinomas from recurrent patients.

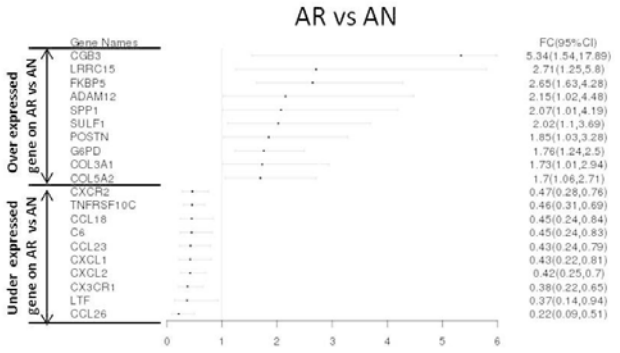

Figure 1. Top 10 gene over-expressed and under-expressed in surgically resected early stage adenocarcinomas from patients with recurrence (AR) versus patients without recurrence (AN)

Conclusion: Our results suggest that recurrence in early stage lung adenocarcinoma might be related to impaired immune defense such as decreased immune cell trafficking and antigen release in tumor micro-environment. Further study with larger sample size is warranted.

Keywords: Early Stage Lung Cancer, Immunotherapy, biomarker of recurrence

P2.17-15 CLINICAL FEATURES AND PROGNOSIS OF LUNG CANCER WITH CAVITY LESION

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Background: There have been conflicting results about the clinical features and prognosis of primary lung cancer with cavity lesion (LC-CL). We, therefore, revisited the clinicopathological features of primary LC-CL and reassessed whether they exhibited poor prognosis in non-small-cell lung cancer. **Method:** Between 2006 and 2014, 377 patients underwent complete resection for clinical T1aN0 non-small-cell lung cancer. Clinical stage was adapted to the seventh edition of the lung cancer stage classification system. Among these cases, 23 (6.1%) were diagnosed as LC-CL. We compared the characteristics and prognosis between LC-CL and the others. **Result:** LC-CL showed higher CEA (≧5 ng/mL) (p<0.01), higher SUV max (≧2.5) (p=0.02), the status of smoking history (p<0.01), larger actual pathologic tumor size (≧3cm) (p<0.01), lymphatic invasion (p=0.03), as compared with the others. The overall and recurrence-free survival of the patients with LC-CL were shorter than those of the others (p=0.01 and 0.03, respectively). Univariate analysis revealed that sex (p=0.01), age (≧70) (p<0.01), CEA (p<0.01), SUV max (p<0.01), smoking history (p<0.01), pathologic tumor stage (≧II) (p=0.01), vascular invasion (p<0.01), lymphatic invasion (p=0.04), pleural invasion (p<0.01) and cavity lesion (p=0.01) showed significant poor prognostic factors. Multivariate analysis revealed that age (p=0.02) and SUV max (p<0.01) remained significant prognostic factors, but cavity lesion was not significant (p=0.17). **Conclusion:** Although the value of its prognostic factor was not significant, primary LC-CL should be considered to have aggressive malignant behavior in non-small-cell lung cancer.

Keywords: Lung cancer, cavity lesion

P2.17-16 GENOMIC HETEROGENEITY AND EVOLUTIONARY TRAJECTORY IN MULTIFOCAL SYNCHRONOUS LUNG CANCER

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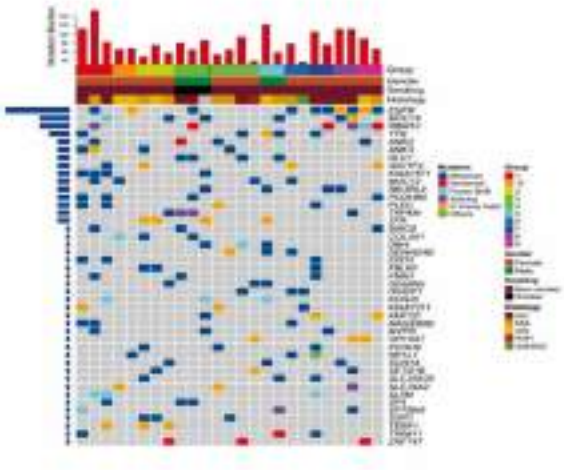
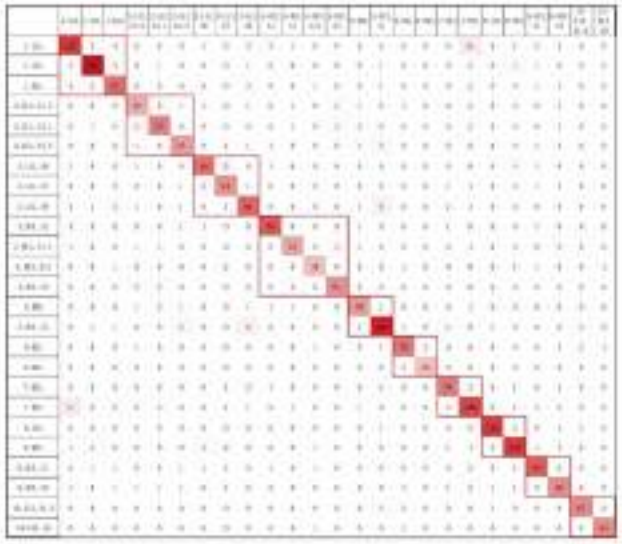
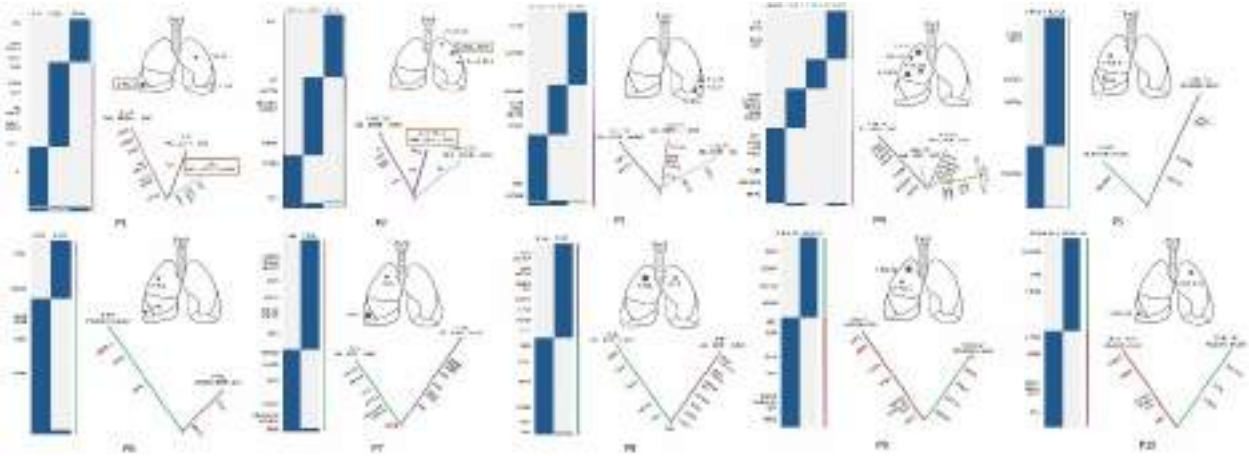
Background: Multifocal synchronous lung cancer (MSLC) presented as coexistence of multiple tumor lesions that share an identical germline genetic background and environmental exposure in individual patients. Along with the improved resolution of cross-sectional imaging, multiple types of ground glass opacities (GGOs) have been detected in increasing frequency as well as solid nodules even in an unique patient. However the molecular origins and relationships among the synchronous lesions remain unclear. **Method:** 10 treatment-naive MSLC patients were retrospectively collected while 25 tissue samples were performed whole exosome sequencing. In addition, we constructed phylogenetic trees to estimate the ancestral relationships of individual foci. **Result:** 79 somatic mutations in average were identified in MSLC tissues. The most significant mutated gene *EGFR* has been detected in 10 samples from 7 patients in our cohort. Tumor mutation burden as was significantly higher in IAC lesions than AIS/MIA ones. The mutation spectra of single-nucleotide variations (SNVs) were fairly consistent across the same histologic type even from different patients. Compared to AIS/MIA, IAC samples displayed a preponderance of A>T/T>A transition (Ti) while less frequency of A>C/T>G transversion (Tv). However few share mutations were located by pair of lesions in individual patients. Distinct genomic profiles suggested all were primary tumours. WNT pathway was enriched in AIS/MIA lesions exclusively while IAC appeared TGFβ/TP53 pathway mutation associated with cell proliferation and apoptosis.







Conclusion: Even in the same individual patient different lung cancer lesions may be driven by distinct genomic profiles so that each presented its own evolutionary trajectory. A deeper understanding of tumorigenesis is still in need to improve the diagnosis and treatment of MSLC.

Keywords: genomic heterogeneity, multifocal synchronous lung cancer

P2.17-17 CLINICAL EFFECT OF ADJUVANT CHEMOTHERAPY ON STAGE IB NSCLC WITH HIGH-RISK FACTORS

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Background: The efficacy of adjuvant chemotherapy in stage IB NSCLC with high-risk factors remains unclear. We analyze the clinical effect of adjuvant chemotherapy in patients with high-risk factors such as visceral pleural involvement, and micro-papillary type, etc. **Method:** This study is a multicenter retrospective study. We retrospectively analyzed 269 stage IB NSCLC with high-risk factors receiving lung resection operation from four academic hospitals. We defined the high-risk factors as visceral pleural invasion, vascular invasion, peri-neural invasion, lymphatic invasion, neuroendocrine tumors, and micro-papillary pattern. We used a Kaplan-Meier survival curve to analyze recurrence-free survival and overall survival. **Result:** There were 139 (51.7%) males and 130 (48.3%) females and the mean patient age was 65.6 ± 9.7 years. There were 142 patients without adjuvant chemotherapy and 127 patients with adjuvant chemotherapy. The median follow-up duration was 31.7 months (range, 2.7 to 60.0 months). And the recurrence-free survival was 48.8 ± 1.8 months in the no adjuvant group, and 54.0 ± 1.5 months in the adjuvant group (*P=0.028*). And the overall survival was 57.9 ± 0.9 months in the no adjuvant group, and 59.3 ± 0.7 months in the adjuvant group (*P=0.124*). In the sub-group analysis (visceral pleural involvement group), the recurrence-free survival was 48.2 ± 2.1 months in the no adjuvant group, and 55.3 ± 1.6 months in the adjuvant group (*P=0.011*) **Conclusion:** Adjuvant chemotherapy may be useful for patients with Stage IB NSCLC with high-risk factors. And, adjuvant chemotherapy should be considered especially when there is visceral pleural involvement

Keywords: NSCLC, adjuvant chemotherapy, High risk

P2.17-18 ACUTE RESPIRATORY DISTRESS SYNDROME AFTER CURATIVE SURGICAL RESECTION FOR LUNG CANCER

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Background: Bilateral lung infiltration is the most dreadful sign after lung cancer surgery. Either it is post -operative pneumonia or exacerbation of underlying lung disease (Interstitial lung disease), the lungs gradually shut down and finally develop ARDS (Acute Respiratory Distress Syndrome). Here, we report our experience and treatment outcome of post-operative ARDS after curative surgical resection for lung cancer. **Method:** From October 2008 to April 2017, the patients who underwent curative surgical resection for primary lung cancer were analyzed. We retrospectively reviewed medical records in two hospitals. **Result:** A total of 2140 patients were enrolled. Among them, 1246 were male (58.2%) and 894 were female (41.8%). The mean age was 64.5±10.0. In surgical procedures, 1496 (70%) cases of lobectomy, 117 (5.5%) cases of segmentectomy, 201 (9.4%) cases of wedge resection, 71 (3.3%) cases of bilobectomy, and 31 (1.4%) cases of pneumonectomy were performed. Combined procedures (lobectomy with wedge resection) were 222 (10.4%) cases. With Berlin definition of ARDS, a total of 29 (1.4%) patients were diagnosed. In table 1, we compared two groups and analyzed risk factors using univariable analysis. In multivariable analysis (table 2), advanced age, %VC(vital capacity), and underlying lung disease were associated with ARDS. Of 29 ARDS patients, 19 (65.5%) patients died in spite of maximum treatment. Broad antibiotics (96.6%), and steroid therapy (86.2%) were most applied treatments. We compared the patient's characteristics and the timing of treatment between two groups (survivor / non-survivor). But, there was no clinical significance.

	Non ARDS (n=2111)	ARDS (n=29)	P-value	Odds ratio	P-value	95% Confidence interval
Age(years)	63.9	71.3	<0.01	1.10	<0.01	1.04 – 1.16
Male/female(%)	55.4/44.6	90.5/9.5	<0.01	7.66	<0.01	1.78 – 32.96
Never/ever smoker(%)	56.0/43.1	23.8/76.2	<0.01	4.22	<0.01	1.54 – 11.57
%FEV1	95.4	82.9	0.04	0.97	<0.01	0.95 – 0.99
FEV1/FVC	71.8	67.8	0.11			
%VC	102.5	93.4	0.01	0.97	<0.01	0.94 – 0.99
%DLCO	85.3	68.8	<0.01	0.95	<0.01	0.92 – 0.97
More than 2lobes(%)*	5.7	14.3	0.12			
Inflammatory lung disease(%)	6.9	19.0	<0.01	19.31	<0.01	3.44 – 105
COPD(%)**	10.9	28.6	<0.01	11.69	<0.01	2.35 – 58.25
ILD(%)***	4.6	9.5	<0.01	14.32	<0.01	1.99 – 103.19
CPFE(%)****	1.9	33.3	<0.01	58.69	<0.01	7.92 – 188.95
Non-adenocarcinoma(%)	36.3	83.4	<0.01	8.01	0.01	1.88 – 7.80
Stage I/II/III/IV (%)	71.8/14.8/10.9/2.6	47.6/23.8/28.6/0	0.06			
Neoadjuvant treatment (%)	12.3	14.3	0.76			

Table 1. *surgical resection in more than two lobes(pneumo : lobectomy, pneumonectomy), **Chronic Obstructive Pulmonary Disease, ***Interstitial Lung Disease, ****Combined Pulmonary Fibrosis and Emphysema

	Odds ratio	P-value	95% Confidence Interval	
Age	1.08	0.02	1.01	1.16
%VC	0.97	0.02	0.94	0.995
Inflammatory lung disease	12.55	<0.01	2.05	76.87
COPD	7.92	0.01	1.57	40.06
ILD	7.73	0.048	1.02	58.69
CPFE	20.49	<0.01	4.06	103.51

Table 2. Multivariable risk factor analysis for ARDS

Conclusion: In conclusion, ARDS after lung cancer surgery is rare but fatal. Advanced age, low vital capacity, and patient's underlying lung diseases are possible risk factors for ARDS after surgery. In practice, various treatments including broad antibiotics and steroid therapy are applied to treat or control this disaster. But still, mortality is extremely high and their role is uncertain.

Keywords: Lung cancer, surgical resection, Acute Respiratory Distress Syndrome(ARDS)

POSTERS

P2.17-19 QUALITY OF LIFE AFTER PULMONARY STEREOTACTIC FRACTIONATED RADIOTHERAPY: LONGTERM RESULTS OF THE PHASE II STRIPE TRIAL

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Background: Preserving health related quality of life (HRQOL) plays an important role in considering stereotactic body fractionated radiotherapy (SBRT). The prospective monocenter phase II STRIPE trial investigated long-term HRQOL after SBRT, efficacy and toxicity. **Method:** Patients with ≤ 2 pulmonary lesions ≤ 5cm were treated with 4DPET/CT-based SBRT (3X12.5Gy or risk-adapted 5X7Gy, to the 60% isodose). Follow up (FU) was performed 2 and 7 weeks after SBRT, then 3monthly for 2 years with assessment of response (primary endpoint: 2-year cumulative incidence of local progression (LP); secondary endpoints: local progression free (LPFS), overall survival (OS) and toxicity (CTCAE)). Impact of predefined patient and treatment related factors on HRQOL (EORTC QLQ-C30 and EORTC QLQ-LC13) was evaluated. **Result:** Between 02/2011 and11/2014, 100 patients were given SBRT for 56 NSCLC and 44 pulmonary metastases. Long-term FU overall revealed stable Quality of Life (QoL)/Global health status (GHS), functions-scores and symptoms. For QoL/GHS, patients with low initial QoL/GHS-Score below the median of 50, revealed significantly stronger improvement than those with good QoL/GHS-scores ($p < 0.001$). Probability for LP, LPFS and OS 2 years after SBRT was 8.1%, 53.3% and 62.2%. Lower risk for LP was revealed for 3X12.5Gy ($p=0.043$) and for Dmin (Biological Effective Dose10) in the Planning Target Volume>100Gy ($p=0.023$). ≥G3-Toxicity was < 4%, except dyspnea: ≥G3 dyspnea was 6% at baseline and 14.5% 2 years after SBRT. **Conclusion:** These prospective data on a representative cohort of pulmonary SBRT patients confirm a stable preservation of HRQOL after SBRT and furthermore demonstrate a QoL/GHS-benefit for patients with low initial QoL/GHS-scores, the regimen of 3x12.5 Gy SBRT being efficient and well tolerated. This result may inform shared decision making when discussing SBRT for frail patients

Keywords: Quality of life, SBRT, health related patient reported outcome

P2.17-20 A RADIOMIC APPROACH TO PREDICT NODAL AND DISTANT RELAPSE IN PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY FOR EARLY STAGE NSCLC

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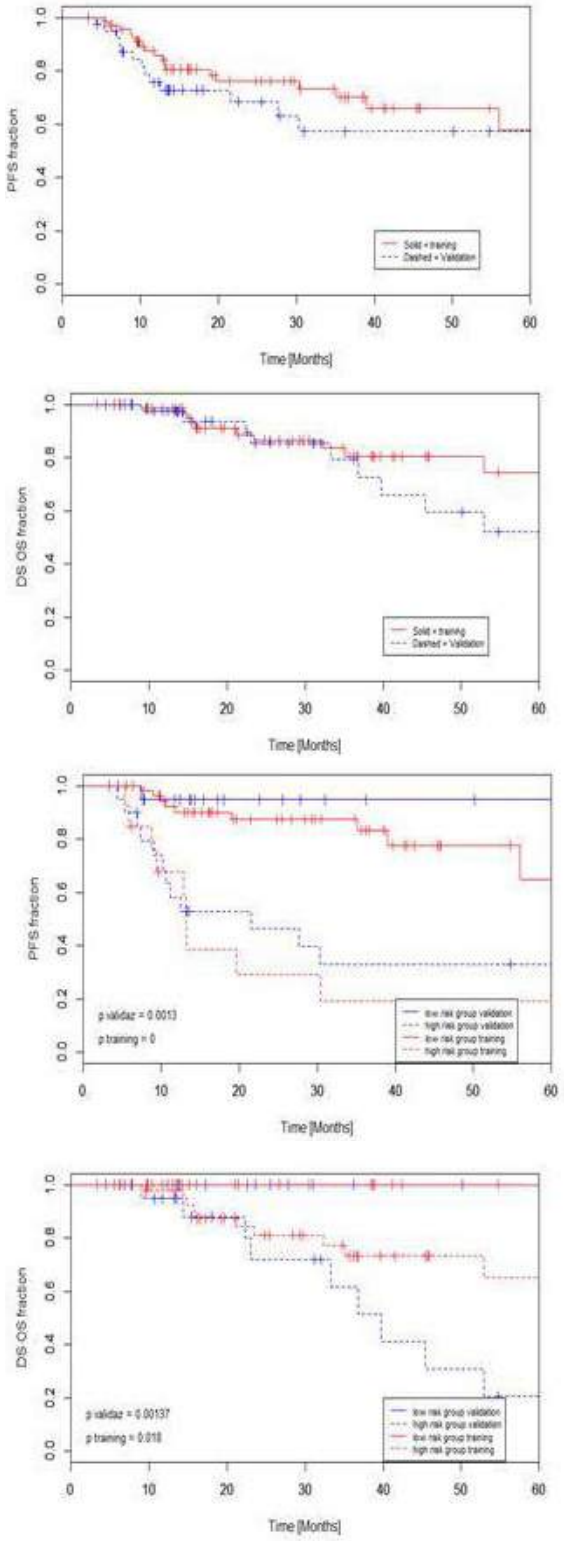
Background: Regional and distant relapse remain a significant issue in the treatment of early stage non small cell lung cancer with Stereotactic Body Radiation Therapy (SBRT). There is a need for predictive biomarkers able to identify patients that are at higher risk of relapse. In this work we present a radiomic approach using features extracted by routine planning CT, to predict the risk of nodal and distant recurrence. **Method:** A cohort of 102 patients was retrospectively investigated. All patients were affected by early stage (T1-T2) lung cancer and received the same radiation treatment with 48Gy delivered in 4 fractions. For all patients, a set of 45 radiomics textural features was computed for the tumor volumes segmented on the treatment planning CT images. Patients were split into two independent cohorts used for training (70% of cases) and validation (30% of cases). A stepwise backward linear discriminant analysis (LDA) was applied as a classifier to identify patients at risk of lymph-nodal progression. The performance of the model was assessed by means of standard metrics derived from the confusion matrix. Furthermore, all textural features were correlated to survival data to build predictive models: the features/predictors found significant at univariate analysis and to elastic net regularization, were included in a multivariate model to predict disease specific progression free survival (PFS) and disease specific survival (DS OS). Low and high risk groups were identified by maximizing the separation by means of the Youden method. **Result:** In the total cohort (77 (75.5%) males and 25 (24.5%) females, median age 76.6 years), 15 patients presented nodal progression at the time of analysis (11 in the training and 4 in the validation sets); 19 patients (18.6%) died because of disease specific causes, 25 (24.5%) died for other reasons, 28 (27.5%) were alive without disease and 30 (29.4%) with either local or distant progression. The mean tumor volume was 5.6±6.4cm3. Figure 1 illustrates the actuarial curves for PFS and DS OS over the entire training and test cohorts (in both cases the difference was not significant) and the same data stratified in low and high risk groups identified. In all case highly significant differences were identified.



Conclusion: Radiomics features extracted from treatment planning CT images can distinguish patients with low and high risk of tumor progression and disease specific death in early stage lung cancer treated with SBRT.

Keywords: Early Stage Lung Cancer, Predictive factors, Radiomic

P2.17-21 A POST-HOC ANALYSIS OF TROG 09.02 (CHISEL) PHASE III TRIAL INVESTIGATING PULMONARY FUNCTION CHANGES AFTER SABR AND CONFORMAL RADIATION THERAPY

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Background: The TROG 09.02 (CHISEL) trial compared conventional radiotherapy (CRT) administered over a period of four to six weeks with stereotactic ablative body radiotherapy (SABR).(1) Patients randomised to the SABR arm had superior freedom from local failure and longer overall survival.(1) The aim of this analysis was to assess differences in lung function and spirometry tests between SABR and CRT and describe longitudinal changes in respiratory function. **Method:** We conducted a post-hoc analysis of all patients recruited to the CHISEL trial. During this trial patients underwent serial Respiratory Function Tests (RFT) including Forced Expiratory Volume in one second (FEV1), Diffusing capacity of the lungs for carbon monoxide (DLCO), Distance Walked in 6 minutes (SMWT) and Forced Vital Capacity (FVC). These were performed at baseline then 3-6 monthly post-treatment. Patients were assessed per treatment received. Linear regression models were used to compare FEV1, FVC and DLCO between SABR and CRT. Separate models at 3 and 12 months post-treatment were created to assess the two different processes impacting lung function post radiation therapy (acute pneumonitis and chronic fibrosis). Linear regression models were used to assess the association of baseline PFT Measures with decline in respiratory function at 3 and 12 months. **Result:** Between December 2009 and June 2015, 101 patients were treated in 11 centres in Australia and New Zealand. 34 patients were treated with CRT and 63 with SABR. On regression analysis at 3 months there was no evidence of a difference between arms in the change from baseline in absolute values of FEV1 (beta 0.037, 95% CI [-0.063, 0.14], p=0.47), DLCO (beta -0.5, 95% CI [-1.4, 0.37], p=0.26) nor forced VC (beta 0.024, 95% CI [-0.17, 0.22], p=0.81). At 12 months there were no differences observed in change from baseline of FEV1 (beta0.031, 95% CI [-0.12, 0.18], p=0.69), DLCO (beta -0.43, 95% CI [-1.7, 0.84], p=0.51) nor forced VC (beta 0.047, 95% CI [-0.28, 0.18], p=0.69) between arms.There was no evidence of a difference in the change from baseline in SMWT (m) between two arms at 3 months (beta 35.9, 95% CI [-10, 82.3], p=0.13).Patients in both arms demonstrated similar deterioration in all RFT parameters with time. **Conclusion:** Despite the considerably higher biologically effective doses delivered to the tumour in SABR there was no difference in decline in respiratory function observed between the two groups. This is likely due to the higher integral dose, steep dose gradients and reduced margins possible with SABR relative to CRT.

Keywords: pulmonary function, Stereotactic ablative body radiotherapy, Early Stage Lung Cancer

P2.17-22 RETROSPECTIVE ANALYSIS OF SPREAD THROUGH AIR SPACES AND OTHER FEATURES IN PATIENTS WITH STAGE IA ADENOCARCINOMA BY THE 8TH TNM CLASSIFICATION

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Background: We have recently demonstrated that the presence of the Spread Through Air Spaces (STAS) increased the risk of recurrence after resection for small lung adenocarcinoma (ADC). Currently, the TNM classification of lung cancer was revised and T-factor was changed to be basically determined by its invasive size. The purpose of this study is to examine the impact of presence of STAS in stage IA ADC according to the 8th TNM classification. **Method:** Patients with pleural invasion, lymph node metastasis, distant metastasis, and neoadjuvant therapy were excluded. All available tumor slides from patients with surgically resected solitary lung ADC (2000-2015) were reviewed. Patients with stage IA ADC according to the 8th TNM classification were collected. Overall survival (OS) and recurrence-free probability (RFP) were estimated using the Kaplan-Meier method. Propensity score was generated from age, operation year, gender, lymphatic invasion, vascular invasion, the presence of solid component ≥5%, the presence of micropapillary component ≥5%, limited resection, and invasive size. One-by-one nearest neighbor matching by the presence of STAS was adapted to reduce the bias. **Result:** In all, 295 patients met study criteria with median age of 68. Male gender comprised 48.8% (n=144), lymphatic invasion positive 4.7% (n=14), and vascular invasion positive 14.9% (n=44). By T-factor (7th edition), 216 (73.2%) were T1a, 53 (18.0%) T1b, 23 (7.8%) T2a, 2 (0.7%) T2b, and 1 (0.3%) T3. By T-factor (8th edition), 100 (33.9%) were T1mi, 111 (37.6%) T1a, 70 (23.7%) T1b, and 14 (4.7%) T1c. By operation method, 241 (81.7%) underwent lobectomy, 15 (5.1%) segmentectomy, and 39 (13.2%) partial resection. Adjuvant chemotherapy was given in 2.7% (n=8) of patients. STAS was seen in 22.7% (n=67) of patients. Five-year OS was 95.3% for STAS-negative and 91.1% for STAS-positive (p=0.0262), and the 5-year RFS was 96.8% and 83.9%, respectively (p=0.0003). In matched cohorts, each cohort included 48 patients and the 5-year OS was 95.0% for STAS-negative and 90.6% for STAS-positive (p=0.3201). The 5-year RFS was 93.3% and 91.3%, respectively (p=0.9363). **Conclusion:** Patients with pathologic stage IA ADC with STAS, according to the 8th TNM classification, had a worse prognosis in unmatched cohorts even though adenocarcinoma in situ was excluded. Because of various confounding factors, the propensity score matching revealed the presence of STAS as a non-significant prognostic factor in our matched cohorts. This study was a retrospective analysis, and a prospective study is needed regarding the indication of limited resection.

Keywords: adenocarcinoma, STAS, Early lung cancer

P2.17-23 THE ROLE ADJUVANT CHEMOTHERAPY IN RESECTED STAGE 1 NSCLC WITH HIGH RISK FACTORS: A TURKISH ONCOLOGY GROUP STUDY

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Background: Adjuvant chemotherapy is accepted as a standard treatment for suitable patients who have undergone surgery for T2N0 non-small cell lung cancer with tumors larger than 4 cm. Despite similar relapse rates, the benefit of adjuvant chemotherapy for smaller tumors with high risk features is not clear. In this retrospective analysis our aim was to evaluate the prognostic impact of adjuvant platin-based chemotherapy in high-risk stage 1 NSCLC patients. **Method:** This cooperative group study included 250 NSCLC patients who underwent curative surgery for stage 1 NSCLC with tumor size 2-4 cm and adverse prognostic factors consisting of visceral pleural invasion(VPI), lympho-vascular invasion(LVI), high grade, presence of solid-micropapillary(SMP) components or STAS. Records of patients were analyzed to investigate the prognostic impact of adjuvant chemotherapy in this cohort. DFS was defined as the time from surgery to the last follow-up, until relapse or death, CSS;time from surgery to death related to cancer or last known contact, OS;time from diagnosis to death or last known contact. Statistical analysis was performed using SPSS 20.0 software(SPSSInc,Chicago,USA). **Result:** Median age at presentation was 63 years (range 18-90). The mean tumor size was 29.4 ± 7.4 mm. The frequency of patients with specified risk factors were: VPI: n: 92 (36.8%); LVI: n: 91 (36.4%); Grade 3:n: 49 (19,6%); SMP:n: 76 (30.4%); STAS:n: 15 (6%). A total of 51 patients had received adjuvant platin-based chemotherapy. There were significantly more patients who received chemotherapy

in the younger age group (<65 ears old, ≥65 years old) and those with larger tumors (2 – 3 cm, 3 – 4 cm). During a median follow-up period of 91.8 months; 79 patients(31.6%) experienced recurrence, 62 patients(24.8%) have died, 144 patients(57.6%) were alive without disease and 24 patients (9.6%) were alive with disease. 5-year and 10-year OS rates were 72.7%(± 3,5) and 46.8%(± 8), respectively. There was a significant improvement in DFS with adjuvant chemotherapy, especially in groups with VPI (93.3% vs 53.6%, p:0.016) and SMP (92.3% vs 57.3%, p:0.03). There was also a non-significant trend for improved CSS and OS among patients who received CT.

Table 1. Effects of chemothrapy on survival.

	Chemotherapy Group Events/N Median 5-years DFS	Non - treatment Group Events/N Median 5-years DFS	P Value
DFS	12/51 NE % 74.9 ± 6.3	81/190 71.1 months % 54 ± 4.2	0,032*
CSS	4/49 NE % 89 ± 5	41/179 91.8 months % 76.9 ± 3.8	0,078
OS	10/49 NE %77.4 ± 6.4	51/179 88.9 months % 72.1 ± 4	0,541

*All values are stratified, respecting to significant confounding factors such as age, gender and tumor size. **Conclusion:** Adjuvant platin-based chemotherapy should be considered for this subset of patients having high grade tumors, or those with VPI, LVI or solid-micropapillary components. Prospective, randomized trials incorporating clinical and molecular risk factors are required to clarify the role of adjuvant chemotherapy for stage 1 NSCLC patients.

Keyword: NSCLC, Adjuvant Chemotherapy, Early Stage

P2.17-24 MINIMALLY INVASIVE SURGERY FOR LUNG CANCER IMPROVES SHORT TERM OUTCOMES IN PATIENTS WITH HISTORY OF HEAD AND NECK CARCINOMA

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Background: Lung cancer resections are at high risk for major complications in patients with history of head and neck carcinoma (HNC). We initiated a minimally invasive video assisted thoracic surgery (VATS) program since 2014. Our objective was to determine whether VATS lobectomy had better short term outcome than open lobectomy in this subset of patients. **Method:** We performed a retrospective monocentric analysis of consecutive standard lobectomies performed for lung cancer in patients with history of HNC at our institution between January 2010 and December 2017. Patients with more complex procedures were excluded. Patients' characteristics and short term outcome were compared between VATS and open lobectomy (OL) groups. Quantitative data were compared using parametric test when normally distributed and using non-parametric test when not normally distributed. Qualitative data were compared using Chi2 or exact Fischer's test when appropriate. P<0.05 was considered significant. **Result:** Among 85 patients, 52 underwent an OL and 33 VATS lobectomy. There was no significant difference between the two groups regarding age, sex ratio, HNC location, history of HNC treatment, pathology and stage of lung cancer, history of coronary artery disease, respiratory function or neutrophil to lymphocyte ratio. Postoperative death occurred in 2 patients only in the OL group. In the VATS group, there was a significant decrease in proportion of postoperative life-threatening complications requiring hospitalization in intensive care unit (12/52 vs. 1/33, P=0.01). The main results are reported in the Table.

	All (n=85)	Open lobectomy (n=52)	VATS lobectomy (n=33)	P
Age (median [IQR], y)	63 [59; 70]	64 [59; 71]	63 [59; 69]	NS
Sex (male/female)	68/17	44/8	24/9	NS
BMI (median [IQR], kg/m^2)	22.5 [20.0; 24.9]	23.4 [20.3; 31.3]	23.0 [20.0; 24.6]	NS
HNC location				
Oral cavity	25 (29.4%)	18 (34.6%)	7 (21.2%)	NS
Oropharynx / nasopharynx	13 (15.3%)	5 (9.6%)	8 (24.2%)	
Hypopharynx	18 (21.2%)	13 (25.0%)	5 (15.2%)	
Larynx	21 (24.7%)	13 (25%)	8 (24.2%)	
Other	8 (9.4%)	3 (5.8%)	5 (15.2%)	
Metachronous lung cancer (≥6months delay)	57 (61.2%)	39 (75.0%)	18 (54.5%)	NS
HNC treatments				
Preop HNC surgery +- other	44 (51.8%)	28 (53.8%)	16 (48.5%)	NS
Preop radio chemo +- HNC surgery	38 (44.7%)	20 (38.5%)	18 54.5%)	
Preop radio +- HNC surgery	15 (17.6%)	9 (17.3%)	6 18.2%)	
Preop chemo +- HNC surgery	6 (7.0%)	5 (9.6%)	1 (3.0%)	
HN treatment pending	13 (15.3%)	7 (13.5%)	6 18.2%)	
Comorbidities				
Coronary artery disease	10 (11.8%)	4 (6.1%)	6 (18.2%)	NS
%PreopFEV$_1$ (mean, SD)	86 ± 17	87 ± 15	84 ± 21	NS
Preop N/L ratio (median [IQR]	42 [2.4; 6.3]	3.9 [2.3; 6.2]	4.8 [3.0; 6.9]	NS
Preop swallowing disorder	9 (10.6%)	7 (13.5%)	2 (6.1%)	NS
Peroperative tracheotomy	6 (7.1%)	4 (7.7%)	2 (6.1%)	NS
Lung cancer staging				
stage I	61 (71.8%)	36 (69.2%)	25 (75.8%)	NS
stage II	16 (18.8%)	9 (13.3%)	7 (21.2%)	
stage III	8 (9.4%)	7 (13.5%)	1 (3.0%)	
stage IV	0 (0%)	0 (0%)	0 (0%)	
Lung cancer pathology				
adenocarcinoma	43 (50.6%)	23 (44.2%)	20 (60.6%)	NS
SCC	36 (42.4%)	25 (48.7%)	11 (33.3%)	
other	6 (7.1%)	4 (7.7%)	2 (6.1%)	
Postoperative outcomes				
In-hospital mortality	2 (2.4%)	2 (3.8%)	0 (0%)	-
Postoperative ICU	13 (15.3%)	12 (23%)	1 (0.03%)	**0.01**
Postoperative hospital stay duration	9.0 [7.0; 17.0]	9.5 [7.0; 21.0]	8.0 [4.0; 15.5]	NS
Pneumonia	27 (31.8%)	21 (40.4%)	6 (18.2%)	NS
90 days re-hospitalization	7 (8.2%)	6 (11.5%)	1 (0.03%)	NS
Without postoperative morbidity	31 (36.5%)	16 (30.8%)	15 (45.5%)	NS
Complication classification (Clavien-Dindo)				
Grade I	7 (8.2%)	3 (5.8%)	4 (12.1%)	NS
Grade II	10 (11.8%)	5 (9.6%)	5 (15.2%)	
Grade III	24 (28.2%)	16 (30.8%)	8 (24.2%)	**0.03**
Grade IV	11 (12.9%)	10 (19.2%)	1 (3.0%)	
Grade V	2 (2.4%)	2 (3.8%)	0 (0%)	

Table: Patients characteristics and short term outcomes after video-assisted (VATS) or open lobectomy among patients with history of head and neck carcinoma (HNC). IQR: interquartile range; BMI: body mass index; preop: preoperative; N/L ratio: neutrophil to lymphocyte ratio; SCC: squamous cell carcinoma; ICU: intensive care unit. P<0.05 was considered significant.

Conclusion: We found that minimally invasive thoracic surgery was associated with better short term outcomes compared to open surgery for lung cancer resection in patients with history of HNC. Therefore, we suggest that standard lobectomy in patients with history of HNC should be performed by VATS procedure. Further studies are required to confirm our finding.

Keywords: Head and Neck carcinoma, lung cancer resection, VATS lobectomy

POSTERS

P2.17-25 GENOMIC INSIGHT INTO STAGE I PULMONARY ADENOCARCINOMA FOR RECURRENCE BY TARGETED NEXT-GENERATION SEQUENCING ANALYSIS

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Background: Despite surgical resection, stage I pulmonary adenocarcinoma has a recurrence rate of 18.4%–25%. Prognostic markers of localized lung adenocarcinoma remain undefined. Targeted next-generation sequencing (NGS) is supposed to be useful to identify recurrence-related genes. We aimed to identify genes and co-occurring mutations that might predict recurrence after surgical resection of stage I pulmonary adenocarcinoma through targeted NGS. **Method:** Tissues from 202 patients who had complete resection of stage I pulmonary adenocarcinoma at Konkuk University Medical Center, from 2005 to 2017 (median follow-up: 48 months), were analyzed by targeted NGS using a panel of the 170 cancer-related genes (KF1 panel by Macrogen Inc. Korea,). We compared RFS (relapse-free survival) according to frequent genetic alterations using the Kaplan-Meier method and compared their combinations to identify recurrence-related genes by multivariate analysis. **Result:** The most frequent genetic alterations were EGFR (56.9%), TP53 (37.7%), KRAS (13.4%), and PIK3CA (10.4%) in surgically resected stage I pulmonary adenocarcinoma. In the tumors with single gene mutation, EGFR mutation was a good prognostic factor and TP53 mutation was a poor prognostic factor for recurrence. (EGFR mutation, HR 0.26, 95% CI 0.07-0.95, p=0.024 vs TP53 mutation, HR 3.39, 95% CI 1.17-9.8, p=0.02). In the tumors with two gene mutations, similar tendency has been observed but there was no statistical significance. Mutation of CTNNB1 was significantly related to recurrence in multivariate analysis (HR3.76, P=0.003) and this finding suggests the CTNNB1 as a molecular biomarker for recurrence by NGS method. TP53 and KRAS combination mutations tended to be associated with shorter RFS (HR=1.89, p=0.08). Recurrence was not associated with the number of the co-occurring mutations but with their specific combinations such as the combination of CTNNB1 and EGFR. **Conclusion:** The CTNNB1 mutation is associated with shorter RFS as compared with wild-type CTNNB1 in resected stage I adenocarcinoma. Larger datasets are required to validate whether the CTNNB1 gene is an independent predictive factor of early stage adenocarcinoma recurrence. NGS can be useful tool to predict the risk of recurrence and select the patient to need the adjuvant chemotherapy in stage I adenocarcinoma.

Keywords: Next-generation sequencing, early resected pulmonary adenocarcinoma, Recurrence

P2.17-26 INDOCYANINE GREEN VIRTUAL ASSISTED LUNG MAPPING (ICG-VAL-MAP): ANYONE CAN PERFORM A SUCCESSFUL PREOPERATIVE MARKING FOR A SMALL LUNG NODULE

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Background: As a preoperative marking of small pulmonary nodules, we developed Virtual Assisted Lung Mapping (VAL-MAP), which is consisted of preoperative simulation using three-dimensional CT images and transbronchial dye marking using indigocarmine (IC). Between 2012 and 2016, we performed VAL-MAP in more than 200 cases in a single institution; however, we sometimes came across a situation, in which an identification of marked IC was difficult at post-marking CT and/or during surgery. Herein, we have developed a new VAL-MAP (ICG-VAL-MAP) using indocyanine green (ICG) and contrast agent. The purpose of this study was to prospectively evaluate the visibility of newly-developed ICG-VAL-MAP in an identification of ICG at post-marking CT as well as during surgery. **Method:** Between January in 2017 and February in 2019, we performed ICG-VAL-MAP, using ICG and contrast agent in addition to IC as a marker for preoperative nodule identification, in 88 patients at our institution. Preoperative marking was performed on the same day as surgery or 1 day before surgery. During surgery, fluorescence endoscope system was used for identification of marked ICG. **Result:** Targeted lesions were 105 nodules with the diameter ranging from 2 to 38 mm (median 8 mm). The depth of the lesion from the pleural surface ranged from 0 to 49 mm (median 8 mm). Total marking numbers were 208 (IC: 99, ICG: 109). At post-marking CT, IC was easily identified in 78 markings (78%), difficult to be identified in 10 markings (10%), and unable to be identified in 11 markings (11%). On the other hand, ICG was easily identified in all markings at post-marking CT. During surgery, IC was easily identified in 74 markings (74%), slightly identified in 4 markings (4%), and unable to be identified in 21 markings (21%). On the other hand, ICG was easily identified in 108 markings (99%) during surgery. Only in 1 case, ICG marking was accidentally placed far from a pleural surface, but ICG was slightly identified in a collapsed lung during surgery. In summary, ICG was significantly easily identified than IC during surgery (P<0.0001) as well as at post-marking CT (P=0.0002). There were no significant perioperative complications related to ICG-VAL-MAP. All nodules were identified intraoperatively and an appropriate surgical resection was conducted in each patient. In details, 53 wedge resections, 48 segmentectomies and 2 lobectomies were performed. Furthermore, all nodules were diagnosed pathologically (74 primary lung cancer, 24 metastatic lung cancer, and 7 benign nodule). **Conclusion:** We confirmed that ICG-VAL-MAP was a novel and promising technique with better visibility than conventional VAL-MAP for the complete resection of small pulmonary nodules.

Keywords: Lung cancer, preoperative marking, small nodule

P2.17-27 EVALUATION OF MEDIASTINAL LYMPHADENECTOMY QUALITY IN PATIENTS OPERATED FOR NSCLC FROM THE PAULISTA LUNG CANCER REGISTRY(PLCR)

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Background: To describe the quality of mediastinal lymphadenectomy in patients operated on for NSCLC considering the resectability criteria proposed by IASLC in 2005 and to evaluate the impact of the definition of complete, uncertain and incomplete resection in overall survival and disease free survival in 5 years. **Method:** Retrospective data from patients operated on for NSCLC between Jan/ 2002 and Dec/2018 in 4 institutions in the state of São Paulo were extracted from a prospective database, the Paulista Lung Cancer Registry (PLCR). Complete resection was defined by the absence of gross and microscopic residual disease, systematic lymph node dissection, and negativity of the highest mediastinal lymph node removed. Uncertain resection was defined by free resection margins, but with less rigorous lymph node evaluation than systematic dissection and/or positivity of the highest mediastinal lymph node removed. Incomplete resection was defined by the presence of gorss or microscopic residual disease. Patient follow-up was updated until Jan/2019. Overall survival was analyzed by the Kaplan-Meier method, Log rank test and Cox proportional regression. **Result:** A total of 663 patients were identified. Mean age was 65.64 years, 338 men(50.9%). The predominant histological type was adenocarcinoma(n = 466, 70.2%), followed by squamous cell carcinoma(n = 162, 24.4%). Lobectomy was the most commonly performed procedure(n = 576, 86.8%), followed by segmentectomy and pneumonectomy(n = 40, 6.0% and n = 34, 5.1%, respectively). There was 388 patientes(59.81%) classified as stage I, 146(23.1%) stage II, 97(15.3%) stage III and 11(1.74%) stage IV. Resection was complete in 374 cases (56.4%), uncertain in 252 cases(38.0%) and incomplete in 37 cases(5.5%). Mediastinal lymphadenectomy was adequate in 421 cases (63.4%) and inadequate in 242 (36.5%). Reasons for inadequate lymphadenectomy were: no nodal station sampling (n = 30, 4.5%), no station 7 sampling (n = 103, 15.5%) and sampling of less than 3 mediastinal stations (n = 109, 16.4%). The highest mediastinal lymph node removed was positive in 45 cases (6.7%). Surgical margins were positive in 37 cases (5.5%). The median follow-up was 19.5 months (IQR 7.4 - 42.5), and 5 years follow-up was completed in in 15.5%. During follow-up, 133 (20.4%) patients had recurrence of the disease. Median disease-free survival was 64 months in the general group and 84.0, 58.6 and 31.5 months in the complete, uncertain and incomplete resection groups, respectively (log rank p = 0.15). Median overall survival in the complete resection group was 98.3 months, in the uncertain resection group it was 64 months. The incomplete resection group did not reach the median. There was no statistical difference in survival between groups (log

rank p = 0.22). **Conclusion:** The analysis showed a high prevalence of uncertain resection, but comparable to other studies already published. This demonstrates that lymphadenectomy is not being performed according to IASLC recommendations. However, in this study, there was no impact on overall survival and disease-free survival at 5 years, which may be due to the small sample size and the short follow-up time of the vast majority of patients included in the PLCR.

Keywords: Non small cell lung cancer, lobectomy, Lymphadenectomy

P2.17-28 EXAMINATION OF THE INDICATION AND VALIDITY OF SEGMENTAL RESECTION AS INTENTIONAL AND PALLIATIVE LIMITED RESECTION FOR LUNG CANCER

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Background: Segmental resection with lymph node dissection as intentional limited resection is now regarded as the effective surgical procedure for early lung cancer from the view point of curability and preservation of respiratory function. But the curability of this procedure for more advanced cancer is not well known. We may show it by investigating the detailed results of all segmental resection cases as intentional and palliative limited resection. **Method:** We targeted 167 cases who passed more than five years after operation among 240 lung cancer cases on whom we have performed segmental resection with lymph node dissection between January in 2003 and March in 2019. It was decided that the indication of segmental resection as intentional limited resection was cStage 0, IA1 and IA2 (UICC 8th) with meeting the SUVmax value of FDG-PET was 1.5 or less (=group A). Segmental resection as palliative limited resection was performed on cStage IB or less patients who had difficulty in lobectomy because of poor respiratory function, multiple lung cancer or presence of serious other disease, etc, (=group B). We investigated prognosis and pathological recurrent factors in both groups, and we considered each indication of segmental resection as intentional or palliative limited resection again. **Result:** Group A contains 102 cases and 5-year survival rate was 97% (All death cases died of other disease). In group A, local recurrence occurred in 1 case (pStage IA1, surgical margin insufficient) but distant metastasis did not occur. Group B contains 65 cases and 5-year survival rate was 71% (The original death from lung cancer was 5 cases among 17 death cases). In group B, local recurrence occurred in 4 cases (pStage IA2: 1(surgical margin insufficient), pStage IB: 2, pStage IIIA: 1), distant metastasis occurred in 6 cases (pStage IA3: 1, pStage IB: 1, pStage IIIA: 3, pStage IIIB: 1) and 3 cases on which postoperative adjuvant chemotherapy had been performed had no recurrence (pStage IB: 1, pStage IIB: 2). Recurrence of pStage IA3 was only 1 case (10% in all pStage IA3 cases, Sm, distant metastasis). The multivariable analysis of pathological recurrent factors (pStage, p, v, ly) in group B (except for 3cases on which postoperative adjuvant chemotherapy was performed) showed that lymphatic involvement had a significant influence on recurrence (p-value / Hazard ratio: lymphatic involvement: 0.03 / 6.49, more than pStage II: 0.37 / 2.50). **Conclusion:** We are convinced that the current indication of our intentional limited resection to be almost proper but we have thought that we should include a part of Stage IA3 depending on a condition. In palliative limited resection cases, postoperative adjuvant chemotherapy should be considered if possible when pathological result show lymphatic involvement or more than pStage II.

Keywords: indication, Segmental resection, Lung cancer

P2.17-29 IMPACT OF SECOND PREDOMINANT PATTERN ON RECURRENCE IN EARLY STAGE RESECTED LUNG ADENOCARCINOMA: A MULTICENTRIC STUDY

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Background: The ATS/ERS/IASLC adenocarcinoma classification allowed not only a better anatomical-pathological definition, but it showed a significant influence on long-term outcomes. It has been proposed that adenocarcinoma patterns could be divided in three groups according to their clinical and pathological behaviors: low (lepidic), moderate (papillary or acinar) and high grade (micropapillary and solid). Moreover, different patterns might mingle influencing biological features and prognosis. We focused on resected adenocarcinomas analyzing the impact of second predominant pattern on recurrence rate and Disease-Free Survival (DFS). **Method:** We retrospectively collected all stage I and II lung adenocarcinoma operated on between January 2014 and December 2017 in seven European thoracic surgery departments. We selected all patients who underwent an anatomical resection with lymphadenectomy; patients with incomplete follow up, pure adenocarcinoma or those composed by more than two subtypes (if third pattern accounted for more than 10%) were excluded. Mucinous adenocarcinoma were considered separately from other patterns. DFS, incidence and localization of recurrence were calculated according to the second predominant pattern. **Result:** Among 500 patients, 331 were selected. There were 186 male, mean age was 68.1 years (±SD 8.2) and 105 (31.7%) patients were active smokers at the moment of diagnosis. The majority of patients (271, 81.9%) underwent a lobectomy. Low, medium and high-grade first predominant pattern were 45 (13.6%), 208 (62.9%), 57 (17,2%) respectively and 21 cases were mucinous. Second predominant pattern was present as follow: acinar 96 (29%), lepidic 86 (26%), papillary 74 (22.4%), solid 29 (8.8%), micropapillary 26 (7.9%), 20 mucinous (6%). DFS analysis showed a significant impact of grade of the second predominant pattern (p=0.046), while first predominant pattern's grade did not significantly impact on DFS (p=0.322). According to the subtypes of second predominant pattern, lepidic pattern showed a better mean DFS (56.1 versus 49.6 months, p=0.014) and a lower recurrence rate (p=0.018, and, in particular, a lower distant recurrence rate, p=0.016), while micropapillary had a worse DFS (42.3 versus 52.1 months, p=0014), higher recurrence rate (p=0.017, and in particular, a higher regional recurrence, p=0.038); moreover, also pleural invasion influenced DFS significantly (p=0.001). At multivariate analysis, lepidic second pattern and pleural invasion confirmed their influence on DFS (p=0.044, IC 0.28-0.98 and p=0.001, IC 1.36-3.4). When we analyzed the subgroup with only moderate grade (acinar and papillary) first predominant pattern (208 patients), lepidic and micropapillary second predominant patterns and pleural invasion confirmed their significant impact on DFS (p=0.015; p=0.021; 0.015 respectively). **Conclusion:** Our multicentric study confirms the impact of adenocarcinoma patterns on recurrence rate and DFS. The second predominant pattern in early stage resected adenocarcinoma seems to play an important role in influencing the outcomes. Micropapillary and lepidic second pattern demonstrated to be significantly related to recurrence development and their presence should require different and dedicated postoperative management.

Keywords: lung adenocarcinoma, adenocarcinoma patterns, early stage adenocarcinoma

POSTERS

P2.17-30 SUPERIOR VENA CAVA RESECTION AND PROSTHETIC REPLACEMENT FOR NSCLC: IS IT WORTHWHILE?

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Background: Direct involvement of superior vena cava (SVC) by NSCLC requires en-bloc tumor resection with complete vascular clamping and prosthetic replacement. We present our experience with this highly demanding procedure in order to determine whether this complex surgery is warranted **Method:** Since 1980, complete en-bloc resection of NSCLC invading the SVC followed by prosthetic replacement was performed in 48 patients (30 squamous, 18 non-squamous) in our Department. Patients with partial resection of the SVC with or without patch reconstruction, less complex procedure, were excluded. There were 38 male and 10 female with a mean age of 57 years (range, 38-82 years). N2, N3 disease and distant metastasis diagnosed on preoperative workup were considered as a surgical contraindication. Neoadjuvant therapy was given to 17 patients including chemotherapy (n=11), radiotherapy (n=1) or both (n=5). Surgical approach was a right thoracotomy (n=40), median sternotomy (n=5) or an anterior cervico-thoracotomy (n=3). Although vascular shunt was never used, in one patient a VA-ECMO was necessary for ventilation difficulties. Lung resection was carinal pneumonectomy (n=15), pneumonectomy (n=14), upper bilobectomy (n=1), lobectomy (n=16) or a sublobar resection (n=2). Mean SVC clamping time was 31.6 minutes (range, 10 to 120 minutes). On definitive histology, an R0 resection was achieved in 41 (85%) patients, and lymph node involvement was pN0 in 8, pN1 in 23, pN2 in 14 and pN3 in 3 patients. Tumor size ranged from 1.9 cm to 17 cm with a medium size of 5.2 cm. 31 patients received adjuvant therapy including chemotherapy (n=5), radiotherapy (n=1) or both (n=25). **Result:** Postoperative death occurred in 5 patients (10%), all of them underwent a right pneumonectomy (p=0.02). 13 other patients experienced postoperative complications. No neurologic events related to SVC clamping occurred. Graft thrombosis occurred in 2 patients who died postoperatively from bronchopleural fistula. With a median survival of 24 months, 3, 5 and 10 years survival rates were 45%, 40% and 35%, respectively. During follow-up, recurrence occurred in 31 patients and was mostly systemic (n=26). Disease free survival at 3, 5 and 10 years were 37%, 37% and 30%, respectively. By univariate analysis, only incomplete resection was found to be associated with poorer survival (p=0.04). **Conclusion:** In highly selected patients with NSCLC involving SVC, complete en-bloc resection and prosthetic replacement is feasible in expert center with acceptable mortality mainly due to right pneumonectomy. Good long-term survival is obtained provided a complete R0 resection is achieved.

Keywords: surgery, superior vena cava, NSCLC

P2.17-31 CENTRAL LUNG TUMORS TREATED WITH STEREOTACTIC RADIOTHERAPY. TOXICITY AND EARLY RESULTS IN A SINGLE INSTITUTION

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Background: Stereotactic ablative radiotherapy (SABR) for stage I-II inoperable non-small-cell lung cancer (NSCLC) peripherally located has become a standard treatment. However the role in central located lung cancer remains controversial because potential severe toxic effects. When adaptive dose regimens to location and appropriated dose-volume constraints for normal tissues are used, the expected toxicity are mild and the local control are comparable to those for peripheral lesions. We report our experience with central SABR. **Method:** Retrospective analysis of patients diagnosed with inoperable centrally located early lung cancer, defined as a tumor within 2 cm in all directions of any mediastinal critical structure, who were treated in a single institution between May 2017 and January 2019 with VMAT-SABR. All patients underwent 4DCT simulation. Cone beam CT (CBCT) and fluoroscopy prior and CBCT after to each treatment fraction was performed. Dose to the PTV was prescribed to the 95% isodose line. Acute toxicity was assessed by the CTCAE v.4.03 scale and local control was reported using RECIST criteria. **Result:** 40 patients were treated with stereotactic ablative radiotherapy for early inoperable NSCLC and 15 male patients had centrally located lesions. The mean age of included patients were 75 years (65-81) with a median follow-up of 6.6 months (2,2-19,8). The main cause of inoperability was pulmonary functionalism and cardiac comorbidities. 2 (13%) were treated previously with lobectomy for another primary lung cancer. 8 (53%) were adenocarcinoma, 2 (13%) were squamous carcinoma and 5 (33%) with no biopsy-proven malignancy. The most frequent location were inferior lobes (53%). 10 (66%) were stage cT1b-cN0M0, 4 (27%) cT2a-bN0M0 and 1 (7%) were cT3N0M0 (<5cm) as defined by the 8th edition of TNM. In the majority of patients (53%) the mediastinal staging was performed with PET-CT, however 7 patients underwent pathological mediastinal lymph node evaluation (endobronchial ultrasonography in 4 and mediastinoscopy in 3). The prescribed dose ranged from 48 Gy to 70 Gy in 4 to 10 fractions. Most patients were treated using 50 Gy in 5 fractions, BED 100 Gy10 (47%), followed by 48 Gy in 4 fractions, BED 105.6 Gy10 (20%) and 60 Gy in 8 fractions, BED 105 Gy10 (20%). There were no G3-5 toxicity. Acute G1 toxicities were fatigue (40%), pneumonitis (27%), dermatitis (13%) and cough (7%). 1 patient presented acute toxicity consistent with cough G2. At last follow-up, in terms of disease control, 87% the lesions had partial response or stable disease. 1 patient had local progression. 13 patients (87%) were alive and 2 (13%) died. **Conclusion:** In our serie, VMAT-SABR for centrally located lung tumors is safe and effective and should be considered for its acceptable acute toxicity profile and good early results.

Keywords: SABR, centrally located, Early lung cancer

P2.17-32 USING NEXT-GENERATION SEQUENCING TO IDENTIFY GENETIC PREDICTORS OF LOCAL FAILURE AFTER LUNG STEREOTACTIC BODY RADIATION THERAPY

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Background: Lung stereotactic body radiation therapy (SBRT) is a well-established therapy for primary lung tumors or metastatic lung lesions from other primary sites. However, local failure after SBRT still occurs. We hypothesized that next-generation tumor sequencing may identify genetic characteristics that predict local failure. **Method:** We conducted a retrospective analysis of all patients at our institution who received SBRT to the lung for either primary or metastatic tumors, and who underwent next-generation tumor sequencing utilizing an FDA-approved targeted panel of at least 341 genes. Patient and tumor characteristics, local failure, radiation dose, and all genetic alterations identified by the panel were collected. Univariate Cox proportional hazards analysis was performed. Because of the large number of genes in the panel, we limited analysis to genes with at least a 5% incidence of alteration in this cohort. To correct for multiple testing, we used a p-value of $\leq$ 0.001 as the significance threshold for genetic alterations. **Result:** Between 2013 and 2018, 140 patients with 160 lung lesions (76 primary lung, 84 non-lung primary) were treated with SBRT to a median radiation biologically effective dose of 100 Gy (range 48-151 Gy). Median follow-up for local failure was 13.8 months. There were 39 local failures (24.4%) during the study period. On univariate analysis, colorectal histology (HR 2.2, p=0.037), BED<100 Gy (HR 2.1, p=0.019), and larger lesion size (HR 1.2, p=0.023) were associated with higher risk of local failure. 45 mutations occurred with greater than 5% frequency (≥8 times) in our cohort. Univariate analysis identified three genes for which alterations were significantly associated with local failure: APC (mutated 17 times, HR 3.5, p<0.001), ARID2 (n=8, HR 5.5, p<0.0005), and MGA (n=8, HR 5.2, p<0.001) **Conclusion:** Next-generation tumor sequencing was able to identify genetic alterations associated with higher risk of local failure after lung SBRT. This hypothesis-generating study yielded three candidate genes significantly correlated with local failure. Further study is needed to validate the predictive value of these gene mutations, and their potential for selecting patients at higher risk for treatment failure after lung SBRT.

Keywords: stereotactic body radiation therapy, Next-generation sequencing, Biomarker

P2.17-33 DETERIORATION IN HEALTH-RELATED QUALITY OF LIFE IS ASSOCIATED WITH LOWER LUNG RESECTION RATES IN OLDER ADULTS

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Background: Decision making for surgical resection of lung cancer is based on disease characteristics as well as patient-reported health factors. However, data regarding influence of functional status and health-related quality of life (HRQOL) on consideration for lung surgery are currently lacking. **Method:** We identified lung cancer patients with localized disease from the SEER-Medicare Health Outcomes Survey (MHOS) linked database. HRQOL survey data captured physical/mental health, activities of daily living (ADLs), and medical comorbidities. Patients who had 1) baseline HRQOL survey prior to cancer diagnosis and 2) follow-up survey at least one year after diagnosis were selected. Generalized estimating equation (GEE) model was used to compare patients who underwent surgery versus those who did not in regard to demographics and HRQOL measures. **Result:** Overall, 108 patients were evaluated, of whom 75 (69%) underwent surgery. Surgical patients were younger (mean 73 versus 80 years, p<0.0001); otherwise, patient groups were demographically similar. Surgery was not performed based on surgeon recommendation (n=21, 64%), contraindication(s) (n=9, 27%), or patients' decision (n=3, 9%). Surgery and non-surgery groups experienced similar declines in physical HRQOL, mental HRQOL, and Katz aggregate ADL scores; and an increase in the number of major comorbidities (see Table). However, non-surgical patients had significant declines in specific individual ADLs, namely mobility and personal care activities, compared to surgical counterparts. On GEE, adjusting for age, non-surgical patients were significantly more likely to have decreased physical HRQOL (OR 5.7, p=0.008), mental HRQOL (OR 2.1, p=0.049), or ADL scores (OR 2.7, p=0.02); and multiple comorbidities (OR 2.3, p=0.046) compared to surgical patients.

Variable		Surgery Group N = 75 N (%)	Non-Surgery Group N = 33 N (%)	p Value
Physical HRQOL Scores	Decreased	45 (60)	19 (58)	0.81
	Stable or improved	30 (40)	14 (42)	
Mental HRQOL Scores	Decreased	29 (39)	18 (55)	0.13
	Stable or improved	46 (61)	15 (45)	
Major Comorbidities	Increased	16 (23)	10 (37)	0.18
	Stable	52 (77)	17 (63)	
Katz Aggregate ADL Scores	Decreased	16 (21)	9 (27)	0.50
	Stable or improved	59 (79)	24 (72)	
Individual ADLs				
Eating	Decreased	6 (8)	5 (15)	0.26
	Stable or improved	69 (92)	28 (85)	
Bathing	Decreased	18 (24)	14 (42)	0.053
	Stable or improved	57 (76)	19 (58)	
Using the toilet	Decreased	7 (9)	8 (24)	**0.04**
	Stable or improved	68 (91)	25 (76)	
Dressing	Decreased	12 (16)	11 (33)	**0.04**
	Stable or improved	63 (84)	22 (67)	
Getting in and out of chairs	Decreased	16 (22)	16 (48)	**0.005**
	Stable or improved	58 (78)	17 (52)	
Walking	Decreased	27 (37)	24 (73)	**0.0006**
	Stable or improved	46 (63)	9 (27)	

HRQOL = health-related quality of life; ADL = activity of daily living

Conclusion: Patient-reported outcomes reflect patients' perception of their own health, potentially providing information critical to surgical decision making that is not similarly reflected in other assessment tools. Identification and mitigation of such factors may increase surgeons' recommendation for lung resection for patients with localized malignancy.

Keywords: patient-reported outcomes, Surgical Decision Making, Health-related quality of life

POSTERS

P2.17-34 INTEGRATED CLINICO-RADIOMIC NOMOGRAM FOR PREDICTING DISEASE-FREE SURVIVAL (DFS) IN STAGE I AND II NON-SMALL CELL LUNG CANCER

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Background: Early stage non-small cell lung cancer (ES-NSCLC) comprises about 45% of all NSCLC patients, with 5-year survival ranging between 30-49%. Surgical resection is the standard of care curative modality in these patients but about 30-55% of patients often recur following surgery within the first 3 years. There is currently no validated method to stratify patients based on their risk of recurrence following surgery in these patients. In this project, we develop and validate a nomogram using a combination of CT-derived radiomic textural features and clinco-pathologic factors, in order to predict DFS in ES-NSCLC. **Method:** This study comprised 350 ES-NSCLC patients from two different institutions who underwent surgery (75 patients relapsed). Radiomic textural features were extracted from tumor region (Intratumoral - IT) as well as from the annular ring shaped peritumoral region (PT) with 3mm as a ring thickness and extending 9 mm outside the nodule. A total of 124 features from Gabor, Laws, Laplace, Haralick and Collage feature families were extracted from IT and each PT ring for all patients. The most stable, significant and uncorrelated features were selected from D1 (N=221) and used to build a Lasso-regularized multivariate Cox-regression model to generate a Radiomic Risk Score (RRS) derived from weighted Lasso coefficients. Further, RRS was integrated with clinic-pathologic variables (Lympho-vascular invasion LVI and AJCC stage) which were independently predictive on DFS in multivariate analysis to build a clinical-radiomics score (CRS). A nomogram was constructed to visually assess the CRS and RRS on DFS. Performances were evaluated using hazard ratios (HR), concordance index (C-Index) along with decision and calibration curves to show the differences between the individual and integrated risk scores. **Result:** Top 14 radiomic features included 6 from IT and 8 from 0-9 mm PT distance. The constructed RRS could predict DFS (n=221, C-index=0.69, HR = 3.8; 95% CI- 2.7-5.6, p<0.05) on training (D1) and (n=129, C-index=0.69, HR – 2.5; 95% CI – 1.8-4.7; p<0.05) on a blinded validation cohort (D2), Addition of LVI and pN to build the CRS, increased C-index to 0.74, (p<0.05). Decision and calibration curve analysis shows improved performance of CRS over RRS or clinco-pathologic factors alone.

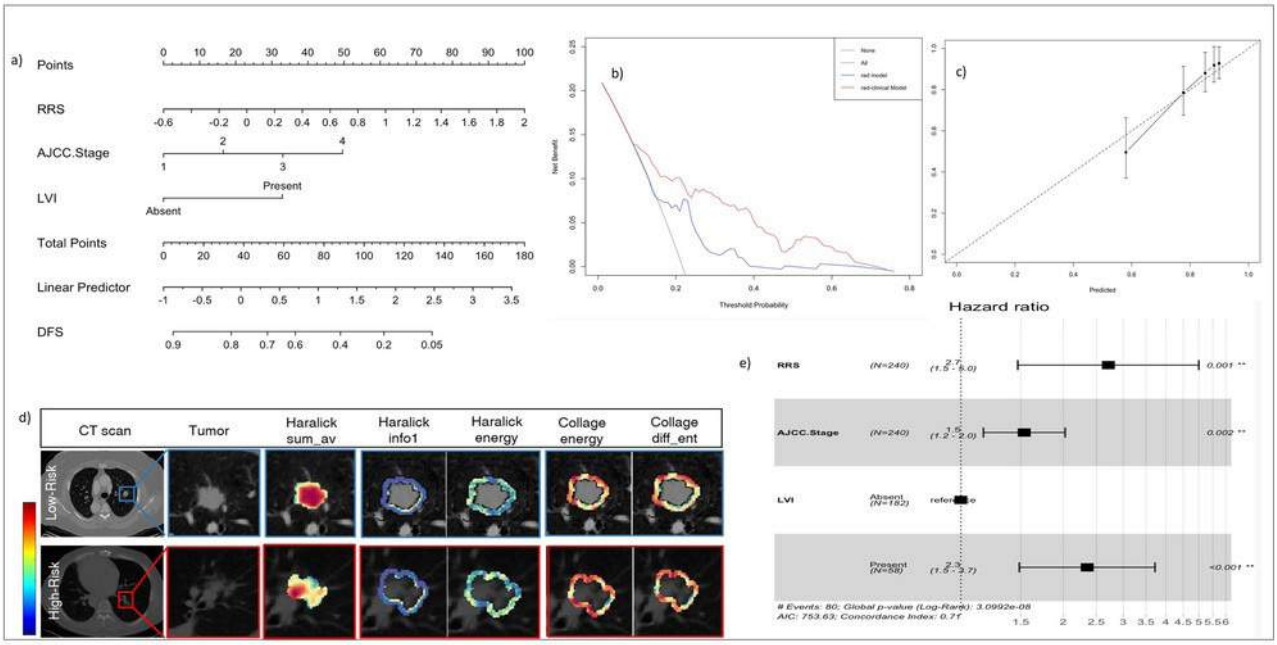

Figure 1: *a) Nomogram with radiomics risk score (RRS) and clinico-pathologic factors (LVI, pN stage) to build a Clinical-Radiomics score to predict DFS following surgery for ES-NSCLC b) Decision curve analysis c) Calibration curve analysis d) Radiomic feature maps from the intra- and peri-tumoral region for high and low- risk patients e) d) Forest plot showing the Hazard Ratios for RRS and clinico-pathologic factors (LVI, Overall AJCC pathological stage)*

Conclusion: Addition of prognostic clinical factors (LVI, AJCC stage) improved the performance of the Radiomic Risk Score model in order to accurately predict DFS in ES-NSCLC patients undergoing surgery.

Keywords: prognostic biomarker, Radiomics, Early stage non-small cell lung cancer

POSTERS

P2.17-35 INTEGRATING CT RADIOMIC & QUANTITATIVE HISTOMORPHOMETRIC WHOLE SLIDE IMAGE FEATURES PREDICTS DISEASE FREE SURVIVAL IN ES-NSCLC

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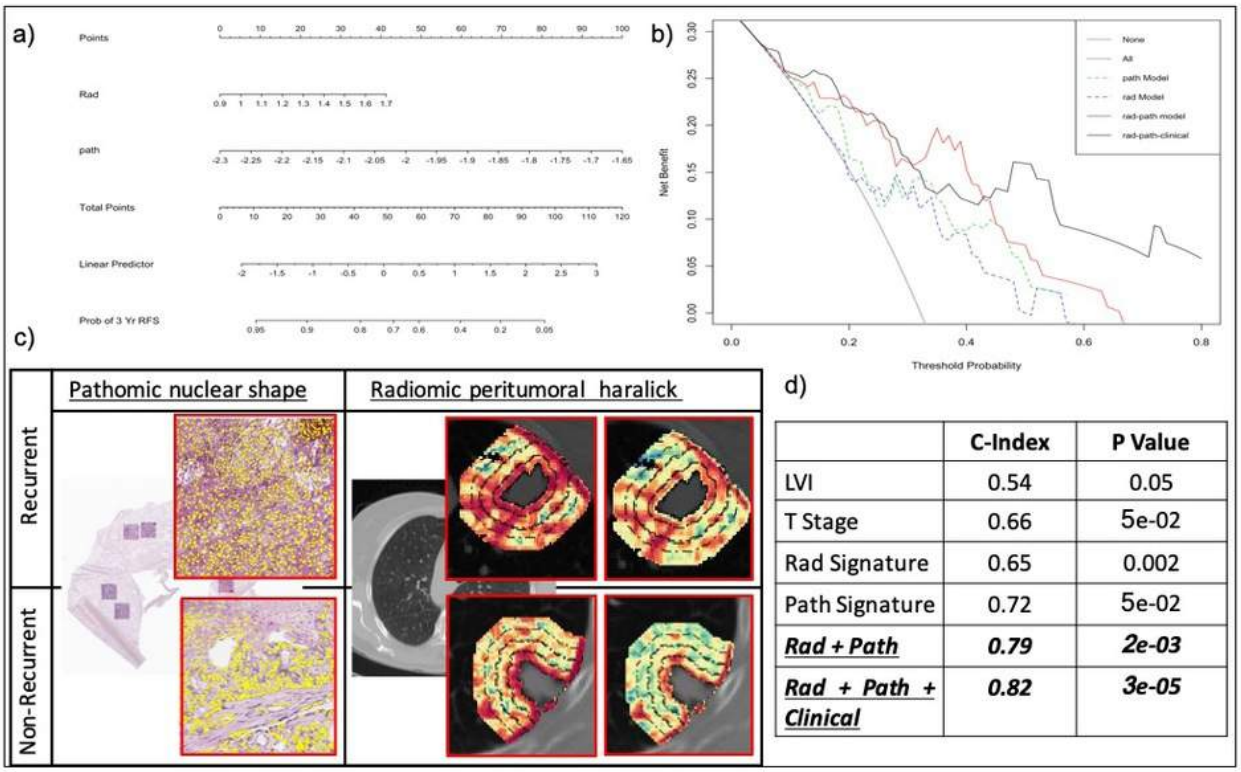
Background: Early-Stage non-small cell lung cancer (ES-NSCLC) accounts for approximately 40% of NSCLC cases, with 5-year survival rates varying between 31-49%. Radiomic textural features from pre-treatment CT scans and QH features from H&E stained WSIs have been shown to be independently prognostic of outcome. With diagnostic CT scans and surgical resection, the standard of care in ES-NSCLC, in this work we seek to take a multimodality approach using routine imaging to improve the predictive performance in determining DFS following resection. **Method:** A retrospective chart review of Stage I and II (ES-NSCLC) pts undergoing surgical resection between 2005-14 with available CT and resected tissue yielded 70 pts. A total of 248 radiomic CT textural features from inside the tumor (Intratumoral –IT) and outside the tumor (Peritumoral – PT) and 242 QH features related to the nuclear shape, texture and spatial orientation and architecture from H&E WSI were extracted. We developed two risk models, Radiomic and QH using the most stable, discriminative and uncorrelated features from CT and WSI respectively determined by Lasso-regularized Cox regression to predict Disease free survival (DFS). Model performances were analyzed using Hazard Ratios (HR), Concordance Index (C-index) and Decision curve analysis. We built a nomogram to calculate the DFS based around the individual models as well as an integration of the QH and Radiomic models. **Result:** Top 6 Radiomic features included 2 IT and 4 PT features from the Haralick and Collage families. The QH model comprised 6 nuclear shape and graph features. In predicting DFS, While the Radiomic model had a HR of 2.4 (p <0.01) with C-index – 0.67, the QH model had HR – 3.1 (p <0.01) with C-index – 0.74. Integration of the Radiomic and QH model yielded a C-index of 0.78 (p< 0.01). After addition of prognostic clinical factors (LVI, AJCC stage) to the model, the C-index was 0.80, almost doubling either modalities alone. The constructed nomogram visualized the apparent benefits of the three models while a decision curve clearly demonstrated the increased benefit of combined integrated model. **Conclusion:** Integration of CT-derived radiomic and tissue-derived QH features was found to show improved performance in predicting RFS when compared to either radiomics or QH alone.



	C-Index	P Value
LVI	0.54	0.05
T Stage	0.66	5e-02
Rad Signature	0.65	0.002
Path Signature	0.72	5e-02
Rad + Path	***0.79***	***2e-03***
Rad + Path + Clinical	***0.82***	***3e-05***

Figure: a) Nomogram representing integrated Rad-Path risk score for predicting DFS; b) Decision curve analysis showing net benefit for the integrated model. The combined Rad-Path-clinical model had the highest net benefit; c) QH nuclear shape feature and radiomic peritumoral Haralick feature heatmeps showing difference between high-risk and low-risk groups; d) Table for individual prognostic clinical factors, and integrated (Rad-Path and Rad-Path-Clinical) models.

Keywords: ES-NSCLC, Radiomic, Pathomic

POSTERS

P2.17-36 MOLECULAR MARKERS, THERAPEUTIC AND PROGNOSTIC ANALYSIS OF LUNG SARCOMATOID CARCINOMAS

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Background: Several molecular markers have been established for therapeutic intervention and prognostic prediction of lung cancer. Less is known about their therapeutic potential and prognostic significance in less common lung cancer subtypes. The present study was therefore designed to assess a set of well-defined molecular markers in patients with lung sarcomatoid carcinomas and their therapeutic and prognostic significance. **Method:** This is a single-center retrospective study of lung cancer patients with histologic types of the sarcomatoid carcinomas who underwent surgical resection at our center during August 2008 to August 2018. The molecular markers analyzed were driver mutations in EGFR, ERBB2, PIK3CA, C-MET, RAS, BRAF, EML4-ALK, RET and ROS1 by ARMS-PCR or NGS, protein expressions of PD-L1 (clone SP-142) in tumors and/or associated lymphocytes by immunohistochemistry. Log-rank test was used to compare the overall survival of patients. **Result:** A total of 74 (1.18%) patients with sarcomatoid carcinomas were identified from 6,285 patients underwent surgical resection. Of the 35 patients underwent mutation testing (including 14 test EGFR and RAS by ARMS), 17 (48.57%) harbored driver mutations (12 RAS, 4 EGFR L859R and 4 EGFR 19del). Proteins expressions of PD-L1 were found in 67.86% of patients. No prognostic significance (DFS and OS) was noted regarding to any driver mutations and PD-L1 expression. Half of the patients (37/74, 50.00%) received adjuvant therapy, 27 of whom used platinum-based chemotherapy (72.97%). Platinum-based adjuvant chemotherapy showed improved DFS (P=0.011) but similar OS (P=0.079). **Conclusion:** A part of lung sarcomatoid carcinomas harbor driver mutation or PD-L1 expression, although they are not prognostic. Platinum-based chemotherapy was preferable in these patients. The role of targeted or immune agents as adjuvant therapy needs further study.

Keywords: driver mutation, lung sarcomatoid carcinomas, Chemotherapy

P2.17-37 PROGNOSTIC IMPLICATION OF SURGICAL TREATMENT FOR THE DOMINANT LUNG ADENOCARCINOMA ASSOCIATED WITH PART-SOLID NODULES

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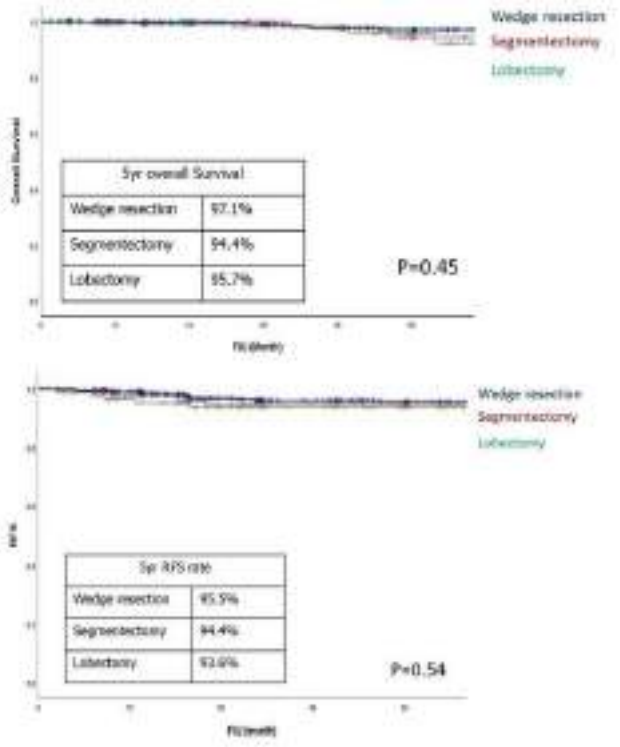
Seoul National Bundang Hospital, Seongnam-si/Korea, Republic of

Background: The aim was to analyze the prognostic implication of surgical resection for lung adenocarcinoma appearing as part-solid nodules (PSNs) on computed tomography scans . **Method:** From 2004 to 2017, the cases of a total of 651 patients (male:female = 259:392, median age, 65years) with surgically resected lung adenocarcinomas manifesting as PSNs were retrospectively reviewed. We compared patient characteristics with t tests for continuous variables and $\chi 2$ tests for categorical variables. The prognostic implication of the multiplicity of the surgical extent and other clinical variables in relation to overall-survival (OS) and disease-free survival (DFS) was analyzed by using Cox regression. **Result:** Median maximum diameter and solid component diameter of PSNs were 2.0cm and 1.1cm.(range 0.8-7, 0.5-3.4) PSNs were resected by wedge resection, segmentectomy, or lobectomy in 94 (14.4%), 92 (14.2%), and 465 (71.4%) cases, respectively. Pathologic diagnosis was adenocarcinoma in situ, minimally invasive adenocarcinoma (MIA), or invasive adenocarcinoma (IA) in 4 (0.6%), 70 (10.8%), and 577 (88.6%) cases, respectively. The median follow-up duration was 35.4 months. There was no significant difference of OS and DFS among the surgical extent and type of lymph node dissection (Figure 1). Multivariate Cox regression analysis demonstrated that multiple pulmonary nodules [hazard ratio (HR) = 8.3; 95% confidence interval (CI): 3.5-19.8 1.173; p <0.001] and wedge resection (HR = 3.8; 95% CI: 1.19-11.9; p = 0.02) were independent risk factors for the tumor recurrence.



Conclusion: Among the resected lung adenocarcinoma associated with PSNs, multiple PSN and wedge resection is a significant prognostic factor in the lung cancer recurrence.

Keywords: part-solid nodule, Sublobar resection, risk factor

P2.17-38 PREDICTIVE FACTORS FOR LYMPH NODE METASTASIS IN PATIENTS WITH CLINICAL STAGE I PART-SOLID LUNG ADENOCARCINOMA

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Background: Accurate clinical staging of small part-solid nodule is essential for developing a treatment plan and evaluating suitability for minimally invasive surgery. The aim of this study was to evaluate predictive factors for metastasis of N1 and N2 lymph nodes in clinical stage I part-solid lung adenocarcinoma. **Method:** Medical records of patients with clinical stage I part-solid adenocarcinoma who had undergone anatomic pulmonary resection with systematic node dissection or node sampling between January 2009 and June 2018 were retrospectively reviewed. To identify predictive factors for lymph node metastasis, univariate and multivariate logistic regression analyses were performed. **Result:** Among the 602 patients in this study, the overall prevalence of lymph node metastasis was 3.7% (n = 22), which included 3.0% of N1 lymph nodes (n = 18) and 1.5% of N2 lymph nodes (n = 9). Combined N1 and N2 nodal involvement was found in 5 patients. Nodal metastasis was not observed in tumors with a solid part ≤1.0 cm (cT1mi and cT1a). The nodal metastasis rate in cT1b, cT1c, and cT2a tumors was 4.7% (10/215), 4.8% (3/63), and 12.9% (9/70), respectively. Predictive factors for N1 node metastasis included size of solid part (p = 0.001), and for N2 node metastasis included visceral pleural invasion (p < 0.001) by multivariate analysis. The ratio of ground glass opacity was not associated with lymph node metastasis.

Prognostic factors for N1 lymph node metastasis

Variables	Univariate	Multivariable	
	p value	HR (95% CI)	p value
Age (y)	0.312		
Sex (male)	0.776		
Never smoker	0.073		
Tumor centrality	0.893		
mSUV of mass	0.935		
Size of solid part (mm)	<0.001	1.090 (1.036-1.147)	0.001
Ground glass opacity proportion (%)	0.131		
Visceral pleural invasion (yes)	0.006		
CEA (ng/mL)	0.009		
CYFRA (ng/mL)	0.107		

Prognostic factors for N2 lymph node metastasis

Variables	Univariate	Multivariable	
	p value	HR (95% CI)	p value
Age (y)	0.745		
Sex (male)	0.118		
Never smoker	0.107		
Tumor centrality	0.009		
mSUV of mass	0.116		
Size of solid part (mm)	0.004		
Ground glass opacity proportion (%)	0.943		
Visceral pleural invasion (yes)	<0.001	12.121 (3.143-46.838)	<0.001
CEA (ng/mL)	0.418		
CYFRA (ng/mL)	0.643		

Conclusion: Among the patients with clinical stage I part-solid adenocarcinoma, 3.7% of the patients showed unexpected lymph node metastasis, and large size of solid part and visceral pleural invasion of the tumor were predictive factors of lymph node metastasis in clinical stage I part-solid adenocarcinoma. Sytemic lymph node dissection and anatomic pulmonary resection should be performed, especially in those who have the larger size of solid part and suspicion of visceral pleural invasion.

Keyword: part-solid nodule, adenocarcinoma, lymph node metastasis

P2.17-39 RELATIONSHIP BETWEEN EGFR MUTATION AND PATHOLOGICAL DIFFERENTIATION IN PATIENTS WITH CLINICAL STAGE IA LUNG ADENOCARCINOMA

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Tokyo Medical University, Tokyo/Japan

Background: Pathological differentiation is an established prognostic factor for patients with lung adenocarcinoma. There are some correlations between epidermal growth factor receptor (EGFR) mutations and pathological differentiation. EGFR mutation-positive adenocarcinoma is considered to be highly differentiated types that show development of alveolar epithelial substitution. However, the distribution of pathological differentiation and the prognostic impact of the presence or absence of EGFR mutations in early adenocarcinoma are not clear. **Method:** We collected the records of 569 patients who underwent surgical resection for clinical stage IA lung adenocarcinoma between 2008 and 2015, and were also examined their EGFR mutation status. Based on the presence or absence of EGFR mutations and pathological differentiation (well;G1/moderately;G2/poorly;G3), patients were categorized into 6 groups: EGFR mutation positive (E+) with G1, E+ with G2, E+ with G3, EGFR mutation negative (E-) with G1, E- with G2, E- with G3. We examined the distribution of each group,(clinicopathological features and prognosis. **Result:** 303 lung adenocarcinoma had EGFR mutations. The distribution was E+/G1:85,E+/G2:209,E+/G3:9,E-/G1:50,E-/G2:178,E-/G3:38. E+/G3 group was significantly fewer (P<0.001). The 5-year recurrence-free survival (RFS) rates were 95% in E+/G1 group, 78% in E+/G2 group, 33% in E+/G3 group, 100% in E-/G1 group, 75% in E-/G2 group, 61% in E-/G3 group. The 5-year overall survival (OS) rates were 98% in E+/G1 group, 91% in E+/G2 group, 44% in E+/G3 group, 100% in E-/G1 group, 87% in E-/G2 group, 79% in E-/G3 group. The prognosis was significantly worse in the E+/G3 group. There were more women (77%) and non-smokers (89%) in the E+/G3 group. Six patients (66%) had recurrence, and in all cases EGFR-TKI was administered and the response rate was 100%. **Conclusion:** Most of the c-IA EGFR positive adenocarcinomas were highly differentiated, and significantly fewer poorly differentiated cases. Among the poorly differentiated group, EGFR gene mutation positive is particularly poor prognosis. However, The therapeutic effect of EGFR-TKI was not different from other EGFR positive patients.

Keywords: Lung cancer, EGFR, pathological differentiation

P2.17-40 ANALYSIS OF 7 YEARS EXPERIENCES OF UNIPORTAL VIDEO-ASSISTED THORACIC SURGERY FOR STAGE I AND II LUNG CANCER

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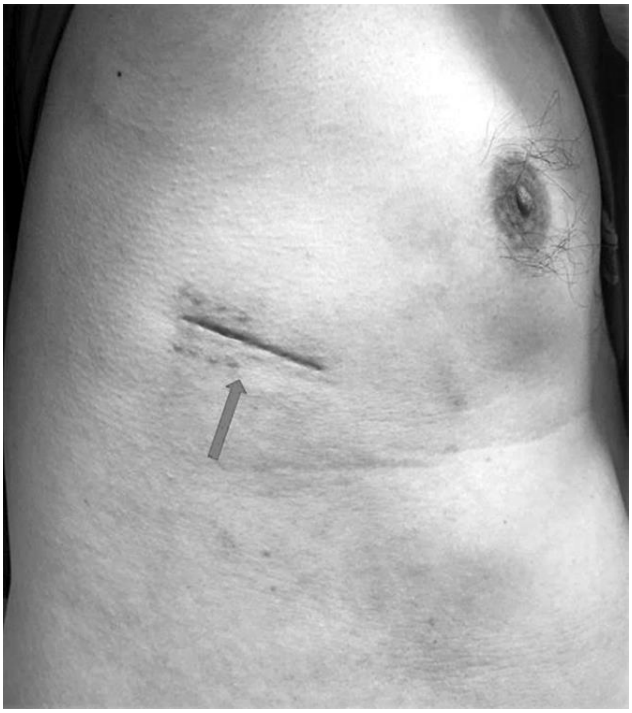
Background: Recently, video-assisted thoracic surgery (VATS) has been accepted as a feasible, safe and effective approach for the treatment of early lung cancer. With the evolution of the VATS technique, uniportal VATS for early lung cancer has been performed and its advantages has been reported including less postoperative pain, less paresthesia and favorable cosmetic results because only one intercostal space is involved. We analyzed our experiences to evaluate results of uniportal VATS in patients with early lung cancer **Method:** We analyzed retrospectively medical records of patients who underwent surgical treatments for stage I and II lung cancer at our institute between March 2011 and December 2018. There were 126 patients in multiportal group (MG) and 102 patients in uniportal group (UG). All patients underwent the lobectomy and mediastinal lymph nodes dissection. Multiport VATS was performed through 3 small incisions (2cm, 2cm and 4-5cm). Uniportal VATS was performed through only one 4-5cm sized incision (Figure 1).



Result: There was no difference between both groups in gender, age, underlying diseases, location of tumor, TNM stage, cell type and the number of dissected lymph nodes. The mean tumor size of UG was slightly smller than that of MG (2.5 vs 3.0 cm, p=0.02). The mean operation time of UG was shorter than that of MG (189 vs 214 minutes, p=0.01). The mean duration of tube drainage and hospital stay of UG was shorter than those of MG (tube drainage:

5.3 vs 6.7 days, p=0.01, hospital saty: 8.1 vs 11.1 days, p<0.01). There were 7 hospital mortalities in MG and 1 hospital mortality in UG (p=0.06). The cause of hospital mortality was ARDS in all patients. There were 4 complications (empyema, pneumothorax, chylothorax and persistent air leak) in MG and 4 complications (chylothorax, pneumothorax in 2 and pleural effusion) in UG. The 5-year disease free survival rate was 77% in MG and 90 % in UG (p=0.59). The 5-year survival rate was 81% in MG and 99% in UG. However, there was no statistically significant difference. **Conclusion:** In our study, uniportal VATS showed similar results with a smaller incision when compared to multiport VATS in the surgical treatment for stage I and II lung cancer. Uniportal VATS might be one of options in the surgery for stage I and II lung cancer.

Keywords: Lung cancer, Video-Assisted Thoracic Surgery, Uniportal VATS

P2.17-41 TREATMENT OUTCOMES OF PULMONARY RESECTION IN NSCLC PATIENTS WITH AUTOIMMUNE DISEASES

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Background: Surgical resection for early stage non-small cell lung cancer (NSCLC) patient with autoimmune disease(s) is a relatively rare occasion. Most of such patients have received steroid therapy with/without immunosuppressant agent for a long period before the surgery. However, short-term or long-term treatment outcomes of NSCLC patients with autoimmune disease are unclear. **Method:** Between January 2007 to December 2018, thirty-nine NSCLC patients with autoimmune disease(s) received pulmonary resection with curative intent in our department. Patients with interstitial lung disease were excluded from this study. Patient clinical and pathological characteristics and treatment outcomes were evaluated. **Result:** There were 17 males and 22 females in out cohort. The median age was 68 years old (39 – 84), and thirty patients were smokers. Twenty-three patients had rheumatoid arthritis, and among them, three patients had additional autoimmune disease (autoimmune hepatitis, Sjogren syndrome, or polyneuropathy). Other autoimmune diseases included Hashimoto disease (n = 4), systemic lupus erythematosus (n = 3), Behcet's disease (n = 2), primary biliary cirrhosis (n = 2), and others. Only three patients received limited resections (2 partial resections and one segmentectomy), and 36 patients received lobectomy or bi-lobectomy. At the post-operative pathological diagnosis, there were 13 patients with squamous cell carcinomas, 21 patients with adenocarcinomas, four patients with pleomorphic carcinomas, and one patient with adenosquamous cell carcinoma. Post-surgical complications included pneumonia (n = 1, 3%), prolonged air leakage (n = 1, 3%), and no patient experienced bronchopleural fistula or empyema. The median post-surgical hospital stay was eight days (4 – 28 days). **Conclusion:** Pulmonary resection for NSCLC patients with autoimmune disease(s) were safely performed. We will also report the long-term outcome for this cohort at the conference.

Keywords: NSCLC, rheumatoid arthritis, surgery

P2.17-42 SURGICAL CHOICE FOR CLINICAL STAGE IA NON-SMALL CELL LUNG CANCER: NOVEL RATIONALE FROM INTRAPULMONARY LYMPH NODE METASTASIS PATTERN

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Background: Current available surgical resection methods for early-stage NSCLC mainly consisted of lobectomy and sublobar resection (including segmentectomy and wedge resection) with lobectomy being the preferred option, which was established by the only completed RCT study finding that sublobar resection yielded a significantly higher recurrence rate and a trend toward worse survival than lobectomy. However, there are growing interest in observational studies and systematic reviews exploring the efficacy of sublobar resection in treating early-stage NSCLC, aiming to justify for applying sublobar resection as an alternative to lobectomy for treating these patients but with conflicting conclusions.We aimed to investigate the pattern of intrapulmonary lymph node (LN) metastasis of clinical T1N0M0 peripheral non-small cell lung cancer (NSCLC) to provide novel rationale for surgical choice (lobectomy, segmentectomy, or wedge resection) for these patients. **Method:** We retrospectively collected clinical data of patients undergoing lobectomy with systematic mediastinal LN dissection or sampling for early-stage NSCLC from January 2015 to December 2018. The intrapulmonary LN metastasis pattern was analyzed by tumor size. **Result:** We included a total of 354 patients for final analysis. The rate of intrapulmonary LN metastasis was 13.6% (Table 1). When stratified by tumor size, NSCLC ≤1cm had no hilar/intrapulmonary LN metastasis while NSCLC >2 but ≤3cm had significantly high rates of hilar/intrapulmonary LN metastasis (18.4%) and the rates of hilar, interlobar and peripheral LN metastasis were relatively high (5.4%, 5.4% and 12.2%, respectively). NSCLC >1.5cm but ≤2cm also had a relatively high rate of hilar (6.5%) and peripheral (18.3%) LN metastasis while NSCLC >1cm but ≤1.5cm had a significantly low rate of hillar/intrapulmonary (2.5%) and peripheral (2.5%) LN metastasis. Table 1. Intrapulmonary lymph node metastasis pattern among clinical stage IA (cT1N0M0) peripheral non-small cell lung cancers with different tumor size.

Characteristics	Total (N=354)	Tumor size group			P value
		≤1cm (N=35)	>1cm but ≤2cm (N=172)	>2cm but ≤3cm (N=147)	
Total dissected N1 LN number (Mean±SD)	5.6±3.0	3.6±1.9	5.4±2.7	6.3±3.3	<0.001
Total dissected N2 LN number (Mean±SD)	8.1±4.0	7.0±3.4	7.6±3.6	8.8±4.4	0.008
Lymph node metastasis rate	16.9% (60/354)	0 (0/35)	14.5% (25/172)	23.8% (35/147)	0.002
N1 LN metastasis rate (10-14#)	13.6%(48/354)	0(0/35)	12.2%(21/172)	18.4%(27/147)	0.013
Hilar LN metastasis rate (10#)	4.2%(15/354)	0(0/35)	4.1%(7/172)	5.4%(8/147)	0.348
Interlobar LN metastasis rate (11#)	3.4%(12/354)	0(0/35)	2.3%(4/172)	5.4%(8/147)	0.263*
Peripheral LN metastasis rate (12-14#)	10.5%(37/354)	0(0/35)	11.0%(19/172)	12.2%(18/147)	0.092
N2 LN metastasis rate (1-9#)	8.8%(31/354)	0(0/35)	8.1%(14/172)	11.6%(17/147)	0.088

Note: LN=lymph node; SD=standard deviation. *Fisher's exact test

Conclusion: Based on the pattern of intrapulmonary LN metastasis, our study provided novel perspectives on surgical choice of lobectomy, segmentectomy, or wedge resection for clinical stage IA peripheral NSCLC: for NSCLC ≤1cm both segmentecotmy and wedge resection could be utilized, and for NSCLC >1cm but ≤1.5cm segmentecotmy could be utilized provided that sufficient resection margin could be achieved; while for NSCLC >1.5cm lobectomy should be the preferred surgical option.

Keywords: Non-Small Cell Lung Cancer, surgical option, early-stage

P2.17-43 COMPLETE UNIPORTAL THORACOSCOPIC ANATOMIC LUNG RESECTION WITH SYSTEMATIC MEDIASTINAL LYMPHADENECTOMY FOR NSCLC

Y.-J. Deng[1], G.-S. Wang[2], Z. Wang[1], J.-W. Mu[1], Z. Wang[2]

[1]*National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen/China,* [2]*Shenzhen People's Hospital, Second Affiliated Hospital, Medical College of Jinan University, Shenzhen/China*

Background: With its growing popularity and potential outcome, complete uniportal thoracoscopic surgery has been used in the treatment of thoracic diseases. This study aimed to summarize a personal experience of complete uniportal thoracoscopic anatomic lung resection with systematic mediastinal lymphadenectomy (CUT–ALR–SML) for non-small cell lung cancer (NSCLC) and to evaluate the feasibility and safety of CUT–ALR–SML in our institute. **Method:** A total of 326 patients with NSCLC were chosen to undergo CUT–ALR–SML in our institute from August 2013 to July 2018. Data such as clinicopathologic characteristics and perioperative outcomes were restrospectively reviewed in this article. **Result:** For the 326 cases of anatomic lung resection, the specific procedures and corresponding number of cases were as follows: segmentectomy, 90; lobectomy, 218; sleeve lobectomy, 9; ipsilateral lobe combined with segment resected synchronously (i-L+S), 6; and pneumonectomy, 3. A total of 31 cases required conversion to open surgery, and 4 cases were converted to multiportal thoracoscopic surgery. All patients underwent systematic mediastinal lymphadenectomy. The average mediastinal lymph node stations and mediastinal lymph nodes dissected under CUT–ALR–SML was 3.3±1.4 and 9.6±8.4,respectively. Approximately 99.7% of the patients acquired free resection margins. A total of 42 (12.9%) patients suffered from postoperative complications, and 1 patient died of pneumonia during the perioperative period. **Conclusion:** Complete uniportal anatomic lung resection, particularly for segmentectomy and lobectomy is safe and feasible with low complication rates, and excellent free resection margin rates. Systematic mediastinal lymphadenectomy during complete uniportal thoracoscopic surgery adequately assesses the N2 lymph node. However, further studies need to be conducted to evaluate the role of CUT–ALR–SML in the treatment of NSCLC.

Keywords: systematic mediastinal lymphadenectomy (SML), Non-small cell lung cancer (NSCLC), uniportal thoracoscopic anatomic lung resection

P2.18 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 9 10:15 – 18:15

P2.18-01 A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED STUDY OF BINTRAFUSP ALFA (M7824) IN UNRESECTABLE STAGE III NSCLC

E. Vokes[1], A. Adjei[2], M.-J. Ahn[3], F. Barlesi[4], E. Felip[5], E. Garon[6], I. Grenga[7], A. Koenig[8], C. Martin[9], T. Mok[10], F. Mornex[11], N. Munshi[7], D. Raben[12], C. Robinson[13], L. Paz-Ares[14]

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Background: The TGF-β pathway promotes tumor immunosuppression, and its inhibition may enhance the antitumor activity of PD-(L)1 monoclonal antibodies and reduce radiation-induced lung fibrosis. Bintrafusp alfa is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-βRII (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. In a phase 1 study, second-line bintrafusp alfa therapy demonstrated promising antitumor activity in advanced non-small cell lung cancer (NSCLC) (NCT02517398). In preclinical studies, bintrafusp alfa plus radiotherapy showed enhanced antitumor activity compared with radiotherapy alone in mouse models. This study is evaluating the efficacy and safety of bintrafusp alfa with concurrent chemoradiation (cCRT) followed by bintrafusp alfa vs cCRT plus placebo followed by durvalumab in patients with unresectable stage III NSCLC. **Method:** This global, multicenter, double-blind, randomized, controlled study of bintrafusp alfa (NCT03840902) includes adults with histologically documented stage III locally advanced, unresectable NSCLC, ECOG performance status ≤1, adequate pulmonary function, and life expectancy ≥12 weeks. Patients with tumors with actionable mutations (EGFR, ALK translocation, ROS-1 rearrangement) are also eligible. Mixed small cell lung cancer and NSCLC histology; pleural effusions greater than minimal, exudative, or cytologically positive; significant acute or chronic infections; prior chemotherapy or immune checkpoint inhibitor therapy for NSCLC; and current use of immunosuppressive medication are exclusion criteria. Patients are randomized to receive either bintrafusp alfa 1200 mg IV every 2 weeks (Q2W) with cCRT for 6 weeks followed by bintrafusp alfa 1200 mg IV Q2W (arm A) or placebo with cCRT for 6 weeks followed by durvalumab 10 mg/kg IV Q2W (arm B) until confirmed disease progression, unacceptable toxicity, or treatment ≤1 year. The primary endpoint is progression-free survival; secondary endpoints include overall survival, safety, lung function assessment, objective response, duration of response, pharmacokinetics, and immunogenicity. This phase 2 trial was activated on April 2, 2019 and first patient in is anticipated for May 22, 2019. Target enrollment: 350 patients. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: bintrafusp alfa, M7824, NSCLC

P2.18-02 PNEUMONECTOMY AND LUNG CANCER: A TREACHEROUS COMBINATION

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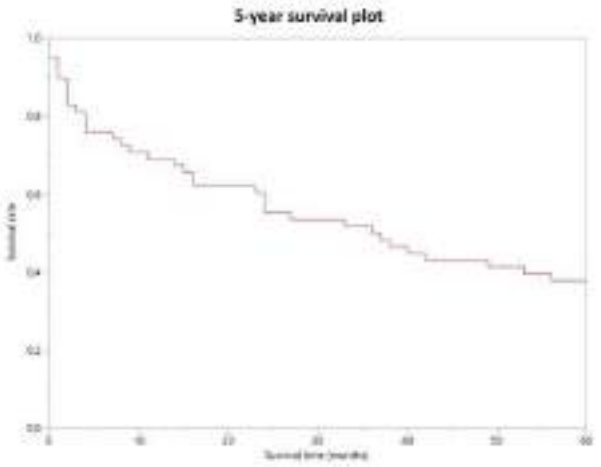
Background: In spite of the progress made in recent years regarding minimally invasive and parenchymal-sparing surgery, pneumonectomy is still necessary in cases where lesser resections are not possible. However, pneumonectomy remains a high-risk surgical procedure associated with significant postoperative morbidity and mortality. We investigated early and long-term results in a recent series of patients undergoing pneumonectomy for lung cancer. **Method:** Clinical and pathological characteristics of non-small cell lung cancer (NSCLC) patients treated by pneumonectomy between January 2008 and December 2013 were retrospectively reviewed. Overall 30- and 90-day mortality and 1-, 2-, and 5-year survival rates were calculated. Postoperative complications and disease progression or recurrence were analysed by descriptive statistics. Univariate and multivariate analyses of factors related to long-term survival were also performed. **Result:** A total of 61 patients, 48 men and 13 women with an overall mean age of 64±8.9 years, underwent pneumonectomy. The 30- and 90-day mortality rates were 6.6% and 16.4%, respectively. Ninety-day mortality was significantly correlated to tumour pathology (p=0.0410) and occurrence of postoperative complications (p=0.0078). Overall 1-, 2-, and 5-year survival rates were 70.5%, 57.4%, and 37.7%, respectively. Progressive or recurrent disease occurred in 45.7% of all patients. Most frequent early complications were atrial fibrillation (41.0%), pneumonia (23.0%), and acute respiratory failure (18.3%).



POSTERS

Conclusion: Despite careful patient selection, pneumonectomy yields high mortality and morbidity rates. Therefore, it should only be performed when no other therapeutic options are available. Furthermore, rigorous preoperative work-up and risk stratification models are necessary to determine whether pneumonectomy is the most suitable treatment option and to obtain acceptable long-term results.

Keywords: NSCLC, pneumonectomy

P2.18-03 SALVAGE SURGERY AFTER CURATIVE-INTENT CHEMO AND/OR RADIATION FOR LOCALLY ADVANCED LUNG CANCER

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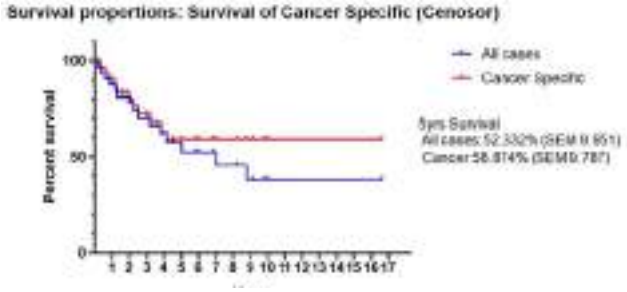
Background: A chemo and/or radiotherapy (CRT) was thought to be the curative treatment for locally advanced lung cancer (LALC) before 2017. However, after the CRT the cancer sometimes remained at the treatment field. The radical pulmonary resection after CRT (Salvage surgery) is the option for the curative treatment. The safety and perioperative complications of salvage surgery after CRT for locally advanced lung cancer have been problematic. Thisa study aimed to identify the long-term survival and the operative results of this kind salvage surgery. **Method:** The Salvage surgery is defined as resection after platinum based 2-drugs CRT or curative dose radiation therapy for LALC. We retrospectively reviewed our medical records in our institute from January 2008 to March 2019 and collected 33 patients who received salvage surgery. This study was approved by our institutinal review board. **Result:** The mean age at the surgery was 63 years (range 39-86), with 5 women and 28 men. The initial curative-intent therapy were; concurrent CRT in 26, sequential CRT in 2, and stereotactic body radiotherapy in 5. The mean interval from CRT to the surgery was 31 months (range 3-128). All patients except 2 cases underwent complete surgical resection with mediastinal nodal dissection including lobectomy in 20 cases, lobectomy with bronchoplasty in 2 cases, broncho/ pulmonary angioplasty in 7 cases, pneumonectomy in 2 cases. The bronchial stump was covered with pericardial fat tissue or intercostal muscle. Histological type were adenocarcinoma in 19 cases, squamous carcinoma in 10 cases, large-cell-carcinoma in 2 cases, 1 combined cell small-cell carcinoma, and 1 adenosquamous cell carcinoma. The mean operation time was 302 minutes and mean blood loss was 687g. There was no operative mortality nor in-hospital death. Post-operative complication was seen in 12 cases (36%), however there was no broncho-pleural fistula or bronchial dehiscence. The 3-years and 5-years overall survival after the surgery were 70% and 52.3 % with 53 months median follow-up period. Six years after the salvage surgery, there was no recurrence of lung cancer. **Conclusion:** The salvage surgery after curative-intent chemotherapy and/or radiotherapy for LALC is feasible with cautious patient selection, careful operative procedure, and meticulous perioperative care. Six years after salvage surgery the survivors may be expected to be free from lung cancer recurrence.



Keywords: Chemo-radiotherapy, Muti-modality therapy, salvage surgery

P2.18-04 IMPROVED OUTCOME IN FEMALE STAGE III NSCLC DIAGNOSES IS DRIVEN BY NON-CURATIVE INTENT TREATMENT, AND ADENOCARCINOMA HISTOLOGY

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Background: Biological sex disparities in incidence, molecular alterations and outcome in NSCLC have been well documented in the literature; however, there are no sex-based approaches to diagnosis and treatment in lung cancer. Recognising differences in therapeutic outcome and survival between the biological sexes could help inform clinical research and further personalized interventions in an effort to improve survival for NSCLC patients. **Method:** Using the Glans-Look Lung Research (GLR) database, a retrospective analysis was undertaken for Stage III (AJCC 7th edition) NSCLC patients diagnosed between 1999 and 2014. Demographic, clinical, treatment and outcome data were extracted to assess sex-based differences in histology, treatment uptake and survival. Univariate methods, including Kaplan-Meier survival analysis were performed to compare outcomes by sex, histology and treatment-intent. **Result:** 1040 Stage III NSCLC were identified, median age 69.6 years (IQR 61.3-76.8), 57.9% female, 89.1% 'ever' smokers, 34% adenocarcinoma (ADC), 36% squamous cell carcinoma (SCC), 20% 'other', 10% unknown. Among female patients ADC is more prevalent (42% vs. 28%, p<0.001), while in SCC patients are more likely to be males (44% vs. 26%, p < 0.001). Males were more likely to receive palliative-intent treatment (44% vs. 37%), while females more likely to receive best supportive care (BSC) (31% vs. 22%), p=0.006. Median overall survival (mOS) for the entire stage III cohort favoured females (14.1 vs. 10.7 months, p=0.001). This trend was also observed across different treatment categories, where female survival significantly exceeded that of males: curative-intent (25.5 vs. 18 months, p=0.035), palliative-intent (9.5 vs. 8.0 months, p = 0.025) and BSC (11.2 vs. 7.2 months, p=0.014). Although no differences in treatment patterns were seen between males and females within ADC or SCC, sex-based disparities in survival were also present within the ADC histology: female ADC mOS exceeded that of males, in overall comparisons (17.6 vs. 12.2 months, p=0.047), within palliative-intent treatment (15.1 vs. 8.0, p=0.008) and BSE (13.2 vs. 3.4, p=0.005), but not in curative-intent combined modality chemo-radiation (26.8 vs. 21.7 months, p =0.972). No differences in mOS, either overall or by treatment category were observed in SCC. **Conclusion:** Higher mOS among females in stage III NSCLC appears to be driven by both the ADC histology and non-curative-intent treatments. Sex-based differences in outcomes should be assessed more deeply as prognostic variable in patients with NSCLC.

Keywords: #Adenocarcinoma #Sex #Outcomes, #NSCLC #Women #Palliative

P2.18-05 PATIENTS WITH YPN2 NSCLC AFTER NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY CAN BENEFIT FROM PORT – A RETROSPECTIVE STUDY OF SEER DATABASE

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Background: Neoadjuvant chemotherapy followed by surgery (NCS) is a common therapy pattern of resectable non-small cell lung cancer (NSCLC). However, for patients with ypN2 disease after aforementioned treatment, there is no evidence that postoperative radiotherapy (PORT) should be adopted or not. Our study is to evaluate the effect of PORT on survival of patients with ypN2 NSCLC after NCS from Surveillance, Epidemiology, and End Results (SEER) database. **Method:** We filtrated data from SEER database by the inclusion criteria of patients with NSCLC diagnosed at 2004-2015, treated with NCS, and with ypN2 disease (2004-2009 AJCC 6th, 2010-2015 AJCC 7th). We excluded patients with unclear basic information (such as sex, histology or cause of death), multiple primary malignant tumor and M1 disease. All data were analyzed using the SPSS Statistics (version 25) and propensity-score matched analysis was used to match the base-line characteristics between

PORT group and non-PORT group. Kaplan-Meier method was used to estimate overall survival (OS) and cancer specific survival (CSS). Univariable and multivariable Cox proportional hazards models were adopted to estimate hazard ratios (HR) of predictors of survival. **Result:** From 331 patients receiving NCS, 215 meeting the criteria were included in the final analysis. There were 112 patients (52.1%) with PORT. The baseline characteristics of majority were as follows: age≤65 (55.3%), white (82.3%), female (54.4%), grade 3-4 (63.3%), adenocarcinoma (60.0%), tumor size of 3-5 cm (38.6%), lobectomy (80.0%) and positive lymph nodes≥4 (51.2%). There were 200 patients remained after the prosperity score matching between the PORT group and the non-PORT group, with 100 cases in each. The median OS of the two groups were 36 months vs 26 months and 5-year OS rates were 36.2% vs 20.3%, respectively (P=0.011). The median CSS were 36 months versus 27 months and 5-year CSS were 38.5% vs 21.1%, respectively (P=0.010). Univariable analysis showed that only PORT significantly improved OS (HR=0.648, P=0.013) and CSS (HR=0.639, P=0.012). Multivariable analysis confirmed that PORT was the only significant predictor of OS (HR=0.615, P=0.011) and CSS (HR=0.614, P=0.013). **Conclusion:** For patients with ypN2 NSCLC after NCS, PORT can significantly improve the OS and CSS . However, the result needs to be clarified by prospective randomized clinical trials.

Keywords: PORT, N2, Neoadjuvant chemotherapy

P2.18-06 TRENDS AND OUTCOMES OF MINIMALLY INVASIVE APPROACHES FOR LUNG CANCER RESECTION AFTER INDUCTION THERAPY IN THE UNITED STATES

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Background: Lung resection following induction-therapy (IT) is technically challenging. To date, a paucity of national data exists on the feasibility of minimally invasive surgical (MIS) approaches in this setting. We assessed national trends and outcomes associated with MIS following IT, compared to open approach. **Method:** The National Cancer Database was queried for NSCLC patients undergoing resection following IT (2010-2016). Trends in MIS utilization were assessed using Mantel-Haenszel test. Propensity-matching (MIS vs. open) was performed (1:1-Caliper 0.2), controlling for age, gender, comorbidity, clinical stage, and histology. Perioperative outcomes and survival were compared between the matched groups. **Result:** Lung resection following IT was performed in 11287 patients. The utilization of MIS approaches increased from 19% in 2010 to 41% in 2016 (Mantel-Haenszel, P<0.001). The number of hospitals performing at least one MIS increased from 166 in 2010 to 305 in 2016. Compared to the traditional open approach, MIS approaches were used more frequently in patients with higher annual-income (>$63000, 37%vs.33%,P<0.001), and in patients treated in academic hospitals (54%vs.47%,P<0.001). The open approach was used more in males (54%vs.49%, P<0001), and in patients with larger tumor size (4.4cm vs. 3.8cm, P<0.001)(Table). In propensity-matched groups, there were no differences in 30-day readmission (3% vs. 4%,P=0.513), or 30-/90-day mortality between the two approaches (3%vs.4%,P=0.145; 6%vs.7%,P=0.685). However, MIS was associated with a shorter median length of stay (5vs.6 days,P<0.001). 5-year overall survival (OS) was slightly better in the open group (45% vs.39%,P=0.002). However, on multivariable analysis, surgical approach was not associated with OS (open approach: HR:0.99, 95%CI:0.91-1.09).

Lung resection following induction therapy 2010-2016 (propensity matched groups)

Patient characteristics and outcomes	MIS (n=3284)	Open (n=3284)	P value
Age, years (median, IQR)*	64 (56-70)	64 (57-60)	0.692
Gender (Male)*	1680 (51%)	1667 (51%)	0.748
Charlson Comorbidity Index (CCI>1)*	370 (11%)	351 (11%)	0.453
Histology (Adenocarcinoma)*	1701 (52%)	1708 (52%)	0.985
Clinical stage (III-IV)*	2345 (71%)	2297 (70%)	0.193
Surgical Procedure (Lobectomy) (n=6137)	2440 (83%)	2556 (80%)	<0.001
Pathological stage (III-IV) (n=5106)	1030 (41%)	1049 (40%)	0.345
Number of lymph nodes resected (median, IQR)	10 (4-16)	10 (5-16)	0.006
Number of positive nodes (median, IQR)	0 (0-2)	0 (0-2)	0.905
Positive resection margin (n=6199)	285 (9.5%)	256 (8%)	0.048
Length of stay, days (median, IQR)	5 (3-7)	6 (4-8)	<0.001
Unplanned 30-day readmission (n=6522)	188 (6%)	201 (6%)	0.513
30-d mortality (n=5351)	72 (3%)	103 (4%)	0.145
90-d mortality (n=5301)	155 (6%)	185 (6.5%)	0.685

* Variables controlled for in the Propensity Score analysis

Conclusion: National use of minimally-invasive surgery following induction therapy increased significantly over the study period. The current study shows that using MIS after induction therapy is feasible and safe, and is associated with a shorter hospital stay compared to open approach, yet without compromising perioperative outcomes or survival.

Keywords: VATS, minimally invasive surgery, induction therapy

P2.18-07 PROGNOSTIC FACTORS AFFECTING BRAIN METASTASIS-FREE SURVIVAL IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Brain metastasis is a poor prognostic factor for survival in all cancer types.Prophylactic cranial irradiation(PCI)has been considered standard of care for patients with small-cell lung cancer because of its favorable effects on survival, however there is no identifiable effect of PCI on survival in non-small cell lung cancer(NSCLC).The aim of this study is to define the factors which may be related to brain metastasis in patients with NSCLC who developed brain metastases after their definitive treatment. **Method:** Two-hundred-eight patients with NSCLC,without brain metastases who received definitive radiotherapy or radiochemotherapy between January 2005 and January 2016 were evaluated retrospectively. Hematological parameters [platelet, neutrophil, lymphocyte counts, LDH, CRP, hemoglobin(Hb)levels,neutrophil-lymphocyte ratio(NLR)and platelet-lymphocyte ratio(PLR)],andFDG-PET/CT parameters(SUVmax values for the primary tumor and mediastinal lymph nodes),and patient characteristics were evaluated for brain-metastasis-free survival(BMFS).Cut-off values were determined byROC analysis. **Result:** Patient and treatment characteristics were indicated in Figure 1. Median follow-up duration was 25 months.Cut-off values for platelet, NLR, PLR, LDH, CRP, and Hb were 290x103/µL, 2.6, 198, 468 IU/L, 2.5 mg/dL, and 11.5 g/dl. We defined each parameter as low or high according to the cut-off values. Fifty six patients(26.9%) developed brain metastases during follow-up.Median BMFS for the whole group was 21 months. In univariate analysis high NLR(71 vs 80months;p=0.001), PLR(71 vs 74months;p=0.037), LDH (65 vs 85months;p=0.028), CRP(47 vs 95months;p=0.002) values, SUVmax value ≥7.5 for lymph nodes(47 vs 79months;p=0.005) were poor prognostic factors for BMFS. In multivariate analysis high NLR(p=0.022), PLR(p=0.017), CRP(p=0.006), stage ≥IIIA disease(p<0.001), multi-stational N2 disease(p=0.036), adenocarcinoma histology(p<0.001) and SUVmax value ≥7.5(p=0.035) were poor prognostic factors for BMFS. Median survival duration after brain metastases was 6.5 months.

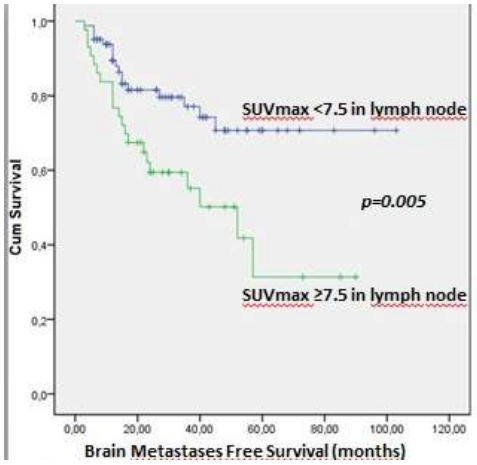
Figure 1a. Patient characteristics

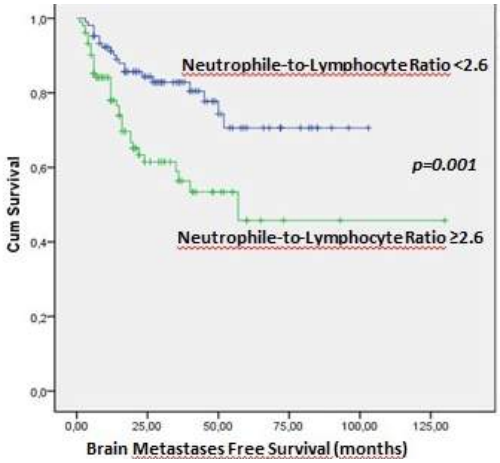
Characteristic	N=208 (%)
Age, year	
Median (range)	63 (31-85)
Sex	
Male	194 (93,3)
Female	14 (6,7)
KPS (%)	
<80	28 (13,5)
≥80	180 (86,5)
Weight loss	
<10%	68 (32,7)
≥10%	29 (13,9)
None/Unspecified	111 (53,4)
Comorbite disease	
None/Unspecified	131 (63)
≥2 disease	77 (37)
Histopathology	
Adenocarcinoma	41 (19,7)
Squamous Cell Carcinoma	124 (59,6)
Unclassified NSCLC	43 (20,7)
AJCC Stage	
IIA/B	18 (8,6)
IIIA	57 (27,4)
IIIB	123 (59,1)
IIIC	10 (4,9)
Nodal Stage	
N0	29 (13,9)
N1	10 (4,8)
N2	154 (74,0)
N3	15 (7,2)

Figure 1b. Treatment characteristics

Characteristic	N=208 (%)
RT tecnique	
3D Conformal RT	176 (84,6)
IMRT	32 (15,4)
RT dose (Gy)	
Median (range)	66 (60-74)
Neoadjuvant CT	
-	86 (41,3)
+	122 (58,7)
Concomitant CT	
-	100 (48,1)
+	108 (51,9)
Adjuvant CT	
-	150 (72,1)
+	58 (27,9)

Abbreviations: KPS=Karnofsky Performance Score; NSCLC=Non small cell lung cancer; AJCC=American Joint Committee on Cancer; RT=Radiotherapy; Gy=Gray; CT=Chemotherapy





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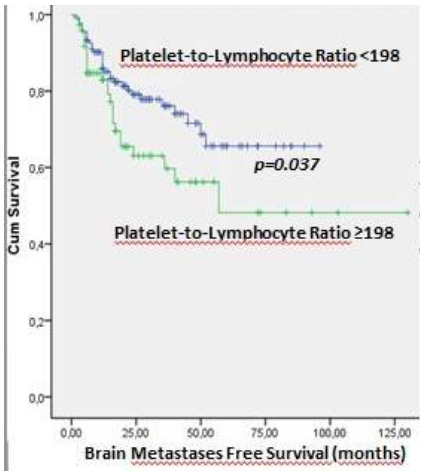

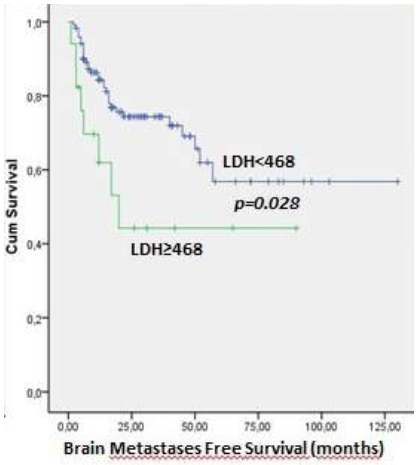

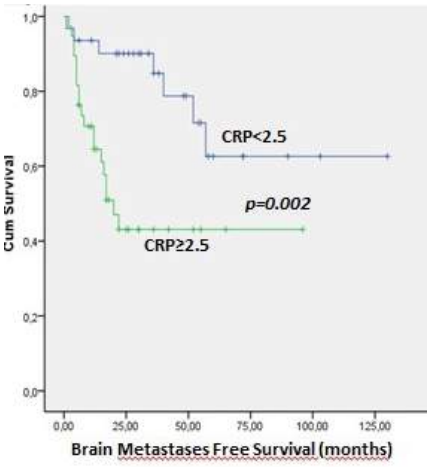

Conclusion: Development of brain metastases after definitive treatment of NSCLC is a serious problem affecting survival unfavorably. High NLR, PLR, LDH, CRP values and high SUVmax values for lymph nodes were additional prognostic factors besides stage, histology, and lymph node status.

Keywords: Non small cell lung cancer, brain metastasis, prognostic factors

P2.18-08 THE NECESSITY AND TECHNIQUE OF THE UPPER ZONE LYMPH NODE DISSECTION FOR NON-SMALL-CELL CARCINOMA OF THE LEFT UPPER LOBE

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Background: The removal of the whole regional lymphatic system together with primary tumor is one of the important rules in oncological surgery.(According to the study of regional lymphatic drainage, we considered reasonable lymphadenectomy contributes the post-operative survival of the Left lung cancer patients with mediastinal lymph node metastasis. Due to anatomical limitations imposed by arch of aorta, it is difficult to perform complete dissection of upper zone mediastinal lymph nodes through the left thoracotomy in the left lung cancer. We had devised Systematic extended bilateral mediastinal dissection through a median sternotomy (ND3 operation) for patient with NSCLC of the left lung. This report aimed to introduce procedure of our operation and investigate the prognostic impact of Upper zone lymph node dissection for left upper lobe NSCLC. **Method:** The our operative procedure is as follows. In the supine position, made a median sternotomy. We dissect the meidastinal nodes before pulmonary resection. The dissection is started on the highest area. Tape the right and left recurrent laryngeal nerve and dissect the highest paratracheal lymph nodes in the thoracic inlet. After making the pericardiotomy, the ascending aorta is retracted to the left. Remove the whole upper zone tissue lying in front of the trachea. And dissect the pre and paratracheal nodes, together with bilateral highest nodes. Then, dissect the subcarinal nodes. Tie off the blood vessels (arteries and veins) and airways leading to the affected lobe, and then remove the lobe. We retrospectively studied 213 patients [157 male and 61 female, mean ages 60.4 years (range, 29-75)], underwent ND3 operation due to NSCLC of the left upper lobe, from January 1990 till December 2017. The patients with NSCLC who are estimated to be able to conventional radical operation and aged 75 year-old or less becomes the adaptation of our operation. **Result:** Overall 5-year survival rate in the 218 patients of left upper lung primary was 65.1%. Operative mortality in 218 patients was 2.8%. Lymph node metastasis to the mediastinum was confirmed in 70 (32.1%) patients (pN2 was 43 ,pN3α was 18 ,pN3γ was 9). According to pathological stages, five-year survival rate was 92.7% in stage IA ,80.1% in stage IB, 53.8% in stage IIA, 66.7% in stageIIB, 51.7% in stageIIIA, 38.4% in stageIIIB. And it was 52.1% in pN2 cases, and 55.0% in pN3α cases. Five-year disease free survival rate was was 85.6% in p-stage IA ,74.0% in p-stage IB,49.7% in p-stage IIA, 49.4% in p-stageIIB, 33.3% in p-stageIIIA, 19.4% in p-stageIIIB, 32.6% in pN2 cases, and 27.8% in pN3α cases. **Conclusion:** In this nonrandomized comrarision, the post-operative survival of patients with pN2 and pN3α NSCLC of the left upper lung primary would be remarkably improved by our Systematic Bilateral Mediastinal Dissection. And better local tumor control by our operation does not increase mortality. When faced with a patient with resectable mediastinal lymph node metastasis, we should consider Extended bilateral mediastinal lymph node dissection through a median sternotomy. To improve survival rate, it is important to perform curative operation with upper zone mediastinal dissection.

Keywords: Upper Zone lymph node dissection, Non-small-cell carcinoma of the left upper lung.

P2.18-09 AGE DOES NOT AFFECT THE BENEFIT OF MODERN CHEMORADIATION FOR LA-NSCLC PATIENTS

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Background: The standard of care for inoperable stage III non-small-cell lung carcinoma (NSCLC) is concurrent chemoradiation which achieves the better results but is affected by higher toxicities. Even if literature data document a significant advantage also for elderly population, these selected group of patients is usually underrepresented in randomized trials. This study analyzed treatment and outcomes at our institution according to elderly (>70 years old) or younger (≤ 70 years) age. **Method:** A secondary analysis on patients with stage III NSCLC treated between January 1992 and September 2014 with concurrent chemoradiation with radical intent enrolled in previous published trials in our institution were analyzed.

Factors analyzed included Eastern Cooperative Oncology Group Performance Status (ECOG PS), sex, stage, histology, treatment period and esophageal and lung toxicities. **Result:** A secondary analysis on 347 patients (≤70years: 188; >70years: 159) with stage III NSCLC treated with concurrent chemoradiation enrolled in previous published trials in our institution were analyzed (age range, 39-92 years). Elderly patients were more frequently male (85% and 72%; p=0.003) and stage IIIB (49% and 34%, p=0.008). ECOG was 0-1 in all cases (elderly: 36% and 29%, p=0.451). No differences were reported according to tumor histology. Median survival was similar between the younger and elderly patients (20,8 and 19,2 months respectively; p=0.503). A significant difference in overall survival was appreciated according to treatment period also for elderly population. Overall survival of all patients treated between 1992-2005 and 2006-1014 was 17.8 and 25,9 months, respectively (p<0.001). According to the same periods, elderly group survival was 16,5 and 24,9 months (p=0.002). No significant differences were reported in esophageal and lung toxicities between elderly and younger patients (Esophageal G2: 18.6% and 21%; Esophageal G3: 1,7% and 2,6%; Lung G2: 6,4% and 6,3%; Lung ≥G3: 5,7% and 3,1%, respectively). **Conclusion:** In this series elderly patients in clinical good condition with locally advanced NSCLC treated with concurrent chemoradiotherapy reached interesting results in terms of overall survival without increased toxicity. The improved outcome obtained in younger patients in the modern era is achievable also for this selected elderly population.

P2.18-10 IMPORTANCE OF THE MULTIDISCIPLINARY TUMOR BOARD IN THE TREATMENT STRATEGY OF STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Stage III Non-Small Cell Lung Cancer (NSCLC) represents a heterogeneous population with different treatment strategies, often in combination. The PACIFIC trial is changing practices. It is therefore necessary to evaluate our current practices in order to identify the patients that should most likely receive this treatment after chemoradiotherapy **Method:** A database constructed from our weekly multidisciplinary thoracic oncology meetings was retrospectively screened from 01/2010 to 01/2017. Consecutive patients with stages III NSCLC were included. We aimed to describe proposed treatment strategies and those really performed **Result:** Of the 411 patients studied, 249 had a stage IIIA NSCLC and 162 a stage IIIB NSCLC. Median age was 65 years [IQR 25%-75%, 58-72], 309 (75%) patients were male. The majority of the patients (n=270, 69%, 20 missing data) had an ECOG-Performance status of 0 or 1. Regarding histology, 199 (48%) patients had an adenocarcinoma and 199 (48%) a squamous cell carcinoma. Treatment strategies are described in Table 1. Sixty-nine (17%) patients received exclusive chemoradiotherapy, and 60 (15%) were planned for neoadjuvant chemotherapy for subsequent surgery. Among these 60 patients, after the first cycles of the initial chemotherapy, only 37 (62%) received surgery in accordance with the multidisciplinary meeting decision; 6 (10%) received concurrent chemoradiotherapy and 6 (10%) sequential chemoradiotherapy.

	Received treatment, n=411 N (%)
Surgery upfront	141 (34)
Chemoradiotherapy upfront	73 (17)
- concurrent	26 (36)
- sequential	43 (59)
- followed by surgery	4 (5)
Planned for chemotherapy neoadjuvant followed by surgery	60 (15)
- chemotherapy neoadjuvant followed by surgery	37 (62)
- chemoradiotherapy (concurrent / sequential)	12 (20) (6/6)
- exclusive chemotherapy	10 (17)
- exclusive radiotherapy	1 (2)
Exclusive radiotherapy	24 (6)
Exclusive systemic treatment (chemotherapy or targeted therapy)	68 (17)
Exclusive palliative care	45 (11)

Conclusion: In our cohort, 8% (32/411) of the stage III patients benefited from a chemoradiotherapy upfront. According to the PACIFIC study, these patients could receive adjuvant immunotherapy. We could ask if the patients planned for surgery after neoadjuvant chemotherapy should not be initially proposed for a concurrent chemoradiotherapy to give them the opportunity to receive adjuvant immunotherapy. Survival analyses according to treatment strategy are ongoing

Keywords: locally advanced NSCLC, concomitant treatments, multidisciplinary team

P2.18-11 REAL-WORLD EXPERIENCE OF CONSOLIDATION DURVALUMAB FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Durvalumab was recently approved as consolidation treatment following concurrent chemoradiation (CRT) in stage III NSCLC based on the positive PACIFIC trial demonstrating improved progression free survival (PFS) and overall survival (OS). Here, we examined the integration of durvalumab therapy after CRT in an urban comprehensive cancer care center serving a high proportion of Black and Hispanic patients. We aimed to examine treatment barriers in this diverse patient population and gain insights into real-world experience. **Method:** Our study included patients treated with CRT for NSCLC (stage II-III) at Montefiore Medical Center (MMC) from 2007-2018. Retrospective analysis was conducted to evaluate patient characteristics, therapies and outcomes. Patients were grouped based on the PACIFIC trial eligibility criteria for durvalumab. PFS and OS were estimated using the Kaplan-Meier method, and comparisons between subgroups were made using log-rank testing, adjusted by Cox proportional hazards regression. **Result:** 146 patients completed CRT for locally advanced NSCLC from 2007 to 2018. 27% (n=40) would be considered ineligible for durvalumab based on the PACIFIC criteria (Table 1: reasons). Patient demographics were similar in ineligible vs. eligible groups: mean age 67.7 vs 67.9 years, male 57.6% vs 43.5%, Black 36.7% vs 43.5%, Hispanic 22.6% vs 30.1%. In the era of durvalumab therapy (since 9/2017), 68% (n=17) received durvalumab, including 4 patients that did not meet PACIFIC criteria due to co-morbidities and/or additional malignancy. The use of durvalumab therapy has increased with time in eligible patients from 33% in 9/2017-12/2017 to 100% in 10/2018-12/2018. The median time to initiate durvalumab following CRT has decreased from 56 days before 7/2018 to 30 days afterwards (p=0.02). Several eligible patients did not receive durvalumab due to questionable benefit in EGFR–mutant NSCLC (n=2), refusal of treatment (n=1), and unkown (n=1). Compared to patients who received durvalumab, patients who did not receive it were found to be of a lower socioeconomic status (p=0.086). Moreover, there was a trend toward improved 15-month OS rates in durvalumab-treated patients compared with patients who did not receive it (100% vs 87.5%, p=0.131).

Table 1: Reasons for ineligibility based on PACIFIC criteria for durvalumab consolidation treatment	
Reasons for ineligibility	**N (%)**
Severe concurrent illness	13 (32%)
Additional malignancy other than NSCLC	6 (15%)
Not stage III	5 (12%)
Progression after chemoRT	3 (7%)
Persisting Grade 3 toxicity related to chemo-RT	3 (7%)
Incomplete chemoRT	2 (5%)
Autoimmune disease	2 (5%)
Recieved alternate study	2 (5%)
Lost to follow up	2 (5%)
Mixed small cell histology	1 (2%)
Unknown	1 (2%)

Conclusion: Our results reveal more frequent use and improved time to initiate durvalumab following CRT, as well as promising initial survival data in a real world setting. A substantial proportion of patients would be ineligible as per PACIFIC criteria, yet several received durvalumab and remain disease controlled, suggesting that further investigation of durvalumab in this population is warranted.

Keywords: durvalumab, consolidation, NSCLC

P2.18-12 PROGNOSTIC NUTRITION INDEX AFFECTS PROGNOSIS OF TRIMODALITY THERAPY FOR LOCALLY ADVANCED LUNG CANCER WITH HIGH T FACTOR

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Background: Pretreatment nutritional status critically affects the clinical outcomes. Induction chemoradiotherapy (iCRT) followed by surgery (trimodality therapy) is a high-invasive treatment option for patients with locally advanced non-small cell lung cancer (LA-NSCLC). LA-NSCLC is a heterogeneous disease. Direct invasion into the surrounding structures easily promotes the invasion-related symptoms which inpair quality of life, but lymph node metastasis rarely causes its related symptoms until the bulky metastatic lymph nodes invade the surrounding structures. These differences of disease extent are expected to affect not only clinical outcome of treatment but also nutritional condition before initiation of treatment. While the prognostic nutritional index (PNI) is known to be correlated with the clinical outcomes after surgery in patients with early NSCLC, the significance of the PNI in LA-NSCLC patients undergoing trimodality therapy has not yet been well examined. In this study, we investigated the clinical impact of PNI in the LA-NSCLC patients who underwent iCRT followed by surgery considering the heterogeneity of disease extent. **Method:** We enrolled 127 patients who received trimodality therapy at our institution between 1999 and 2016. The PNI was examined at all three time-points in the patients: before iCRT, before surgery, and after surgery. **Result:** Fifty-five and 72 patients were diagnosed as clinical T1/2 (cT1/2) and cT3/4 diseases, respectively, and, 42 and 85 patients were cN0/1 and cN2/3, respectively. The PNI significantly decreased as the treatment progressed among all 127 patients. Patients with cT3/4 disease showed significantly lower PNI values before and after surgery than those with cT1/2 disease. By contrast, the PNIs were equivalent at all time-points between patients with cN2/3 and cN0/1 disease. We performed receiver-operating characteristic curve analysis to determine the cutoff the pre-iCRT PNI for overall survival (OS) in all (n = 127), cT3/4 (n = 72) and cN2/3 patients. The ROC curve analyses indicated that a significant cutoff was identified only in cT3/4 patients. Univariate and multivariate analyses revealed that high pre-iCRT PNI values were significantly correlated with better survival in cT3/4 patients. By contrast, the prognostic impact of pre-iCRT PNI values could not be observed in cN2/3 patients **Conclusion:** The nutritional status deteriorates as the treatment progresses during trimodality therapy. Intensive perioperative nutritional intervention is required especially for cT3/4 LA-NSCLC patients receiving trimodality therapy.

Keywords: induction chemoradiotherapy, prognostic nutrition index, locally advanced non-small cell lung cancer

P2.18-13 ENDOBRONCHIAL BRACHYTHERAPY: A SINGLE INSTITUTIONAL EXPERIENCE

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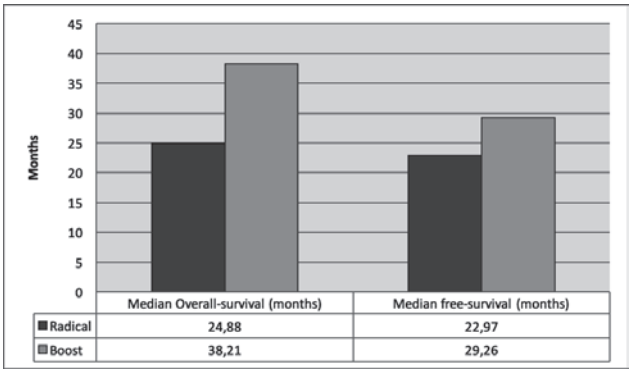
Background: High Dose Rate Endobronchial Brachytherapy (HDR-EB) allows treatment of endobronchial lung cancer with minimal radiation of surrounding tissues. It can be both applied as radical intent in local disease or as palliation in metastatic or non-curative setting. The aim of this study is to describe clinical characteristics, complications and survival of a cohort patients treated with HDR-EB as radical intent. **Method:** Retrospective analysis of consecutive patients undergoing radical HDR-EB in our centre since 2010. Clinical, functional and survival variables were recorded, as well as those related to radiation. HDR-EB was performed after placement of the afterloading catheter in the target bronchus with a flexible bronchoscope. All treatment was delivered weekly. Simulation CT and dosimetry was performed before each fraction. Dose was 5Gy/fr, prescribed at 100% of the implant. **Result:** 16 patients were analysed, 15 (94%) males, age 69 (+/-8) years-old, 3 (19%) were active and 13 (81%) former smokers. Lung function was FEV1 62.3% (+/- 21%), DLCO 60.5% (+/- 13%). Pathological diagnose included in-situ carcinoma (n=1, 6%) and invasive squamous cell carcinoma (n=15, 94%). T staging was T1 in 10 (62.5%) patients, T2 in 3 (18.8%) patients and T4 in 1 (6.3%) patient. All patients had N0 staging. 2 patients had exclusive endobronchial disease. 6 patients received 3 (n=3, 18.6%) and 4 (n=3, 18.6%) fractions after external beam radiotherapy as a boost. 10 patients received 5 (n=2, 12.5%) or 6 (n=8, 50%) fractions as exclusive radical HDR-EB.

2 complications were reported: obstructive pneumonitis (n=1) and bronchial stenosis (n=1). Neither deaths nor haemoptysis occurred in relation with the technique. Mean follow-up was 29 (+/- 21) months. Mean overall survival was 29.0 (+/- 22) months. Mean disease free-survival was 24.9 (+/- 21) months. 4 (25%) progressions were observed, of which 3 (19%) were local progression.

Patients who received boost strategy HDR-EB showed an increased overall survival compared to radical intent (38.2 vs 24.8, p>0.05) and a increased median free-survival; which showed no statistical significance.



Conclusion: HDR-EB is a safe technique applicable in radical intention. Longer survival has been described in patients who received boost strategy. Prospective studies are needed to determine long-term benefits.

Keywords: Brachytherapy, Bronchoscopy, radiotherapy

POSTERS

P2.18-14 THE ROLE OF SURGERY IN HIGH GRADE NEUROENDOCRINE TUMORS OF THE LUNG

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Background: Despite early stage operated lung cancer's better prognosis, high grade neuroendocrine carcinoma (HGNC), including small cell carcinomas and large cell neuroendocrine carcinomas, are rapidly progressive and most cases are inoperable when they are diagnosed (1). The aim of this study is to evaluate the surgical results of HGNCs and try to define what factors influence the prognosis. **Method:** Data was collected retrospecively between the years of january 2009 through December 2017 at Yedikule Hospital for Chest Disease Hospital. Clinical survey has ended in january 2019 . During this period 3946 elective lung cancer operations were performed. Patients with exploratory thoracotomy, neoadjuvan treatment and who lost follow-up were excluded from the study. Seventy-one patients operated for HGNC durig this period were enrolled the study. Sixty-five of them had anatomical resection. The ratio of anatomically resected HGNC to over all anatomic cancer resections was 65 over 3946 (1.64%). Twenty-four of 71 cases were HGN small cell (%33.8) and thirty-five of 71 (%49.3) of the cases were HGN large cell carcinomas. The remaining 12 cases (%16.9) were combined carcinomas.Thirty-one of 71 tumours were T1 (43.6%). Pre-oprerative diagnosis rate in patients with T1 tumors, is 29%. **Result:** Thirty-one of the patients were in stage I (43.6%), twenty-three of the patients were in stage II (32.3%) and seventeen of the cases were in stage III (24.1%). Subgroups of the stages are shown at table I.Overall survival was 60.75 ± 6.93 months when all operated patents were concidered. Five-year -survival was 44.3% .When overall survival were compared by stage there was statistically significant difference. Overall survivals were as follows; in stage I- 67.03±10.86 months, stage II 61.43±10.83 months, stage III- 33.23±8.6 months (p=0.02) (Figure I). Five-year survival were 46% in stage I, 45% in stage II, 32% in stage III for HGNC. When overall survival were compared by histopathologic type, combined neuroendocrine carcinomas reflect the least overall survival value but the difference is not statistically significant. Overall survivals were as follows; in large cell neuroendocrine carcinoma- 59.4±9.23, small cell neuroendocrine carcinoma carcinoma 68.6±12.2 combined type neuroendocrine carcinoma- 40.9±10.1 months (p=0.462) (Figure 2). There is no statistically significant difference betwen small cell and large cell neuroendocrine tumours' overall survival values (p=0.34).When overall survival were compared by N status, overall survival were as follows. Patients with N0 disease 65.9± 8.3, N1 disease 53.6±10.6, N2 disease 37.1±15.3 months. There was no statistically significant difference (p=0.103) (Figure 3). When N0 and N2 patients' survivals are compared p value is 0.094. **Conclusion:** Although high grade nuroendocrine tumors (NET) of the lung have poor prognosis compared with other NSCLCs (11,12,13), satisfactory survival results are asessed in our study. As a result, good overall survival rates can be achieved in surgically operated patients with HGNEC tumors who had post- operative adjuvant chemotherapy, mediastinal radiation therapy when necessary and protective cranial radiotherapy. Nevertheless, thoracic surgeon should be very selective in patients with stage IIIa HGNEC tumors.

P2.18-15 SURGICAL OUTCOMES OF PNEUMONECTOMY AFTER INDUCTION THERAPY FOR NON-SMALL-CELL LUNG CANCER

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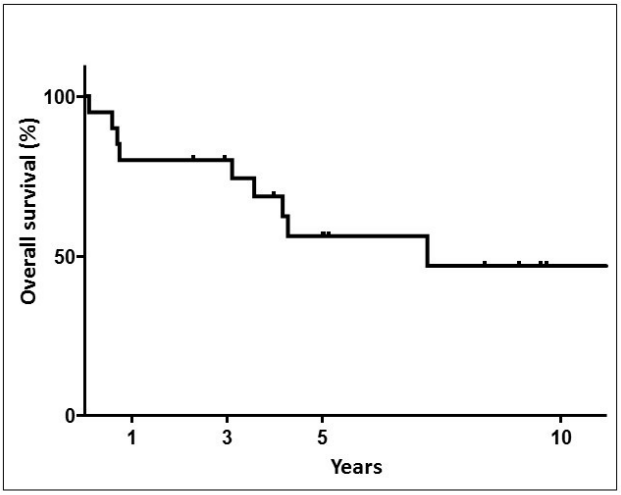
Background: The mortality of pneumonectomy after induction therapy (IT) for locally advanced non-small-cell lung cancer (NSCLC) is reported to be as high as 26%. However, pneumonectomy after IT has also been reported of having an acceptable safety and favorable outcomes. We retrospectively reviewed the postoperative outcomes of this procedure. **Method:** Between April 2004 and September 2016, of 179 patients who underwent neoadjuvant therapy, 20 consecutive patients (11.2%) underwent pneumonectomies for locally advanced NSCLC after IT in our institution. Perioperative management, mortality, postoperative complications and survival were retrospectively analyzed. **Result:** Eighteen patients were men, and the median age was 64 years (range, 38 to 79). Clinical stages (7th edition of TNM classification) were as follows: Stage IIA(n=2), Stage IIB(n=1), StageIIIA(n=15), and StageIIIB(n=2). There were 7 right and 13 left resections. Three patients underwent pneumonectomy after induction chemotherapy and 17 underwent after induction chemoradiation. A pathological complete response(Ef.3)due to IT was obtained in 8 patients (40%). In all cases the bronchial stumps were covered with autologous tissue including pedunculated intercostal muscle or mediastinal fat pad. There were no deaths within 30 days. However, one patient died within 90 days after transferring to a rehabilitation hospital. Postoperative complications of all grades were seen in 15 patients (75%), with major complications (Clavien-Dindo classification ≥IIIa) in 5 patients (25%). Major complications were all late-phase empyema, one with BPF and 4 without BPFs, which were all cured with surgical interventions. 5-year overal and recucurence free suvavals were 56.1 % and 47.4%, respectively. The average observation period of alive patients was 2500 days (range, 836 to 5144 days).



Overall 3-year survival: 80.0%
Overall 5-year survival: 56.1%

Conclusion: Our results suggest that pneumonectomy after IT for locally advanced NSCLC is a feasible and valuable treatment option. However, due to a high complication rate, surgery by experienced surgeons and careful postoperative management are essential for successful outcomes.

Keywords: locally advanced NSCLC, induction therapy, pneumonectomy

P2.18-16 VATS LOBECTOMY AND CHEST WALL RESECTION FOR NSCLC

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Background: The classic surgical approach in patients with NSCLC invading the chest wall is lobectomy and chest wall resection by thoracotomy in the majority of patients. However, this approach can be performed by video-assisted thoracoscopic surgery (VATS) or robotic surgery (RATS) as a result of increased experience and technological developments. The aim of this study was to evaluate the feasibility of the technique and its results in patients undergoing lung and chest wall resection by means of minimally invasive surgery. **Method:** The data of patients who underwent anatomical lung resection using VATS or RATS for NSCLC in three academic hospitals between 2013-2018 were prospectively recorded and reviewed retrospectively. Fourteen patients, all but three males with a median age of 62 ± 6.0 years, undergoing lung and chest wall resection were included in the study. Surgical results were evaluated. **Result:** Neoadjuvant/induction treatment was chemo-radiotherapy in three and chemotherapy in two patients. The preferred surgical technique was RATS in two patients, and multiportal VATS in 10 and uniportal VATS approach in two patients. Upper lobectomy was performed in 11 patients, lower in two patients and upper lobe posterior segmentectomy in one patient. Standard small incision for chest wall resection was performed in four, Hybrid approach in 10 patients. Five

patients had one, 6 patients had two, two patients had three and one patient had four ribs resections. Chest wall reconstruction was not necessary in any of the patients. The mean operation time was 96.4 ± 21.8 minutes. Complications were observed in 5 (35.7%) of the patients without mortality. The most common complication was prolonged, >5 days, air leak in four patients (28.6%). Ten patients (71.4%) were classified as T3N0, one patient (7.1%) as T4N0, one patient (7.1%) as T4N1, and two patients (14.1%) as T3N0M1. Surgical margins were reported as tumor-free (R0) in all patients. Adjuvant chemotherapy was given in eight patients (57.1%). The two-year survival rate was 66.8%. **Conclusion:** Lobectomy and chest wall resection with minimally invasive surgery is a safe and feasible method in patients with NSCLC with chest wall invasion. Compared with thoracotomy, it provides equivalent oncologic outcomes as well as less postoperative pain, smaller incision, and faster recovery.

Keyword: Minimally Invasive Surgery, VATS, RATS, Robotic Surgery, Chest Wall Resection

P2.18-17 OUTCOME OF SURGICAL TREATMENT FOR CLINICAL N1 NON-SMALL CELL LUNG CANCER

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Background: Main stem treatment for clinical N1 NSCLC is surgery, but it is sometimes difficult to perform because tumor or metastatic lymph-node invade hilar structures. Nowadays, treatment outcome has been improved. This study aims to reconsider the surgical outcome of N1 NSCLC. **Method:** The data of 337 cases who underwent at least lobectomy and lymph node dissection for NSCLC from 2000 to 2014 was retrospectively reviewed. The factors which may have impact for survival and treatment related death (TRD) were examined. **Result:** Median follow up period was 51.7 months. 337 cases were 15.3% of all lobectomy and pneumonectomy performed in this period. 248 males and 89 females, average age was 67.1. Lobectomy was 309 including 15 bronchoplasty and pneumonectomy was 28. Mean operative time was 212 minutes, blood loss was 110g. TRD was noted in 6 (1.8%); 3 interstitial pneumonia, 2 myocardial infarction and a stroke, 4 cases (1.2%) died within 30 day after surgery.During this time, TRD of clinical N0 was 8 case (0.46%) and N2 was a case (0.82%). TRD of N1 was significantly frequent (p=0.026). Pathologically, N0 was 152 cases (45.1%), N1 was 116 (34.4%) and N2 (20.5%); pathological accuracy of N1 was only one third. 5 year survival rate of clinical N1 was 59.3%, 83.6% in N0 and 54.1% of N2. In histology, adenocarcinoma was 184, 113 squamous, 8 large, 7 adenosquamous and 25 other. Induction therapy, blood loss and pathological N status had negative impact for survival. On the other hand, operative time and right side had negative impact for TRD. **Conclusion:** The outcome of clinical N1 has been improved compared with historical report, but the accuracy of clinical N1 is not satisfied one. TRD rate in N1 was relatively high, surgery for N1 NSCLC should be performed by certified thoracic surgeons.

Keywords: Lymph node metastasis, prognosis, Lung cancer

P2.18-18 IMPACT OF COMBINED EVALUATION USING TUMOR VOLUME AND METASTATIC NODAL EXTENT IN STAGE III NSCLC TREATED WITH CRT

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Background: Chemoradiotherapy (CRT) is the standard treatment for patients with unresectable stage III non-small cell lung cancer (NSCLC). In those, gross tumor volume (GTV) and number of metastatic nodal stations were proposed as possible prognostic factors, while TNM stage classification (stage IIIA vs. stage IIIB/IIIC) did not show significant prognostic impact. However, these evidences remain controversial. The aim of this study was to investigate the prognostic impact of GTV and metastatic nodal extent. **Method:** We retrospectively reviewed stage III NSCLC patients treated with CRT at our institution between October 2005 and December 2018. Simplified GTV (sGTV) was calculated by oval volume formula. We confirmed statistically significant association between sGTV and standard GTV as previous preparation. Metastatic nodal extent was divided into limited nodal extent (≤ND2a) (defined as "LN") or extensive nodal extent (>ND2a)(defined as "EN"). Prognostic impact of sGTV and metastatic nodal extent was evaluated by univariate and multivariate analysis. **Result:** 58 patients were enrolled in this study. Median progression-free survival (PFS) of all patients were 9.0 months. In univariate analysis, patients with sGTV>90cm3 had shorter PFS compared to those with sGTV≤90cm3 (median PFS: 6.7 vs. 11.7, p=0.03). Further, patients with sGTV>90cm3 and EN showed poorer PFS (HR 3.3; 95% CI,1.40-7.87; p<0.01) and OS (HR 3.3, 95% CI: 1.18-9.32, p<0.01) in univariate analysis. Multivariate analysis also showed an independent poor prognosis in patients with sGTV>90cm3 and EN (adjusted HR of PFS: 3.6, 95% CI: 1.49-8.71, p<0.01, adjusted HR of OS 4.1, 95% CI: 1.37-12.6, p=0.01). **Conclusion:** Combined evaluation using sGTV and metastatic nodal extent can be a useful stratified factor for clinical trial in patients with stage III NSCLC.

Keywords: chemoradiotherapy, gross tumor volume, metastatic nodal extent

P2.18-19 RADIOLOGICAL AND PATHOLOGICAL RESPONSE TO THE INDUCTION OF SURGERY IN THE NSCLC STAGE III

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Background: Neoadjuvant treatment (NT) prior to surgical resection is the standard treatment for operable stage III-pN2 NSCLC. Our objective is to compare the response, radiological and pathological, after induction with radio-chemotherapy (RT-Ch) versus chemotherapy alone (Ch). **Method:** We develop a retrospective study that included 53 patients from four different centres diagnosed of stage III NSCLC (TNM 8th edition). 34 patients received RT-Ch and 19 received Ch between 2012 and 2018, with a median follow-up of 25 months. The radiological response (RR) was assessed by CT at 3-4 weeks after NT using RECIST criteria. The pathologic response (PR) was evaluated in operated patients (44) through the viable residual cells in the tumor and lymph nodes. pN was taken into account to determine the rate of downstaging. The PR, as well as the surgery, were performed in the same center for all 44 patients **Result:** The majority were stage IIIA (33), followed by IIIB (19) and only one was IV (single brain metastasis treated previously with radiosurgery). Comparing the RR in RT-Ch and Ch, we found stable disease and partial response more frequently with a 35.6% vs 52.6% and 61.8% vs 36.9% respectively. A 17.3% and 5.3% of the complete PR was achieved in RT-Ch and Ch respectively. Downstating was feasible in 82.8% of RT-Ch and 40% in Ch. Clinical features and treatment evaluation in Table 1.

Table 1. Clinical, pathological and treatment features (n=53).

	RT-Ch (n=34)	Ch alone (n=19)
Age	59 (53, 67)	68 (58, 73)
Gendre		
Male	21 (61.7%)	14 (73.6%)
Female	13 (38.2%)	5 (26.3%)
Histology		
Adenocarcinoma	21 (61.7%)	16 (84.3%)
Squamous	12 (35.3%)	2 (10.5%)
NSCLC*	1 (3%)	0 (0%)
Large Cell	0 (0%)	1 (5.2%)
Stage		
IIIA	18 (52.9%)	15 (78.9%)
IIIB	15 (44.2%)	4 (21.1%)
IV	1 (2.9%)	0 (0%)
T		
T1	5 (14.7%)	6 (31.6%)
T2	11 (32.3%)	8 (42.1%)
T3	9 (26.5%)	5 (26.3%)
T4	9 (26.5%)	0 (0%)
N		
N0	4 (11.8%)	0 (0%)
N1	0 (0%)	0 (0%)
N2	28 (82.4%)	19 (100%)
N3	2 (5.8%)	0 (0%)
M		
M0	33 (97%)	19 (100%)
M1	1 (3%)	0 (0%)
Ch Regimen		
CDDP + VP-16	18 (52.9%)	0 (0%)
CDDP + VN	11 (32.4%)	4 (21%)
CBDCA based	2 (5.9%)	7 (36.9%)
CDDP based	3 (8.8%)	8 (42.1%)
Surgery		
Lobectomy	26 (76.5%)	13 (68.4%)
Bilobectomy	2 (5.9%)	1 (5.3%)
Pneumonectomy	1 (2.9%)	0 (0%)
Segmentectomy	0 (0%)	1 (5.3%)
No surgery	5 (14.7%)	4 (21%)
Radiological Response		
Pregression disease	1 (2.9%)	2 (10.5%)
Stable disease	12 (35.3%)	10 (52.6%)
Partial response	21 (61.8%)	7 (36.9%)
Complete response	0 (0%)	0 (0%)
Complete Pathological Response		
Yes	6 (17.7%)	1 (5.3%)
No	23 (67.6%)	14 (73.7%)
No surgery	5 (14.7%)	4 (21%)
Pathological Tumor-Nodal Response[&]		
No response	1 (3.4%) - 1 (3.4%)	6 (40%) - 6 (40%)
Stabilization	0 (0%) - 0 (0%)	6 (40%) - 1 (6.7%)
Partial response	8 (27.6%) - 2 (6.9%)	2 (13.3%) - 2 (13.3%)
Maximum response	20 (69%) - 26 (89.7%)	1 (6.7%) - 6 (40%)
Downstaging		
Yes	24 (82.8%)	6 (40%)
No	5 (17.2%)	9 (60%)

Quantitative variables expressed in median, 25th percentile and 75th percentile. Qualitative variables expressed in absolute count and percentages. RT-Ch= Radio-chemotherapy, Ch= Chemotherapy. *Histological study not conclusive. CDDP= Cisplatin, VP-16= Etoposide, VN= Vinorelbine CBDCA= Carboplatin. [&]According to histological cancer cells viability described as maximum response ≤ 15%, partial response= 20-50%, stabilization= 60-70% and no response ≥ 80%.

Conclusion: In our review we observed that a 45% of the patients treated with Ch had a response of 20% or less in the pN or a local progression after the treatment, in comparison with only a 3.4% in the group of RT-Ch. However, the evaluation of the differences in the PR should be associated with a greater follow-up to assess the impact on overall survival.

Keywords: NSCLC, Neaodjuvant treatment, RT-Ch versus Ch

ePosters

EP1.01 ADVANCED NSCLC

EP1.01-01 ATRIAL RESECTION WITHOUT CARDIOPULMONARY BYPASS FOR LUNG CANCER

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Background: Results of resection of lung cancer invading left atrium (T4atrium) without cardiopulmonary bypass (CPB) remain controversial. We reviewed our experience analyzing surgical results and postoperative outcomes. **Method:** Patients who underwent extended lung resection for T4atrium without CPB between 1998 and 2018 were retrospectively reviewed using a prospective database. **Result:** Forty-four patients were collected (34 men, median age, 63 years). Twenty-five patients underwent preoperative mediastinal staging and 27 received induction treatment (IT). Lung resection included 40 (90.9%) pneumonectomies, 3 (6.8%) lobectomies and one bilobectomy (2.3%). Pathological nodal status was N0 in 10 patients (22.7%), N1 in 18 (40.9%), and N2 in 16 (36.4%). Four patients receiving IT had complete pathological response (9.1%). Eight patients (18.2%) had microscopic tumor evidence on atrial resected margins. Mortality was nil. Major complication rate was 11.4%: one BPF, one cardiac herniation, and three hemothorax all requiring re-intervention. Minor complication rate was 25.5%. After a median survival of 37 months (range, 1-144 months), 20 patients (45.4%) were alive. Five-year survival and disease-free interval were 39% and 45.8%, respectively. Patients with N0 and R0 disease had a best prognosis (log-rank test: p=.03, and p=.01, respectively). IT neither influenced survival nor postoperative complications. At multivariate analysis, pN0 [p=.04 (95% CI: 0,65-9,66)] and negative atrial margins [p=.02 (95% CI: 0,96-8,35) were positive independent prognostic factors. **Conclusion:** Resection of T4atrium is technically feasible without mortality and acceptable morbidity. Patients with N2 cancers should not be operated on. Lung cancer invading left atrium should not be systematically considered as a definitive contraindication to surgery.

Keywords: Advanced lung cancer, Atrium, cardiopulmonary by pass

EP1.01-02 NOVEL PARTIAL TUMOR IRRADIATION IMPROVES TREATMENT OUTCOMES FOR INOPERABLE BULKY LUNG CANCER COMPARED WITH STANDARD OF CARE

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Background: Purpose: to report on the improved outcomes by newly developed SBRT exploiting the bystander (BE) and abscopal effects (AE) for the treatment of either inoperable, or bulky lung cancer unsuitable for radical radiotherapy compared with standard of care. In a pre-clinical phase of this translational research it was proven that the hypoxic tumor cells show higher potential for tumoricidal BE and AE compared with normoxic tumor cells. In order to improve the radiotherapy outcome by generating BE and AE, these findings were translated to the clinic and new SBRT-based PArtial Tumor irradiation targeting the HYpoxic segment (SBRT-PATHY), but sparing the tumor immune microenvironment, was developed. The hypothesis is that SBRT-PATHY will improve local and distant tumor control, inducing major regression of the partially irradiated bulky tumor due to BE, but also of unirradiated metastases due to AE. The primary endpoint was bulky response rate. The secondary endpoints included: distant tumor control, survival, safety, symptom control. **Method:** 60 patients with stage IIIB/IV bulky lung cancer considered inoperable or unsuitable for radical radiotherapy were treated (Aug. 2013 - Aug. 2018) with: 1.) Conventional radiotherapy only: 3Gy x 10 to the bulky tumor (20 patients), 2.) Standard chemotherapy only (20 patients), 3.) SBRT-PATHY only: 10 or 12Gy x 1-3 to 70% (based on bulky site and volume) to a so-called Bystander (hypoxic) Tumor Volume (BTV) defined using PET-CT as a hypovascularized-hypometabolic (SUVmax<3) junctional zone between the central necrotic and peripheral hypervascularized-hypermetabolic bulky segment, avoiding the tumor microenvironment (20 patients). Immunohistochemistry was performed on the available tissue samples to explore for modifications within the tumor microenvironment. **Result:** 3 treatment groups were comparable in terms of performance status, histology and disease stage. Table 1 summarizes the results.

Treatment Group	Bulky Response Rate (Cr Or Pr)	Distant Tumor Control	Overall Survival	Cancer Spec. survival	Progression Free Survival	Toxicity (G1-4)	Symptom Control
1.	20%	0% (abscopal effect)	5%	10%	0%	15%	25%
2.	20%	55% (chemo effect)	60%	60%	15%	65%	15%
3.	95%	46% (abscopal effect)	55%	80%	55%	5%	80%

Median follow up was 13 months (range: 4-27), mean bulky diameter: 8.1 cm (range: 6-13.5). Histology: 39% squamous, 51% adenocarcinoma, 10% other. On average the BTV volume corresponded to 32% of the bulky. AE was observed in 46% of patients treated with SBRT-PATHY. Immunohistochemistry showed that the apoptosis-inducing factor was massively upregulated in the partially irradiated bulky and also at the unirradiated, abscopal tumor sites, whereas a dense immune reaction was observed only at the border of the partially irradiated bulky but not at the abscopal site. **Conclusion:** Exploitation of the tumoricidal radiation-hypoxia-induced BE and AE by SBRT-PATHY may potentially enhance the radiotherapy therapeutic ratio.

Keywords: Bystander, Abscopal, Partial

EP1.01-03 REAL WORLD OUTCOME OF CRIZOTINIB FOR ANAPLASTIC LYMPHOMA KINASE-POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Crizotinib has shown its superiority in clinical trials compared to conventional chemotherapy in patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) patient, but its use and outcomes in real-world settings are yet to be investigated. This study aimed to assess treatment patterns and outcomes of crizotinib therapy in ALK-positive NSCLC patients, as well as to seek factors associated with progression-free survival and overall survival of ALK-positive NSCLC patients. **Method:** A retrospective medical record review of 176 patients who are diagnosed as metastatic or recurred NSCLC from January 1st, 2006 to June 30th, 2018 and treated with crizotinib was performed. Descriptive analyses were conducted to assess treatment patterns and objective response rate (ORR). Survival analysis to estimate progression-free survival (PFS) and overall survival (OS) was performed. Comparison of the treatment outcomes by the setting of crizotinib initiation was done. Cox regression analysis was used to find predictive factors associated with PFS and OS from initiation of crizotinib. **Result:** Median age was 55.7 (ranged 20 to 84) years and 85 patients (48.3%) were male. Seventy-two (40.9%) patients died at the time of analysis. Seventy-eight patients initiated crizotinib as first-line therapy. Overall response rate was 54.5% (50.0% for first-line recipients, 58.2% for second-/later-line). Median (95% CI) PFS from crizotinib initiation and OS from first dose of chemotherapeutic agent were 14.3 (11.6-17.0) and 41.7 (25.4-58.1) months, respectively. No significant difference of ORR, OS, and PFS, according to the setting of crizotinib initiation was observed. Multivariate Cox analysis showed poor performance status (HR 3.472, p-value < 0.001) and number of metastatic organs (≥3, HR 1.648, p-value 0.017) were independently associated to shorter PFS and OS, while history of getting pemetrexed before use of crizotinib (HR 0.638, p-value 0.039) was independently related to longer OS.

	All patients	Setting of Crizotinib Initiation		
	(n = 176)	First-Line (n = 78)	Second- or Later-Line (n = 98)	P value
Progression-free survival				0.699
Mean (SE)	25.0 (3.1)	28.0 (6.4)	16.6 (1.5)	
Median (95% CI)	14.3 (11.6-17.0)	15.8 (10.0-21.6)	13.1 (9.1-17.0)	
Q1, Q3	5, 27	5, 22	5, 27	
Overall survival				0.137
Mean (SE)	54.1 (4.2)	40.6 (6.1)	57.8 (4.9)	
Median (95% CI)	41.7 (25.4-58.1)	26.3 (14.7-37.9)	43.9 (25.7-62.1)	
Q1, Q3	18, 109	17, 77	19, 109	
1- and 2-year survival rates				
Percent still alive at 1 year after diagnosis (95% CI)	87.1 (86.7-87.5)	85.4 (84.3-86.5)	88.5 (87.8-89.2)	0.483
Percent still alive at 2 years after diagnosis (95% CI)	65.7 (65.0-66.4)	55.4 (51.9-58.9)	69.0 (68.0-70.0)	0.213

Conclusion: Outcomes for crizotinib recipients were in line with previous trials, with PFS and OS appearing more favorable. Poor performance status and number of metastatic organs correlated to worse PFS and OS, while history of previous use of pemetrexed before crizotinib correlated to better OS.

Keywords: crizotinib, Lung cancer, Anaplastic lymphoma kinase

EP1.01-04 PHASE I/II TRIAL OF BIWEEKLY NAB-PACLITAXEL IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER: NJLCG1402

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Background: Nanoparticle albumin-bound paclitaxel (nab-PTX) is a cremophor-free formulation of paclitaxel that can be administered safely as a short infusion without dexamethasone or antihistamine premedication. NJLCG1402 consists of multiple, open-label, single arm, phase I/II trials designed to assess the benefit of biweekly nab-PTX treatment in patients (pts) with previously treated advanced NSCLC (UMIN 000014893). **Method:** Eligible patients were aged ≥20 years; had histologically or cytologically confirmed, advanced-stage, previously treated NSCLC. Nab-PTX was administered biweekly at dose of 100 to 150 mg/m^2 in a 28-day cycle. In the phase I part, we aim to determine the recommended phase II dose of nab-PTX. In the phase II part, pts were assessed for efficacy and tolerability. The primary endpoint for the phase II part is the objective response rate. Secondary endpoints were progression free survival, overall survival, disease control rate, and safety. Assuming an expected the objective response rate of 15% and threshold of 5%, a total of 18 pts were required to have 70% power at a two-tailed alpha of 0.2 at the phase II part. **Result:** A total of 27 pts (median age 68 years, male 78%) were enrolled. The dose escalation cohort included 15 pts administered biweekly with 100 to 150 mg/m^2 across 3 dose levels, and 12 patients in the phase II part were administered with 150mg. No dose-limiting toxicities were observed in the phase I part and 150mg was determined as recommend dose. Of the evaluable pts (n=18) at dose of 150mg/m^2, the objective response rate was 22%(4 of 18 pts; 95% CI, 9.5 to 43.5), median progression free survival was 3.6 months (95% CI 1.4 to 5.9), and median overall survival was 7.2 months (95% CI, 0 to 15.0 months). Adverse events (AEs) of grade 3 or higher were observed in 39% of patients. The most common AEs were leukopenia (22%), anemia (22%), and rash (6%). **Conclusion:** Biweekly nab-PTX monotherapy was well tolerated and exhibits promising systemic antitumor activity in previously treated NSCLC pts.

Keywords: NSCLC, nab-Paclitaxel, biweekly

EP1.01-05 EGFR-2013-CPHG, A REAL-WORLD STUDY OF EGFR MUTANT ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH ERLOTINIB

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Background: Erlotinib (E) is a first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor labelled in France and effective as a first-line treatment in advanced non-small-cell lung cancer (NSCLC). E has demonstrated a better efficacy than chemotherapy in EGFR mutant NSCLC in phase III trials. **Method:** We undertook a multicentric study in 42 French Nonacademic Hospital Centres. Patients aged 18 years and older with histologically confirmed stage IIIB or IV NSCLC and harboring a confirmed activating mutation of EGFR received oral E (150 mg/day). We report here patient characteristics, progression-free survival (PFS), overall survival (OS), and safety data. Statistical analyses by R software were based on a Cox model and Kaplan-Meier method. **Result:** Between April 1st, 2014 and March 31st, 2016, 184 patients were recruited: mean age = 72 years old, 125 (69.5%) female, 158 (90.8%) Caucasians, 112 (63.6%) non-smokers, 167 (94.9%) adenocarcinoma (21 stage IIIB and 156 stage IV), 127 (65.6%) ECOG 0-1, 40 (26%) brain

metastasis at inclusion and 75 (42.4%) were treated by E in second- or latter line. 179 patients were included in the PFS and OS analysis. Median follow-up was 23.8 months, median PFS was 11.7 months and median OS was 25.8 months. Median survival rates at one year were 48.6% for PFS and 75% for OS. Risk of death was not correlated with brain metastasis (HR=1.15, IC95:0.67-1.97, p=0.296) but with ECOG = 2 (HR=4.55, IC95:2.05-10.10, p<0,001). E had a manageable safety profile (7.7% grade 3-4 adverse events at 6 months) and no new safety signals were identified.

	N	%
Patients	184	
Mean age (years)	72	
Sex		
Males Females	59 125	30.5 69.5
Race		
Caucasians	158	90.8
Smoking status		
Non-smokers	112	63.6
Histological type		
Adenocarcinoma	167	94.9
Staging		
Stade IIIB Stade IV	21 156	
ECOG		
0 or 1	127	65.7
Brain metastases at inclusion	40	26
Second-lind therapeutic strategy and more		
Erlotinib	75	42.4
Progression-free survival and overall survival	179	
Median Progression-free survival (Months) Median Overall Survival (Months)	11.7 25.8	

Conclusion: Data from EGFR-2013-CPHG real-world study are consistent with the efficacy and safety of E in EGFR mutant NSCLC patients seen in phase III clinical trials.

Keywords: non-small-cell lung cancer, real-world study, erlotinib

EP1.01-06 LOSS OF HETEROZYGOSITY OF ONCOGENE ERBB2 WITH AN ACTIVATING MUTATION WAS IDENTIFIED AS DRIVER EVENTIN LEPTOMENINGEAL METASTASIS OF NSCLC

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Background: Due to limited access to leptomeningeal lesions, cerebrospinal fluid (CSF) may be the most representative liquid biopsy to get genomic information from leptomeningeal metastases (LM) in non-small-cell lung cancer (NSCLC). Loss of heterozygosity (LOH) is a common genetic event during cancer tumorigenesis. LOH of tumor suppressor gene in which loss-of-function occurs on alternative allele serves as "second hit" and leads to loss of the remaining functional allele. LOH of tumor suppressor gene, such as *TP53*,in CSF had been reported for its associated with EGFR-TKI resistance in LM. Here, through CSF derived liquid biopsy, we report a LOH of oncogene ERBB2 in LM of NSCLC patient. To the best of our knowledge, this is the first report of LOH of oncogene, no matter in a primary or metastatic tumor. **Method:** Three CSF biopsies and matched peripheral blood were collected within 6 months from one NSCLC patient with LM. Cell-free DNA (cfDNA) was extracted, and somatic mutations were examined using a designed lung cancer panel of 180 genes. SCNAs were further identified through 2x whole genome sequencing (WGS). Genomic alternations identified in all three matched biopsies were included in the subsequent analysis. **Result:** A rare oncogene *ERBB2* activating mutation (V659E) was identified in CSF but not in plasma. V659E lies within the transmembrane domain and results in constitutive activation of Src and Akt signaling. Extreme high variants allele fraction (96.8%) of *ERBB2* V659E in CSF implied the LOH of *ERBB2* in LM. SNPs heterozygosity analysis and low pass WGS were further carried out and confirmed the LOH of entire chromosome 17, but not limited to *ERBB2* region. Furthermore, A consecutive an amplification was observed on the remaining copy of chromosome 17q, on which the activated oncogene *ERBB2* located. The amplification, following *ERBB2* LOH with a concomitant activating mutation, may enhance constitutively active ERBB2 expression and drive the evolution of LM. Besides, there were two more unique mutations in CSF, *TP53* T256fs (45.31%) and *JAK3* R582Q (32.85%). Relatively Low variants allele fraction indicated that they were subclonal mutation occurring after *ERBB2* activating mutation and LOH of chromosome 17. **Conclusion:** We first reported an oncogene *ERBB2* LOH in CSF from one NSCLC patient with LM. Based on phylogeny inference, the *ERBB2* activating mutation and LOH of chromosome 17 were likely to be the earliest driver event.

Keywords: leptomeningeal metastases, cerebrospinal fluid, ERBB2 LOH

EP1.01-07 DEFINITIVE RESULTS OF A CLINICAL AND MOLECULAR MULTICENTRIC CHARACTERIZATION OF LONG-TERM SURVIVORS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Long survivors (LS) in non-small-cell lung cancer (NSCLC), defined as an overall survival (OS) greater than 2 years, are less than 10% in most series. Classical prognosis factors include stage, weight loss and ECOG, but more information is missing in the literature. Recently, EGFR, ALK and ROS 1 population (less than 20%) reach OS longer than 2 years. Immunotherapy has demonstrated very promising results with more LS compared to chemotherapy in first and second line setting. In this study, we focused in the analysis of LS patients with advanced NSCLC EGFR wt (wild type) and ALK nt (non-translocated), defined as those with OS greater than 36 months, in 7 hospitals in Madrid. **Method:** In this serie, first of all, we will try to make a clinical, histopathological characterization collecting data from clinical reports according to a previously defined information. In a second step, we will carry out a genetic analysis of these patient samples comparing to an opposite extreme short survivors (SS) samples (OS less than 9 months). Initially, we used a NGS method of RNA-seq technology to identify differentiating profiles of gene expression between the two opposite populations. And finally, we confirmed this preliminary profile by RT-PCR in the rest of samples. **Result:** Ninety-six patients were initially included. The majority were men, smokers or former with adenocarcinoma and ECOG 0- 1. We have obtained a differential transcriptome expression between samples from 6 LS and 6 SS, resulting 13 over-expressed and 42 down-expressed genes in LS comparing to SS transcriptome expression. Some of the genes involved in this initial profile belong to different cellular pathways: Secretin Receptor, Surfactant Protein, Trefoil Factor 1, Serpin Family, Ca-bindings Protein channel and Toll like Receptor family. Finally, we carried on by RT-PCR in 40 samples of SS and LS survivors and only four genes were significantly down-regulated in SS compared to LS in the multivariate analysis. These 4 genes were related to Surfactant Proteins: SFTPA1 (p = 0.023), SFTPA2 (p = 0.027), SFTPB (p = 0.02) and SFTPC (p = 0.047) **Conclusion:** We present a sequential genetic analysis of a LS population with NSCLC EGFR wt (wild type) and ALK nt (non-translocated), obtaining a differential RNA seq- and RT-PCR gene profile based on different surfactant proteins expression. A further confirmation in a larger sample is ongoing.

EP1.01-08 EFFICACY OF OSIMERTINIB IN PATIENTS OF ADVANCED NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASIS: A RETROSPECTIVE ANALYSIS

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Background: Osimertinib (AZD9291) is an oral, irreversible, third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations.The aim of this retrospective study was to evaluate the efficacy of AZD9291 for advanced non-small cell lung cancer(NSCLC) patients with brain metastasis. **Method:** We followed up patients diagnosed with advanced non-small cell lung cancer who were detected with EGFR gene mutation and who received EGFR-TKI from 1st October 2006 to 1st June 2018.Patients finally collected were divided into two groups:One group comprised of 45 patients received first-generation or second-generation EGFR-TKI alone,while other group included 45 patients were given AZD9291. And the 95% confidence interval (CI)and the median progression-free survival (mPFS)were calculated by the Kaplan-Meier method. **Result:** The median progression-free survival(mPFS) was longer with osimertinib than with standard EGFR-TKIs (14.0 months vs. 11.0 months; 95%CI: 10.160-13.840, P=0.017). The mPFS of patients with brain metastasis was significantly longer with osimertinib than with standard EGFR-TKIs(13.0 months vs. 7.0 months; 95%CI: 6.087-11.913, P=0.020). The mPFS of patients with osimertinib was longer with combined radiotherapy than with not receive radiotherapy(18.0 months vs. 13.0 months; 95%CI:7.066-18.934, P=0.915). **Conclusion:** In patients with non-small cell lung cancer with brain metastases, the median progression-free time of patients with osimertinib was longer than that of patients with first- or second-generation EGFR-TKIs alone, but osimertinib combined with radiotherapy showed no statistical significance compared with no radiotherapy.

Keywords: brain metastasis, Osimertinib, NSCLC

EP1.01-09 CLINICAL EFFICACY OF CIRCULATING TUMOR DNA TEST IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS WHO MIGHT HAVE T790M MUTATION

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Background: Using EGFR-tyrosine kinase inhibitors (TKIs) in patients with advanced lung cancer led to a significant improvement in survival. However, patients with these TKIs are ultimately resistant to disease, and about 50-60% patients showed EGFR T790M mutation. The purpose of this study was to evaluate the efficacy of tissue biopsy and liquid biopsy in patients undergoing re-biopsy after TKI use. **Method:** We reviewed medical records of 85 NSCLC patients who had done both tissue rebiopsy and liquid sampling from december 2017 to december 2018, at Severance University Hospital, Seoul, Korea. In this patients, the degree of coincidence and an expression level of T790M were examined with rebiopsy tissue for EGFR and circulating tumor DNA (ct DNA). CtDNA in plasma requires 100 copies of EGFRT790M per milliliter of plasma, so allele-specific PCR and digital PCR method were used to increase sensitivity for detection. **Result:** The mean age of the 85 patients was 62.9 ± 11.1 years, and 50 (58.8%) were female. The expression of T790M on rebiopsy was 17.6% (15/85) in ct DNA, and 23.5% (20/85) in tissue. The percentage of T790M from either liquid biopsy or tissue biopsy was 31.4% (27/85). The concordance between liquid biopsy and tissue biopsy was 72.9%. The sensitivity of liquid biopsy was 27%, specificity 72%, positive predictive value 22% and negative predictive value 77%. **Conclusion:** Testing Circulating tumor DNA in patients with NSCLC after TKI use can help to find T790M mutation in addition to rebiopsy of tissue. Combination of liquid biopsy and tissue biopsy is complementary to find the subject of the third-generation TKI, osimertinib. Also, liquid biopsy is less invasive and repeatable than tissue biopsy, it is useful for group of negative finding at tissue biopsy initial

Keywords: Circulating tumor DNA test, EGFR T790M, advanced NSCLC

EP1.01-10 PEMBROLIZUMAB IN COMBINATION WITH CHEMOTHERAPY AS FIRST-LINE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Pembrolizumab, a monoclonal antibody directed against programmed death-1 (PD-1), has been established as preferred treatment as a monotherapy for advanced non-small cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression of ≥ 50%. Combining immunotherapy with chemotherapy have shown synergistic anticancer activities and pembrolizumab has been studied in combination with various traditional chemotherapy regimens as first-line treatment for advanced NSCLC. Hence, we performed a systematic review and meta-analysis of currently available randomized controlled trials (RCTs) to evaluate the efficacy pembrolizumab in combination with chemotherapy as first-line treatment of advanced NSCLC. **Method:** We conducted a comprehensive literature search using PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through March 2019. RCTs utilizing first-line pembrolizumab chemoimmunotherapy in patients with advanced NSCLC were incorporated in the analysis. A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q-test. Random effects model was applied. **Result:** 3 RCTs (Keynote-021,189 and 407) including 1298 patients with advanced NSCLC were included in the analysis. The study arm used standard chemotherapy regimens in combination with pembrolizumab while control arm used only standard chemotherapy regimens. The randomization ratio was 2:1 in Keynote-189 study and 1:1 in other studies. The I2 statistic for heterogeneity was 0, suggesting homogeneity among RCTs. The pooled HR for PFS was statistically significant at 0.54 (95% CI: 0.47-0.62; P < 0.00001), including in PD-L1 tumor proportion score (TPS) of less than 1% cohort (HR: 0.72; 95% CI: 0.56-0.92; P = 0.010) and PD-L1 TPS ≥ 1% cohort (HR: 0.46; 95% CI: 0.39-0.56; P < 0.00001). The pooled HR for OS was 0.59 (95% CI: 0.45-0.76; P < 0.0001). Improvement in OS was also seen across all PD-L1 categories: in PD-L1 <1% group HR was 0.60 (95% CI: 0.43-0.83; P = 0.002) and in PD-L1 ≥ 1% group HR was 0.55 (95% CI: 0.40-0.75; P = 0.0002). **Conclusion:** Our meta-analysis demonstrated that first-line chemoimmunotherapy with pembrolizumab significantly improved PFS and OS compared to standard chemotherapy in patients with advanced NSCLC. The improvement of PFS and OS were consistent across all PD-L1 expression categories.

Keywords: Pembrolizumab, Non-Small Cell Lung Cancer

EP1.01-11 PROGNOSIS OF LUNG CANCER IN PATIENTS WITH INTERSTITIAL LUNG DISEASE; COMPARISON WITH NSIP AND IPF

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Background: Lung cancer is the leading cause of death in worldwide. Some reports revealed that lung cancer with interstitial lung disease (ILD) is associated with poor prognosis. However, the prognosis of lung cancer according to the subtype of ILD is unclear. We analyzed the outcome of lung cancer according to CT findings of ILD. **Method:** Among the non-small cell lung cancer (NSCLC) patients who visited Severance Hospital, Seoul, Korea from July 2005 to October 2018, patients with idiopathic pulmonary fibrosis (IPF) or non-specific interstitial pneumonia (NSIP) in chest CT image were enrolled in this study. Patients were divided into three groups according to

CT findings; (1) definite + possible IPF, (2) intermediate, and (3) definite NISP + possible NSIP. All patients were diagnosed lung cancer NSCLC on biopsy. The characteristics of study population and prognosis of each group were examined **Result:** A total of 151 patients were investigated in this study. Female was 4.6% and mean age was 70.2 years. 84 patients were definite + possible IPF group, 42 patients were intermediate, and 25 patients were definite NISP + possible NSIP group. The proportion of smokers who smoked once was significantly higher in definite + possible IPF group (p=0.006). Age, FVC, FEV_1 and lung cancer stage were not different between the three groups. Median overall survival were 27.0 months in NSIP group, 15.3 months in intermediate group, and 9.5 months in IPF group (p=0.04). Additionally, 25% of patients in definite + possible IPF group experienced acute exacerbation. **Conclusion:** CT findings of ILD in lung cancer patients could be helpful in predicting prognosis. Furthermore, acute exacerbation is more common in IPF patients. Therefore, careful attention should be paid to the treatment of lung cancer in patients with IPF pattern.

Keywords: interstitial lung disease, Lung cancer, prognosis

EP1.01-12 SNPS OF ORGANIC CATION TRANSPORTER 6 ASSOCIATE WITH THE EFFICACY OF PLATINUM COMBINATION CHEMOTHERAPY

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Background: Platinum derivatives (cisplatin or carboplatin) are key antitumor drugs to non-small cell lung cancer in combination therapy with not only other cytotoxic agents or vascular endothelial growth factor but also kinase inhibitors or immune checkpoint inhibitors. However, the predictive biomarker of effectiveness about platinum-based chemotherapy is still unclear. Organic cation transporter 6 (OCT6) is one of the solute carrier transporters (coded by *SLC22A16*) which transport substrates by facilitated diffusion or secondary active transport. We previously reported that OCT6 was involved in platinum drug resistance by mediating platinum drug influx in cancer cell. Single nucleotide polymorphisms (SNPs) in genome sequences bring about changes in the amino acid sequence, alter the protein structure, and result in individual differences. The aim of this study is to solve the association between the efficacy of cytotoxic chemotherapy including platinum derivatives and SNPs. **Method:** We retrospectively screened 78 advanced non-squamous non-small cell lung cancer patients who received platinum derivatives (cisplatin or carboplatin) and pemetrexed combination therapy for the first line chemotherapy between October/2010 and May/2018. We investigated the association between SNPs (*rs714368*, *rs723685*, and *rs12210538*) of *SLC22A16* or patients' characteristics and clinical outcomes. **Result:** The median age of patients was 67 years old. Sixty patients were male and 61 patients were current or former smokers. The historical features of Sixty-eight patients were adenocarcinoma, and 18 patients had positivity of EGFR mutation or ALK fusion. We excluded *rs12210538* from covariable of this study as all patients had major homo allele about *rs12210538*. The clinical outcomes of this study were similar to those of previous clinical studies. We found the patients with phenotype "A" of *rs714368* had higher disease control rate (DCR) and longer duration of progression free survival (PFS) compared to phenotype "G" [response rate (RR), 31.4 % vs 25%, p >0.99; DCR, 85.7% vs 37.5%, p<0.01; median PFS, 154 days vs 26,5 days, p<0.01; median overall survival (OS), 666 days vs 471 days, p=0.69, respectively]. On the other hand, genotype of *rs723685* had no association with treatment outcomes [genotype "TT" vs "TC", RR, 32.8% vs 18.2%, p=0.49; DCR, 83.6% vs 63.6%, p=0.21; PFS, 132 days vs 111 days, p=0.37; OS, 558 days vs 1014 days, p=0.46]. Phenotype A of *rs714368* and earlier stage were good predictive factor about PFS in Cox proportional hazard model. **Conclusion:** Gene polymorphisms of *rs714368* may change the function of OCT6 and influence the efficacy of platinum combination chemotherapy.

Keywords: Non-Small Cell Lung Cancer, Organic cation transporter 6, Platinum derivatives

EP1.01-13 A PHASE 2 TRIAL ASSESSING OSIMERTINIB ACTIVITY AGAINST LEPTOMENINGEAL CARCINOMATOSIS IN EGFR-MUTANT LUNG CANCER

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Background: Leptomeningeal carcinomatosis (LMC) occurs in 10 % of EGFR-mutant lung adenocarcinoma (LA). Retrospective studies have sugeted a clinical benefit of osimertinib in treating LMC in patients with EGFR-mutant LA. We conducted a phase 2 prospective trial to demonstrate the clinical efficacy, activity, and LMC-specific mechanisms of resitance to osimertinib in EGFR-mutant LA patients. **Method:** We performed gadalidium-enhanced brain MRIs at the time of enrollment, followed by scheduled brain imaging once every six weeks. Clinical neurological exams were performed every four weeks. Adverse Events (AEs) were assessed by NCI-CTCAE Ver. 4. Cerebral spinal fluid (CSF) and plasma was obtained on day 1 and 21 for all patients. The CSF osimertinib penetration rate was measured by liquid-chromatography mass spectrometry (LC-MSMS) and compared to plasma osimertinib levels. Targeted droplet digital PCR (ddPCR) was used to detect copy number changes of Met and the EGFR C797S mutation in patients CSF-DNA and plasma cell free (cf) DNA. **Result:** We enrolled six pre EGFR-TKI treated EGFR mutant LA with LMC. We observed a LMC-specific progression free survival of 3.7 months and overall survival of 6.2 months or longer with osimertinib. Four and three of six patients showed neurological and radiological responses, respectively. No patients had any AEs greater than grade 3 and all patients continued osimertinib beyond PD. The osimertinib CSF penetration rate was 1.2±0.5%. Met copy number was normal in plasma, but increased in the CSF of 2/6 patients prior to progression. Met copy number was confirmed in 1/6 patients at the time of progression. An aquired EGFR C797S mutation was observed in 1/6 patients prior to progression.

Patient characteristics	
Male / Female	3/3
Median age	61.5 (50-82)
Performance status (0/1/2)	0/3/3
Median previous EGFR-TKIs	3 (1-4)
Previous RT to Brain metastasis +/-	3/3
L858R / Del19	6/0
T790M in CSF +/-	0/6
T790M outside CSF +/-	6/0

Case	Neurological best response	Radiographical best response	PFS (days)	OS (days)	Acquired resistance
1	Stable	Stable	28	30	Met copy number gain
2	Improve	Improve	57	169	Met copy number gain
3	Improve	Progress	91	469+	Not detected
4	Improve	Stable	182	240+	Not detected
5	Improve	Improve	203+	203+	Not detected
6	Stable	Improve	123	139+	EGFR C797S

Conclusion: Osimertinib 80 mg is efficacious in the treatment of LMC in EGFR mutated LA. CSF-specific MET copy number gain and EGFR C797S mutations arise prior to progression in EGFR-mutant LA patients treated with osimeritinib.

Keywords: Osimertinib, leptomeningeal carcinomatosis, Acquired resistance

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EP1.01-14 THE SCOUR USING PRETREATMENT NLR, LIVER METASTASIS, PD-L1 STATUS AND PS AS A MARKER OF OUTCOMES IN NIVOLUMAB-TREATED PATIENTS WITH ADVANCED NSCLC

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Background: Although nivolumab showed the significantly longer overall survival (OS) compared with docetaxel for non-small cell lung cancer (NSCLC) based on two phase III randomized controlled trials, programed death ligand 1 (PD-L1) expression alone is not yet an adequate biomarker in treating nivolumab for NSCLC patients. Furthermore, some prior analyses indicated the liver metastasis, performance status (PS) and pretreatment neutrophil-to-lymphocyte ratio (NLR) is one of the candidates of effect predictors. This retrospective study aimed to analyze the score combining pretreatment patients' status as a predictive marker in NSCLC patients treated with nivolumab. **Method:** ne hundred and twenty-eight patients treated with Nivolumab who could examine the PD-L1 status from December 2015 to July 2016 were retrospectively reviewed. This study was multicenter study conducted by the three respiratory medical centers in Japan. We collected clinical data including age, sex, smoking history, histological types, PS, NLR, existence of Liver metastasis and PD-L1 status. We made the predictive score (PS2-4: 3 points, >NLR 4: 1 point, Liver metastasis +: 1 point, PD-L1 0%: 1 point and over 50%: -1 point) from pretreatment patients' characteristics and evaluate the score (over 4 points is high risk group, 2-3 points is mediate risk group, and under 1 point is low risk group) as a marker of outcomes. The data cut off was on 31th October 2017. **Result:** Median age was 67 years old, 86 patients were male, 101 patients had smoking history, 99 patients were PS 0-1 and 29 patients were PS 2-4, 26 patients were squamous carcinoma, >NLR 4 were 48 patients, and 16 patients had liver metastasis, respectively. Furthermore, PD-L1 expression 0% were 62 patients, 1-49% were 42 patients, and over 50% were 24 patients. Progression disease rate, median progression free survival (PFS) and median OS was 61.1%, 1.1 months, 2.4 months in high risk group; 60.6%, 1.4 months, 10.9 months in mediate risk group; and 36.4%, 4.6 months, 16.3 months in low risk group, respectively. **Conclusion:** We could classify the three group which could predict an patients' outcome according to the patients' characteristics.

Keywords: nivolumab, Prognostic factor, Non-Small Cell Lung Cancer

EP1.01-15 SYSTEMIC HYPERINFLAMMATION IS A STRONG INDEPENDENT PREDICTOR OF EARLY MORTALITY IN ADVANCED NSCLC

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Background: Prognostic tools in NSCLC are important for treatment decisions and evaluation of new treatment options. Ample evidence support inflammation as a marker of outcome in NSCLC. Our study explores outcome for a population-based real-life cohort of patients in the highest stratum of inflammatory activity. **Method:** The source cohort comprised all patients diagnosed with NSCLC between January 2016 – May 2017 at Gävle County Hospital, Sweden (n=155, inclusion rate 95%). Following exclusion of patients with active infection, the subgroup (n=77) in stage IIIB-IV with complete available laboratory parameters were studied further. Blood parameters were examined individually, and cut-offs (ESR>60 mm, CRP>20 mg/L, WBC>10 x10e9/L, PLT>400 x10e9/L) for high inflammation were set with an aim to pin-point the top echelon of hyperinflamed patients. A prognostic score was developed by assigning one point for each parameter above cut-off (0-4 points). **Result:** One year survival of patients with an inflammation score of ≥2 (n=23) was 0% compared to 50% and 33% among patients with a score of 0 (n=36) and 1 (n=18), respectively (figure 1). The effect of a high inflammation score on overall survival remained significant in multi-variate analysis adjusted for confounding factors (stage, gender, age, smoking status, ECOG PS). The hazard ratio of an inflammation score ≥2 in multi-variate analysis (HR 3.45, CI 1.62-7.34) was on par with a change of ECOG PS from 0 to 2 (HR 3.67, CI 1.44-9.4). **Conclusion:** Inflammation is a well established marker for treatment outcome in solid tumours. Our results show that high level inflammation is a strong independent marker for poor survival in patients with advanced stage NSCLC. This observation may indicate a need to stratify and subgroup patients in clinical studies with regard to systemic hyperinflammation and warrants further research on underlying mechanisms linked to tumour progression.

Keywords: inflammation, advanced NSCLC

EP1.01-16 CHARACTERISTICS OF STAGE III LUNG CANCER PATIENTS IN THE PERIOD 2014-2016 IN VIETNAM

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Background: Despite lung cancer is the leading cause of cancer-related mortality around the world, data and impact on health systems related to characteristics of the diseases is not fully understood in developing countries. The study aims to describe and evaluate the characteristics stage III lung cancer patients in Vietnam. **Method:** Medical records of patient with diagnosis of stage III lung cancer hospitalized in the period 2012-2015 in the National Cancer Hospital (Vietnam) were retrospectively analyzed. Patients were followed up about the survival information in April 2019 to identify overall survival (OS) rates. We compared the efficacy of treatments between 2 patient groups: surgery and/or radio-chemotherapy (group 1) and radiotherapy only or chemotherapy only or supportive care only (group 2). **Result:** From a total of 5220 lung cancer patient hospitalized in the National Cancer Hospital over 3-year period, we reviewed 600 original medical records, of which 70 stage III lung cancer patients having valid survival information were identified (11.7%). We found 60 patients with death outcome (85.7%) and median OS and its 95% confidence interval were 9.80 [5.39, 19.70]. Patients were mainly men (54, 77.1%) with mean age (SD) was 65.96 (8.62). We found 14 patients with surgery and/or radio-chemotherapy in group 1 (4 surgery and 10 radio-chemotherapy). In group 2, 34 patients were treated with chemotherapy or radiotherapy alone, and 22 patients were provided supportive care only. The estimated 1-year, 3-year and 5-year survival probabilities were 40.7 (30.6 - 54.1) %, 15.5 (08.8 - 27.1)% and 10.3 (04.64 - 22.9)% correspondingly. We estimated 3-year survival probability of patients in group 1 was 34.3 (16.24 - 72.4 %) was higher than group 2 which was 10.6 (4.89 - 23.2)% (p=0.055). **Conclusion:** Our results showed a benefit of surgery and/or radio-chemotherapy treatment on stage III lung cancer patients in Vietnam. Further research is required

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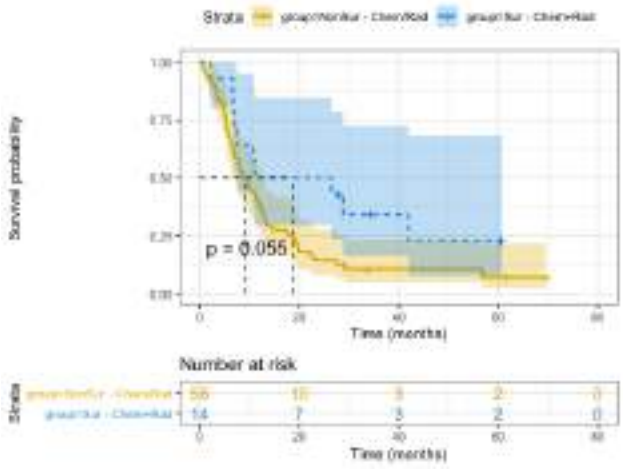

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Table 1: Characteristics of the patients.

Patient characteristics	Overall (N=70)	Group 2 (N=56)	Group 1 (N=14)	*p-value*
Sex				
Male (%)	54 (77.1)	44 (78.6)	10 (71.4)	0.831
Age (mean (sd))	65.96 (8.62)	66.59 (8.80)	63.43 (7.59)	0.222
Age category (%)				0.675
40-49	2 (2.9)	2 (3.6)	0 (0.0)	
50-59	12 (17.1)	8 (14.3)	4 (28.6)	
60-69	30 (42.9)	24 (42.9)	6 (42.9)	
70-79	25 (35.7)	21 (37.5)	4 (28.6)	
80-89	1 (1.4)	1 (1.8)	0 (0.0)	
T class (%)				0.002
T1b	1 (1.5)	1 (1.9)	0 (0.0)	
T2a	5 (7.5)	3 (5.7)	2 (14.3)	
T2b	4 (6.0)	1 (1.9)	3 (21.4)	
T3	31 (46.3)	22 (41.5)	9 (64.3)	
T4	26 (38.8)	26 (49.1)	0 (0.0)	
N class (%)				0.436
N0	1 (1.5)	1 (1.9)	0 (0.0)	
N1	8 (11.9)	5 (9.4)	3 (21.4)	
N2	41 (61.2)	34 (64.2)	7 (50.0)	
N3	13 (19.4)	9 (17.0)	4 (28.6)	
Nx	4 (6.0)	4 (7.5)	0 (0.0)	
Death (%)	60 (85.7)	50 (89.3)	10 (71.4)	0.2
OS (median [IQR])	9.80 [5.39, 19.70]	8.82 [5.21, 17.85]	18.79 [7.07, 32.88]	0.06
Treatments		Surgery: • + radiotherapy: 01 • + radio-chemotherapy: 03 Radio-chemotherapy: 10	Chemotherapy: 08 Radiotherapy: 26 Supportive care: 22	

Keywords: cancer therapy, Vietnam, Lung cancer

EP1.01-17 PREDICTORS OF SURVIVAL OUTCOMES WITH CHEMOTHERAPY IN ADVANCED NSCLC PATIENTS WITH PERFORMANCE STATUS 2 AND ABOVE AND WITHOUT DRIVER MUTATION

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Background: Platinum-based combination chemotherapy is recommended as the standard treatment for patients with advanced non-small-cell lung cancer (NSCLC), but its benefit is limited to patientswith performance status (PS) of 0 or 1. However, it is not clear whether these benefits apply to patients with poor performance status (PS 2 and above) and there are no predictors of outcome to suggest whom to treat .This population accounts for a significant portion (up to 30%) of patients of our practice and some of them have been treated with systemic chemotherapy based on clinician's discretion.We have analyzed the outcome of these patientswho have been treated with chemotherapy despite poor performance status. **Method:** We performed a retrospective analysis of patients of advanced NSCLC with poor PS (ECOG PS 2 or more) registered at our lung cancer clinic between January 2016 and December 2017 and treated with systemic chemotherapy. Patients with driver mutations who were treated with first line TKIs were excluded. Hospital case records were reviewed for baseline characteristics, treatment details and outcome data. Patients who haven't come to the hospital in last 3 months were contacted on phone. **Result:** A total of 95 patients were found to be eligible for this analysis. Median age was 62 years (30-84 years, including 23(24%) patients 70 years or above. At presentation out of these 95 patients, 63(66%) were smokers, 31(32%) had cytological proven pleural/pericardial effusion, 10(10.5%) patients had brain metastasis and 34(35.5%) had extra thoracic metastasis (≥2 sites).Majority(64%) patients had ECOGPS 2 but 36 % had PS 3 or 4 also and 44(46%) had one or more associated comorbidities. The most common chemotherapy regimen used was weekly paclitaxel and carboplatin(57.8%) followed by pemetrexed and carboplatin (16.8%).Majority (64%) patients could complete 4or more cycles of chemotherapy however 15 patients (15.7%) could receive only one cycle and 20(21%) patients even received maintenance chemotherapy. Chemotherapy was interrupted due to poor tolerance in 20(21%) patients and grade ¾ toxicity seen in 22(23%) % patients. At least one point improvement in ECOG PS from baseline was observed in 43 patients (45%) after 4 cycles of chemotherapy. Objective response and disease control rates were 20 % and 48.42% % respectively.Aftera median follows up of 8.6 months, median progression free survival was 6.2 months (95%CI 5-10.33).On univariate analysis ,neutrophil –lymphocytic ratio (<5 vs >5)and induction regimen (weekly Taxol+Platinum vs rest) were significantly associated(p=0.02 and p= 0.04 respectively) with better median PFS **Conclusion:** Systemic chemotherapy in modified doses and schedules in advanced NSCLC patients with PS 2 and above is feasible and may be associated with better symptom palliation with clinical benefit and improvement in survival.neutrophil –lymphocytic ratio (<5 vs >5)and induction regimen (weekly Taxol+Platinum vs rest) are predictors of better median PFS. Further studies addressing this neglected subgroup are indicated.

Keywords: Advanced NSCLC ,NLR ratio ,Poor performance status

EP1.01-18 CLINICAL FEATURES OF LOCALLY ADVANCED LUNG CANCER PATIENTS WITH RADIATION PNEUMONITIS AFTER INDUCTION CHEMORADIOTHERAPY

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Background: The therapeutic management of locally advanced non-small cell lung cancer (NSCLC), such as those in the N2-3, bulky N1, or T3-4 stage, remains controversial. Induction chemoradiotherapy (CRT) followed by surgery is one of the potential therapeutic options for locally advanced NSCLC, however, sometimes develops radiation pneumonitis (RP). Severe RP induce remarkable respiratory

disfunction, resulting in a delay of next treatment. The purpose of this study is to reveal the clinical features of NSCLC patients with RP after induction CRT. **Method:** The clinical data of NSCLC patients who underwent surgical resection of lung cancer after induction CRT between 1999 to 2017 at our institution were analyzed. We compared NSCLC patients who had RP with those who didn't, regarding patient's and therapeutic factors, and their prognosis. RP of our cases was defined as RP which occurred between the administration of induction CRT and 30 days after surgery. **Result:** A total of 172 data of NSCLC patients who underwent surgical resection of NSCLC of stage IIB–IIIC after induction CRT was collected. Among them, 34 NSCLC patients had RP, and 15 NSCLC patients received steroid therapy in 30 NSCLC patients, able to be assessed retrospectively. Non-smoking status was significantly associated with RP in univariate analysis (p = 0.006) and in multivariate analysis (odds ratio: 3.70, 95% confidence interval: 1.05-13.10, p = 0.042). Duration between completion of RT and surgery was longer in NSCLC patients with RP than those without RP (range [median]: 14-141 [45.5] vs 23-91 [40.0], p = 0.029). Adjuvant therapy was more frequently given to the patients without RP (p = 0.019). No significant difference in overall survival (OS) was observed between the 2 groups. **Conclusion:** Non-smoking status was the risk factor of RP of NSCLC patients who received induction CRT followed by surgery. The frequency of adjuvant therapy was more in NSCLC patients without RP than those with RP while OS was not different in the 2 groups.

Keywords: Radiation pneumonitis, induction CRT, NSCLC

EP1.01-19 UPDATED STATISTICS OF NEVER-SMOKER FEMALE LUNG CANCER IN KOREA

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Background: The clinical characteristics and prognostic factors of patients with lung cancer are expected to differ with respect to geographical differences from the past to the future. According to epidemiological, clinical and biological characteristics, lung cancer in never-smokers is a different disease from lung cancer in smokers. **Method:** To investigate the updated statistics of never-smoker female lung cancer in Korea, we analyzed data from the Korean Statistical Information Service and the Korea Central Cancer Registry in 2014. **Result:** According to the Korean Statistical Information Service, lung cancer deaths in the Korean population have been increasing in both men and women since the early 1980s. Among the total of 17,980 deaths due to lung cancer in 2017, men accounted for 13,272 and women accounted for 4,708. Of a total of 25,780 incidences of lung cancer in 2016, men accounted for 17,790 and women accounted for 7,990. Considering that the lung cancer incidence in Korean women was 3,592 in 2000, it increased by more than 2-fold in 16 years. However, after age-standardized adjustment, the lung cancer incidence has recently been stable in women. The smoking rate in Korean women was 6.0% in 2017, which has remained stable since 1998. The passive smoking rate in non-smoking women was 6.3% in 2017, which has been decreasing since 2005. Among the total of 6,460 Korean female patients with lung cancer in 2014, 745 patients were investigated from the Korea Central Cancer Registry. Most Korean women who developed lung cancer were never-smokers (87.5%). According to smoking status, female lung cancer characteristics such as symptoms, stage, histopathology, EGFR mutation positivity, and initial treatment modality were significantly different. Never-smoker female patients with lung cancer showed an increase in asymptomatic disease, stage I lung cancer, histology of adenocarcinoma, EGFR mutation positivity, and curative resection compared to ever-smoker female patients. **Conclusion:** The trends in epidemiology and clinical characteristics of lung cancer in Korea have changed over time. The never-smoker lung cancer incidence was estimated to increase in Korea. The reason for the stable incidence after the age adjustment could be growth in the Korean elderly population. Further research is needed to guide patient management, as well as future therapeutic strategies for lung cancer.

Keywords: never-smoker lung cancer, Korea, Updated Statistics

EP1.01-20 A SINGLE-ARM PHASE II TRIAL OF WEEKLY NANOPARTICLE ALBUMIN-BOUND PACLITAXEL MONOTHERAPY AFTER STANDARD THERAPY FOR ADVANCED NSCLC

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Background: Few studies have investigated the clinical efficacy of later-line treatments after standard therapy for advanced non-small cell lung cancer (NSCLC). Nanoparticle albumin-bound paclitaxel was one of the useful option for treatment of NSCLC. We conducted PII trial for evaluating the efficacy and safety of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) following standard therapy for advanced NSCLC. **Method:** The eligible patients having adequate organ functions with performance status 0–2 were enrolled after completing standard therapy. Standarad therapy defined as chemotherapy including docetaxel and pemetrexed in patients with non-squamous cell lung cancer or docetaxel in patients with squamous cell lung cancer. After the ICI nivolumab was approved by the Ministry of Health, Labor and Welfare of Japan in December 2015, standard therapy was defined as including ICIs treatment. They received weekly nab-paclitaxel 100 mg/m^2 intravenously on days 1, 8, and 15 every 3 weeks. The primary end point was objective response rate (ORR). Median progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were evaluated as secondary end points. **Result:** This trial was discontinued because of late accrual. Twenty-two patients were enrolled from April 2013 and February 2019. All patients recieved chemotherapy including docetaxel and Six patients recieved ICIs tretment. Median follow-up interval was 6.7 months. The total ORR was 22.7% [95% CI: 7.8–45.4] and disease control rate (DCR) was 81.8% [95% CI: 59.7–94.8]. Median PFS was 3.4 months [95% CI: 2.3–4.1] and median OS was 7.4 months [95% CI: 4.2–10.7]. Hematological AEs of Grade 3/4 included anemia (18%), leukopenia (18%), and neutropenia (32%), and the most frequent nonhematological AEs were fatigue (50%) and peripheral neuropathy (36.4%). Severe AEs related to treatment were observed in only one patient. **Conclusion:** Although all patients recieved chemotherapy including docetaxel before protocol tretment, our tral suggested nab-paclitaxel may be a safe and effective later-line chemotherapeutic option for previously treated advanced NSCLC after standard of chemotherapies based on other trials.

Keywords: Advanced non-small cell lung cancer, Nab-paclitaxel, Later-line setting

EP1.01-21 TIME ON TREATMENT OF FIRST-LINE PD-1 INHIBITOR MONOTHERAPY FOR METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS: REAL-WORLD EXPERIENCE DATA

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Background: Clinical trials have established the role of immune checkpoint inhibitors for metastatic NSCLC treatment, but real-world data are limited. We describe the first report of a prospective study on real-world time on treatment (rwTOT) for first-line (1L) anti-PD-1 monotherapy in metastatic NSCLC in a 2.3 million member public health provider in Israel. **Method:** Newly diagnosed stage IV NSCLC patients who initiated 1L anti-PD-1 therapy in 2017 were identified from the national cancer registry. rwTOT was defined as the length of time between first and last administration date of anti-PD-1 therapy. Patients were considered discontinued if they had a record of next line of therapy, or death, or whose last activity date was ≥120 days from the last administration date; others were censored. The Kaplan-Meier (KM) median and restricted mean (rMean) rwToT were estimated. Jun 2018 data cutoff was utilized to allow minimum 6 months follow-up. **Result:** A total of 63 patients initiated 1L anti-PD-1 monotherapy; of these, 59 were PD-L1 TPS≥50%, one was TPS<50% and 3 unknown. This cohort comprised of 97% pembrolizumab monotherapy, 65% males, median age=59 yrs, 76% ever smokers, 71% adenocarcinomas, 11% brain metastases, and 62%/14%/24% with 0-1/2-4/unknown ECOG status. The median rwToT was 4.6 (95% CI 2.8-12.8) mo and estimated rMean at 24 months using parametric

extrapolation was 10.9 mo (4.3-16.8). Patients with ECOG 0-1, n=39, had a median rwTOT of 10.6 mo (1.9-19.2). Time on treatment for anti-PD-1 monotherapy

	1L anti-PD-1 Monotherapy N=63	1L Pembroli-zumab Monotherapy N=61
N discontinued (%)	38 (60.3)	36 (59.0)
KM Median rwToT (95% CI)	4.6 (2.8-12.8)	5.0 (3.5-NE)
rMean rwToT @ 12 months (95% CI)	6.5 (5.3-7.7)	6.7 (5.4-7.9)
Parametric (extrapolat-ed) rMean rwToT @ 24 months (95% CI)	10.9 (4.3-16.8) [Gompertz]	11.2 (4.4-17.1) [Gompertz]
6 months on treatment rate, % (95% CI)	44.1 (31.6-55.9)	45.5 (32.7-57.5)
12 months on treatment rate, % (95% CI)	39.7 (27.3-51.9)	41.0 (28.3-53.4)

Conclusion: The results of this unselected real-world cohort of metastatic NSCLC patients treated with 1L anti PD-1 monotherapy show that rwTOT rates compare favorably with published data from clinical trials and other real-world studies.

Keywords: Non small cell lung cancer, Time on treatment, PD1 inhibitor treatment

EP1.01-22 LIQUID BIOPSY IN THE DETECTION OF EGFR ACTIVATING AND RESISTANCE MUTATIONS IN ADVANCED PULMONARY ADENOCARCINOMA

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Background: Approximately 30% of the advanced pulmonary adenocarcinoma (PADC) patients are found to be mutated with epidermal growth factor receptor (*EGFR*). Nearly 60% of *EGFR* mutated patients develop T790M resistance mutation against which third generation TKIs are available. Detection of T790M mutation is a challenge due to non availability of enough tumour tissues in patients receiving first-generation *EGFR*-TKI treatment. Liquid biopsies (cell- free DNA) are promising for detection of *EGFR* activating and resistance mutations. The current study focuses on detection of *EGFR* mutations in cell-free DNA from patients with histologically confirmed *EGFR* mutation status. **Method:** 50 PADC patients (22 males; 28 females with mean age 63 years) were studied for *EGFR* mutations. Out of them 40 were TKI naïve and 10 patients were treated with *EGFR*-TKIs. Follow up biopsy from TKI treated patients was not available for resistant mutation studies. Real-time PCR and Digital droplet PCR techniques were adopted for studying *EGFR* exon 19 (deletions), 20 (T790M) and 21 (L858R) mutations in tissue and plasma samples respectively. **Result:** Clinically all patients were in stage III-IV and 52% were never smokers. Out of 40 TKI naive cases, 20 cases were positive for *EGFR* activating mutations in tissue and 17 in plasma. Twenty cases were negative for *EGFR* mutations in both tissue and plasma. In 10 *EGFR*-TKI treated patients, founder activating mutation was still present in plasma of 7 cases and 3 of them also showed T790M resistance mutation. Two patients carrying this resistant mutation died subsequently. Remaining three TKI treated patients did not harbour even founder activating mutation in the plasma. **Conclusion:** We observed a concordance of 88% (44/50) between liquid biopsy and tumour tissue. Our study highlights role of liquid biopsy as an alternative for detecting *EGFR* activating and resistance mutations in advanced PADC. *EGFR* mutation analysis in liquid biopsy can be helpful in those patients where the tissue biopsy is not possible.

Keywords: Cell-Free DNA, T790M mutation, NSCLC

EP1.01-23 SRC INHIBITION WITH BOSUTINIB AS A POTENTIAL APPROACH FOR RESTORING PEMETREXED RESPONSIVENESS

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Background: One of the principle approaches in malignant mesothelioma andnon-squamousnon-smallcelllung cancer management is cellular folate-dependentpathways inhibition with pemetrexed(PEM) combined with platinum-basedchemotherapy. Despite the promising activity of PEM, drug resistance demands new approaches allowing for abolishing resistance and better outcomes. In lung cancer, there is an association between*in vitro*PEMresistance, SRC over-expression, and thymidylatesynthase(TS) overexpression. **Method:** We treated lung cancer cell line (A549) and mesothelioma cell line (MSTO) with PEM and bosutinib (a small molecule tyrosine kinase inhibitor (TKI)) which is also an SCR inhibitor. Increasing dose regimen was adopted with these drugs. Then we conducted cellviability assays (MTT tetrazolium), detection of SRC andTS expression by western blot and apoptotic assays (AnnexinV) for drug effect evaluation. **Result:** Data showed that sequential treatment with bosutinib then PEM lowered the IC_{50} of PEM of both cell lines as indicated by cellviability and apoptosis assays. There was a 9% increase in apoptosis with combination regimen compared to PEM only regimen. Nevertheless, a decrease in TS expression was found, with correlation to the decrease in SRC expression. **Conclusion:** Combining bosutinib's SCR inhibition to PEM activity may improve the latter's therapeutic response due to synergism. Further in vivo evaluation for these results are needed to better understand these effects on tumor response

Keywords: lung cancer, bosutinib, thymidylate synthase, SRC, inhibition, response, overexpression

EP1.01-24 LUNG ADENOCARCINOMA: MUTATIONAL PROFILE IN EVER SMOKERS AND NON-SMOKERS PATIENTS

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Background: Lung cancer occurring in never-smokers had become a distinct entity. This study aims to evaluate the mutational profile in ever smokers and non-smokers patients with pulmonary adenocarcinoma. **Method:** Retrospective analysis (Oct-2016 to Aug-2017) of patients diagnosed with pulmonary adenocarcinoma in our pulmonology department. Next generation sequencing (NGS) was used to identify different mutations and translocations. Pathological variants of genes and variants of uncertain clinical significance were included. **Result:** 60 patients were enrolled in this study: 18 (30%) non-smokers and 42 (70%) ever smokers. In 72.2% of non-smokers and 57.1% of ever smokers were identified at least one mutation. Despite this, ever smokers had an overall higher frequency of mutations (72.6% vs 27.4%) because many patients had concomitant mutations. Although not statistically significant, ever smokers had more mutations that are variants of uncertain clinical significance (40% vs 23.5%; p=0,227) Table 1. Frequency of mutations

	Non-smoker		Ever smokers	
Mutated gene	Patho-logical variants (n)	Variants of uncertain clinical signifi-cance (n)	Patho-logical variants (n)	Variants of uncertain clinical signifi-cance (n)
KRAS	3	0	18	0
EGFR	5	0	4	5
ERBB4	0	0	0	1
MET	0	1	0	3
PTEN	0	0	1	1
HER2	1	2	0	7
PI3KCA	0	1	1	1
BRAF	0	0	1	0
ROS	1	0	1	0
ALK	3	0	1	0
Total	13	4	27	18

Conclusion: Although not statistically significant, smokers and non-smokers appear to have a different mutational profile. Smokers have a higher rate of concomitant mutations, although some of them are variants of uncertain clinical significance. NGS will help to increase knowledge about the mutational profile in these patients.

Keywords: Lung cancer, NGS

EP1.01-25 AN INTERACTIVE INTERFACE FOR PREDICTION OF ANTI-PD-1 EFFICACY IN LUNG CANCER PATIENTS

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Background: The past decade has seen a new field of promising treatments for non-small cell lung cancer patients (NSCLC) with immune checkpoint inhibitors (ICI). Medicine community embarks on a biomarker race to identify the one-quarter of responders and potential hyper-progressors. The assessment of PD-L1 tumor expression by IHC is used to select responder patients and is considered as the gold standard biomarker in many studies but it does not predict the absence of anti-PD-1 efficacy. Recent review from Keenan TE *et al.* summaries all potential studied markers in literature as intratumoral T cell infiltration, tumor neoantigens or else mismatch repair deficiency. Despite this abundance of potential markers, recommendations only rely on high PD-L1 expression and more recently on high tumor mutational burden (TMB). In this study, we propose estimations of response probability based on the different data that may be available for clinicians according their molecular biology and material means. **Method:** Based on a cohort of 100 patients with advanced NSCLC treated with nivolumab in second line of treatment, we developed an algorithm enabling the calculation of the probability of survival without progression at 6 or 12 months when treated with ICI. Using Cox proportional hazards multiple regression, we adjusted these three stages of information to estimate the probability of response of a patient based on the type of available data: only clinical data and/or exome analysis and/or RNA sequencing. Stability and predictive ability of these models where evaluated internally and externally through bootstrap procedure. **Result:** Among the 100 patients, 90 had both somatic and constitutional exome sequencings available and 50 had an RNA sequencing. We built a main model based on clinical and pathological data easily available for clinicians. As mandatory criteria, the age, sex, performance status, tumor histology, routine mutational status and PD-L1 immunohistochimical expression were first included in the predictive model. In addition, RECIST response to previous chemotherapy line and antibiotics usage were added into the initial model as they were described significantly associated with respectively good and poor survival to ICI in previous publications. Additional criterion were obtained thanks to extensive DNA tumor analysis such as TMB, mutations in DNA repair pathways, the number of large deletions and intratumoral TCR clones. A third stage of data was added with CD8A and CD274 RNA expressions obtained by RNA sequencing. Thus, several models are available for clinicians to estimate the probability of survival without progression at 6 or 12 months for their patients according to the type of available data. An interactive on-line interface based on R Shiny enables the questioning of all these models for further predictions. **Conclusion:** Altogether, these data provide validated and more complex biomarkers according to the type of available data to predict probability of survival without progression to anti-PD-1 in patients with advanced NLCSC. Further predictions can be obtained thanks to a shiny R free and interactive interface available on-line.

Keywords: immune checkpoint inhibitor, NSCLC, predictive biomarer

EP1.01-26 NON-SMALL CELLULAR PULMON CANCER ALK POSITIVE IN PEDIATRICS

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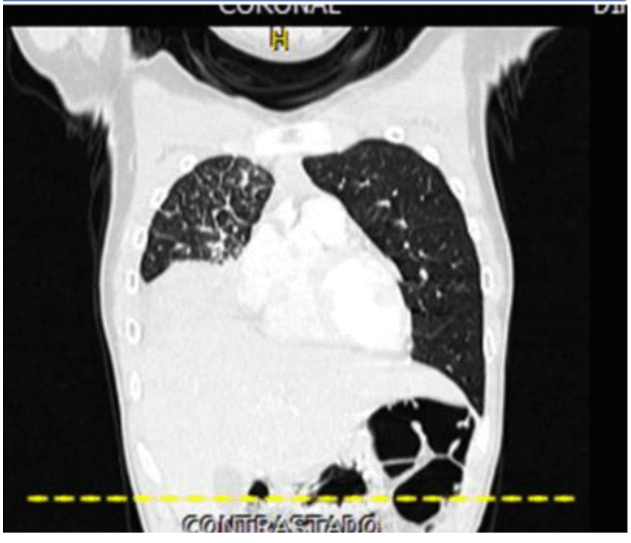
Background: For 2018 the American Cáncer Society reports 234.030 new cases of lung cáncer, 154.050 people will die from this cause, the average age of diagnosis is approximately 70 years old. Lung cáncer in children and adolescents is extremely rare, in Colombia the incidence in children under 18 is less than 1%. The 85% of lung cancers are classified as non-small cell lung cáncer, there are recent advances in treatment with Anaplastic lymphoma kinase (ALK) inhibitors Crizotinib, Alectinib, Brigatinib for non-small cell lung cáncer ALK positive. This case report is from a 14-year-old adolescent patient treated in our institution with an ALK inhibitor. ALK disease is 3% to 5% of all non-cell lung cancers small adenocarcinoma type, more frequent in young people, women, nonsmokers, and with advanced disease. **Method:** Case report and literature review. **Result:** Male patient 14 years with respiratory symptoms productive cough. Tomography computed tomography: injury to the middle lobe and right lower lobe, biopsy: Adenocarcinoma poorly differentiated, immunohistochemistry: positive for cytokeratin 7, napsin-a, MUC-1, CK1E1 / AE3 positive and transcription factor -1 (TTF-1) and cytokeratin 20 negative, EGFR-KRAS wild type, ALK (EML-4 with clone D5F3) positive. Treatment was started with Crizotinib 250mg every 12 hours, obtaining partial response and with PFS of 36 months, gastrointestinal toxicity, hematological I grade. **Conclusion:** We report the experience of a case with excellent tolerability to an inhibitor of ALK, and its clinical benefit, (partial response and stable disease). Patients under 18 years, are excluded in most clinical trials and can benefit from treatment, increase in progression-free survival, overall survival, avoiding the toxicity of chemotherapy.

Figura 1. TAC de Tórax Contrastado .29 Septiembre 2016



EP1.01-27 PRELIMINARY STUDY ON IMMUNE CHECKPOINT AND EMT FEATURE OF CTCS IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Non-small cell lung cancer (NSCLC) is the most common malignant tumor with high morbidity and mortality. Platinum-containing chemotherapy is the standard first-line chemotherapy regimen for patients with advanced NSCLC. However, 65-75% patients would progress after a few weeks of chemotherapy treatment. The programmed cell death 1 (PD-1)/PD-1 ligand 1(PD-L1) has become the rising star of cancer research only because their development of PD-1/PD-L1 inhibitors has bring cancer patient new hope and changed the landscape of NSCLC therapy. Nevertheless, the high degree of non-responders demonstrates that we are still far from completely understanding the events underlying tumor immune resistance. Circulating tumor cells (CTCs), as an accessible source of tumor for biologic characterization that can be serially obtained with minimally invasive procedure. Studies have shown that presence of PD-L1 on CTC might predict resistance to anti-PD-1 therapy, and PD-L1 positive CTCs usually present an elongated morphology, which was associated with epithelia-mesenchymal transition (EMT). Those research provided evidence that CTC might be a promising object to predict whether the patient could be benefit from the second-line checkpoint inhibitor treatment. In this prospective cohort study, we aimed to describe the molecular background of CTCs from patients with disease progress after first-line chemotherapy. **Method:** We consecutive enroll patients who have been treated with platinum-containing chemotherapy in our hospital from May 2018 to the present, and have been assessed for disease progression (PD) by RECIST version 1.1. 6.5ml of peripheral blood was collected before further treatment. Then we enriched the CTCs and performed in situ co-detection of PD-L1 and EMT marker (Vimentin) using SE-iFISH technology. **Result:** To date we have recruited 13 eligible patients. Detectable CTCs counts range from 1 to 22 in 6.5ml blood. Among them, 4 samples presented PD-L1 positive, 4 samples presented Vimentin positive. Only 1 sample has co-expression of PD-L1 and Vimentin. **Conclusion:** Above results proved that SE-iFISH method could be used for CTC enrichment and detection. Next step, we will wait for those patients' checkpoint inhibitor treatment outcome, analysis the correlation between PD-L1 and Vimentin co-expression and patient response. At the same time, we will continue to include cases, collect CTC samples and evaluate the expression of PD-L1 and Vimentin on CTCs.

Keywords: NSCLC, PD-L1, CTC

EP1.01-28 REAL WORLD USE OF AFATINIB IN NSCLC EGFRM+ PATIENTS OUTSIDE CLINICAL TRIALS: A FAETT EXPERIENCE

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Background: Epidermal growth factor receptor (EGFR) tyrosine kynase inhibitors (TKIs) remain the standard of care as first-line therapy for patients with non-small cell lung cancer (NSCLC) harboring an EGFR mutation. These drugs have been associated with improvements in both clinical outcomes and tolerability, compared with platinum-based chemotherapy. Three generations of TKIs are currently approved in the first-line setting, though only first (erlotinib and gefitinib) and second generation blockers (mainly afatinib, but also dacomitinib) have been extensively used in clinical practice nowadays. **Method:** We reviewed 105 patients with NSCLC with advanced or recurrent stages that harbour EGFR mutations, treated with afatinib as first´line therapy among the academic hospitals adhered to the FAETT network. The information of clinical, pathological and treatment characteristics of the patients was collected retrospectively and the statistical analysis was performed with the software SPSS software version 21.0, considering the statistical significance if p-value <0.05. **Result:** The characteristics of the patients are reflected in Table 1. The mean age at the beginning of treatment with afatinib was 61 (37-81) years. 48.6% of the patients were older than 65 years. 27.6% were older than 70 years. With a median follow-up of 15 months (0-82), the median progression-free survival was 14 months (10.74-17.26) Fig 1, and the median overall survival was 31 months (24.00) -37.99). The median PFS and OS among patients older than 65 years, and even those older than 70 years, is not statistically significant (14 vs 13 and 30 vs 31 months, repectively. P-value:0,83 and 0,78 On the other hand, the toxicities between both groups remain similar, with diarrhea and skin rash standing out as the most frequent, as reflected in the data published to date. Table 2

Table1. Baseline characteristics

Characteristic	<65 yrs	>/ = 65 yrs	Total	p-value
Patients (n)			**105**	
Age (years)				
Median Range			61,0 (37-81)	
Sex (n%)				0,207
Male	21	15	36 (34,3)	
Female	33	36	69 (65,7)	
Smoking status (n%)				0,675
Never-smoker	29	30	59 (56,2)	
Current	22	18	40 (38,1)	
Former smoker	2	3	5 (4,8)	
Unknown	1	0	1 (1,0)	
ECOG				0,954
0-1	47	45	92 (87,6)	
2	6	5	11 (10,5)	
3	1	1	2 (1,9)	
Co-morbidity				**0,007**
Yes	18	30	48 (45,7)	
No	36	21	57 (54,3)	
EGFR mutation status (n%)				0,843
Del19	39	34	73 (69,5)	
L858R	7	7	14 (13,3)	
Uncommon	6	9	15 (14,3)	
Double mut	2	1	3 (2,9)	
Starting daily dose n(%)				**0,047**
40 mg	49	39	88 (83,8)	
30 mg	5	12	17 (16,2)	
Dose reduction (n%)				0,132
Yes	27	32	59 (56,2)	
No	27	19	46 (43,8)	
Treatment discontinuation Toxicity (yes/non)	14/37	20/29	34 (32,4)	0,400
Progression free survival (month)	13 (7,46-18,53)	14 (11,74-16,25)	14 (10,74-17,25)	0,83
Overall survival (month)	31 (23,87-38,13)	30 (16,98-43,02)	31 (24,00-37,99)	0,78

Table 2: Most common treatment-related adverse events

Adverse events (n%)	<65 yrs	>/ = 65 yrs	Total	P value
Diarrhea	46	45	91 (86,7%)	0,433
Rash or acne	37	32	69 (65,7%)	0,520
ALT AST increase	2	1	3 (2,9%)	0,529
Pyrexia	0	2	2 (1,9 %)	0,234
Pneumonitis	0	2	2 (1,9%)	0,111

Conclusion: This retrospective study shows no differences in the use of afatinib among older patients in terms of both efficacy and tolerability.

Keywords: Older EGFRm+ NSCLC

EP1.01-29 LUNG ADENOCARCINOMA HARBORING EGFR-19DEL/C797S/T790M TRIPLE MUTATIONS RESPONDS TO BRIGATINIB AND ANTI-EGFR ANTIBODY COMBINATION THERAPY

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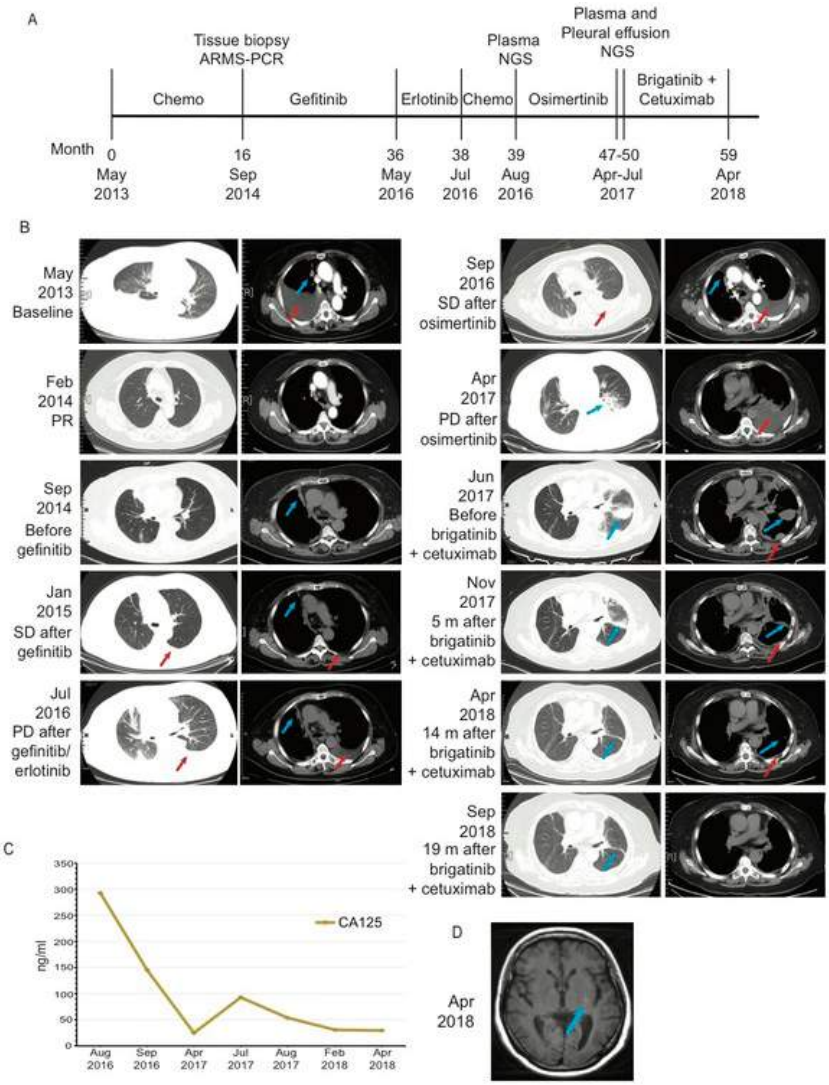
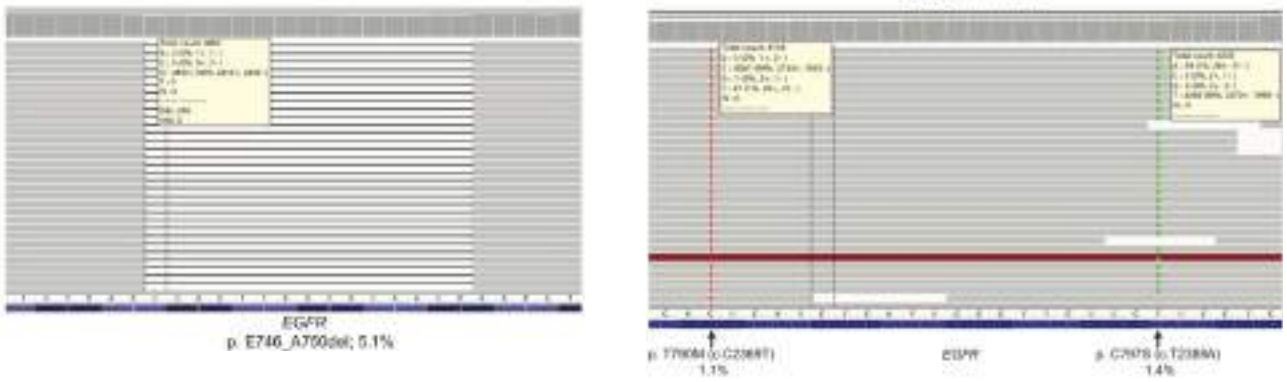
Background: Treatment of non-small-cell lung cancers (NSCLCs) harboring primary EGFR oncogenic mutations such as L858R and exon 19 deletion delE746_A750 (Del-19) using gefitinib/erlotinib ultimately fails due to the emergence of T790M mutation. Though Osimertinib is effective in overcoming EGFR T790M by targeting Cys797 via covalent bonding, their efficacy is again limited due to the emergence of C797S mutation. **Method:** The study showed one patient with advanced NSCLC treated with targeted therapy, who developed acquired drug resistance to 1st to 3rd generation of EGFR-TKIs. The medical records and imaging studies of the patient were retrospectively reviewed under the approval of the institutional review board and the waiver the informed consent. The study was conducted with agreement of the patient herself. **Result:** This is one of the earliest report which describe cis mutations of T790 and C797s as the resistance mechanism observed in circulating tumor DNA (ctDNA) from a patient with initial response followed by progression on osimertinib and sucesesfuly treated with Brigatinib + Erbitux.





Conclusion: This case report,as to our knoweledge, is the first clinical evidence of efficacy using a combination of brigatinib and cetuximab to target concomitant *EGFR*-T790M and C797S *in cis*.

Keywords: EGFR, T790M, C797S

EP1.01-30 CLINICO-PATHOLOGICAL PROFILE OF ADENOCARCINOMA OF THE LUNG – A PROSPECTIVE STUDY IN A NEPALESE POPULATION

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Background: Lung cancer represents the most common cause of cancer related mortality in developing countries including Nepal where patients (pts) often present in advanced stage. The purpose of this study was to determine the incidence and clinico-pathological profile of pts with adenocarcinoma of the lung (ACL) presented to a tertiary care center of Nepal. **Method:** An IRB approved prospective study was conducted in pts with ACL over a period of 15 months from April 2017 to July 2018 at a tertiary care center, Bir Hospital, Kathmandu. Demographic data, history of smoking, histological type, presence and type of epidermal growth factor receptor (EGFR) mutations were studied. EGFR-analysis was performed using TheraScreen EGFR mutation kit. **Result:** A total of 253 pts were diagnosed with lung cancer in the period. Of the 83 (33%) diagnosed with ACL, 45 (54%) were males and 38 (46%) females. The mean age at diagnosis was 59.4 years, and 74 (89%) were in stage III/IV. Forty eight (58%) pts were smoker of whom 30 (63%) pts had less than 10 pack years. Sixty one percent (61%) were illiterate. Eighteen (22%) pts had wrongly received anti-tuberculosis treatment before the diagnosis of ACL was made. All ACL pts were tested for EGFR-mutations which were found in 24 (29%) pts, the most common mutation being exon 21 (L858R) (42%) followed by exon 19 deletion (38%). Exon 18 and exon 20 (T790M) mutation were found in 2 pts (8%) each. One pt had dual mutation in exon 20 (T790M) and exon 21 (L858R). **Conclusion:** The frequency of EGFR-mutations in ACL in this Nepalese cohort was lower than in Eastern Asian studies, but higher than in western population. EGFR mutation testing of ACL has to be encouraged in developing countries like Nepal as presence of these mutations predict durable response to oral tyrosine kinase inhibitors. Interestingly, lung cancer is often mistreated as tuberculosis leading to delay in diagnosis and treatment.

Keywords: Adenocarcinoma Lung, EGFR mutation, Nepal

EP1.01-31 PET CT RADIOGENOMIC DEPICTION IN PDL1 EXPRESSION IN LUNG CANCER IN INDIAN POPULATION

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Background: Non small cell lung cancer (NSCLC) represents an area of paramount importance wherein patients undergo testing for targetable genetic alterations. Association between the imaging and molecular phenotypes needs to be explored highlighting the growing importance of classifications based on radio genomic characterization. This study was conducted to evaluate the correlations between the radiologic and molecular phenotypes in patients with NSCLC. **Method:** 211 patients with lung cancers during the study period of one year from October 2017 till November 2018 in our institution and undergoing both radiologic (PET-CT) and molecular investigations [Programmed death ligand 1 (PDL1)] were included in the study. Both quantitative and qualitative CT findings were evaluated and correlated with the molecular findings. Quantitative data included SUV max obtained from PET component of CT and maximum diameter of lesion according to the RECIST criteria. Qualitative data recorded included location, pleural tail, pleural effusion, pericardial effusion, opacity, margins, calcifications, obstructive changes, pleural nodules, lung nodules, invasion, air bronchogram, emphysema, pulmonary fibrosis, mediastinal lymph nodes and distant metastasis. Statistical analysis was performed to evaluate the association of the qualitative features with the molecular expression. Receiver operating characteristic curves (ROC) were drawn and the corresponding area under curve (AUC) was calculated. *P*-values <0.05 were considered significant. **Result:** PDL1 expression was observed in 69 patients and 13/14 females and 29/34 non-smokers showed the expression (p-value <0.0001). A total of 1, 19, 22 and 27 patients had <1%, 1-10%, 10-50% and >50% PDL1 expression. SUV max was 11.7±3.7 in the group with PDL1 expression. Correlations were observed between PDL1 expression and location (p-value <0.0001), pleural tail (p-value <0.0001), pleural effusion (p-value <0.0001), obstructive changes (p-value 0.001), pleural nodule (p-value 0.001), lung nodules (p-value <0.0001), air bronchogram (p-value <0.0001), emphysema (p-value <0.0001), mediastinal nodes (p-value <0.0001) and distant metastasis (p-value <0.0001). PDL1 expression correlated with pulmonary fibrosis (p-value 0.001). In ROC curves, in case of PDL1 expression, the AUC was 0.728 on the basis of length. **Conclusion:** The correlation between CT findings and molecular findings highlights the importance of newer radio genomic based characterization for patients with NSCLC for better diagnostic and prognostic approaches.

Keywords: PDL1 expression, Non small cell lung cancer, PET-CT

EP1.01-32 IMPROVING THE PROGNOSIS OF NON-SMALL CELL LUNG CANCER AFTER THE APPROVAL OF IMMUNE CHECKPOINT INHIBITORS: A RETROSPECTIVE ANALYSIS

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Background: Anti-programmed death-1/programmed death-ligand-1 (PD-1/PD-L1) blockade represents a revolutionary breakthrough in the treatment of advanced non-small-cell lung cancer (NSCLC). However, it remains unclear whether the immunotherapy for PD-1 axis are associated with overall survival (OS) in real world patients. **Method:** We retrospectively analyzed consecutive 246 patients with stage IIIB or IV NSCLC who underwent at least 1 regimen of chemotherapy. Patients who have EGFR mutations, ALK/ROS1 rearrangements, or received curative thoracic radiotherapy were excluded. Besides, patients administered any immune checkpoint inhibitors in clinical trials were also excluded. Treatment outcomes were compared between patients who started chemotherapy from January 2012 to December 2014 (cohort A; n=135) and those who started it from January 2016 to December 2017 (cohort B; n=111). Baseline characteristics were balanced using propensity score matching, including variables such as age, sex, performance status (PS), histology, clinical stage, bone metastases, central nervous system (CNS) metastases, liver metastases, pulmonary metastases, and pleural dissemination. **Result:** Median OS was 11.4months in cohort A and 16.6mo in cohort B (HR 0.68, 95%CI 0.50-0.93, P=0.016). In 111 propensity-score matching pairs, median OS was 11.2months in cohort A and 16.6months in cohort B (HR 0.68, 95%CI 0.49-0.94, P=0.021), and the 12-month OS rate was 48.7% in cohort A versus 59.9% in cohort B, respectively. PD-1 axis inhibitors were received 13.5% in cohort A and 64.9% in cohort B. Forest plot for the propensity-matched patient analysis demonstrated a significantly better outcome in cohort B, for patients with PS 0 to 1, smokers, number of metastases ≤1, no bone metastases, no CNS metastases, no liver metastases, no pulmonary metastases, pleural metastases, and squamous histology. **Conclusion:** This result indicates the appearance of immunity checkpoint inhibitors improved the prognosis of driver-mutation negative NSCLC in real world.

Keywords: Non-Small Cell Lung Cancer, pd-1, Immune Checkpoint Inhibitors

EP1.01-33 EXTRACELLULAR MEDIUM OF SENESCENT LUNG CANCER CELLS PROMOTED TUMOR PROGRESSION THROUGH ACTIVATION OF YAP AND PD-L1

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Background: Cellular senescence has been perceived as a barrier against carcinogenesis. However, the senescence-associated secretory phenotype (SASP) of senescent cells can promote tumorigenesis. Our previous researches revealed that the secretary cytokines from senescent cancer cells induced by bleomycin promoted migration and invasion of associated non-senescent cells, while the impact of hydrogen peroxide (H_2O_2)-induced senescent epithelial originated tumor cells on associated non-senescent tumor cells was rarely reported and the underlying mechanisms has not been discerned. **Method:** Senescence was induced in

human lung adenocarcinoma cancer cells (A549 and NCI-H1299) by Oxidative DNA damage chemical, hydrogen peroxide (H_2O_2), and verified by senescence-associated β-galactosidase (SA-β gal) staining and flow cytometry. A549 and NCI-H1299 cells were treated with condition medium of senescent/non-senescent A549 and NCI-H1299 (senescent vs. non-senescent group), and their protumorigenic roles were tested by cell viability assay, colony formation assay and cell invasion and migration assay. Label-free quantitative proteomics was performed to detect the expression of cytokines in culture medium of senescent/non-senescent A549 and NCI-H1299. To determine whether the YAP and programmed cell death ligand 1 (PD-L1) were involved in the tumorigenic roles, the protein and mRNA expression levels of PD-L1, YAP, CYR61, c-Myc and CTGF in A549 and NCI-H1299 were assessed by Western blot (WB) and quantitative reverse transcriptase PCR (qRT-PCR). To characterize senescent cells in lung cancer patients, we performed SA-β-Gal staining using fresh-frozen tissue sections from 20 normal lung samples and 40 lung adenocarcinoma cancer samples. To elucidate the relationship between YAP and PD-L1 in the same tumor tissue, immunohistochemistry detected the expression of both YAP and PD-L1. **Result:** A549 and NCI-H1299 could be steadily induced senescence with an induced rate of more than 90% at a dose of 200uM and 100uM of H_2O_2, respectively. The proliferation and migration ability of cells was significantly higher in senescent than in non-senescent group. Senescent condition medium significantly promoted cell proliferation and migration in both PD-L1 high-expressing NCI-H1299 and PD-L1 low-expressing A549. However, the presence of senescent condition medium increased the proliferation and invasion of co-cultured cells was significantly less in PD-L1 low-expression A549 than that seen in PD-L1 high-expressing NCI-1299. The secrete proteins identified following H_2O_2 treatment included extracellular matrix protein, inflammatory cytokines, growth factors, chemokines etc. Further mechanistic investigations revealed that mRNA level of target genes of YAP (CYR61, c-Myc, CTGF) and PD-L1 were increased after H_2O_2 treatment and their expression were positively correlated. Besides, in senescent lung adenocarcinoma cancer tissue, PD-L1 positive lung adenocarcinoma cancer samples showed significantly higher nuclear YAP positive ratios compared to PD-L1 negative samples. **Conclusion:** H_2O_2 successfully induced senescence on epithelial tumor cells A549 and NCI-H1299, whose secretary phenotype significantly promoted the proliferation and invasion of associated PD-L1 high-expressing non-senescent lung adenocarcinoma cancer cells compared with PD-L1 low-expressing NSCLC cells *in vitro*. PD-L1 and nuclear YAP are co-expressed in senescent lung adenocarcinoma cancer tissues, enlightening a therapeutic target of the combination of Hippo/YAP signaling pathway with immune checkpoint PD-L1/PD-1 inhibitors.

EP1.01-34 A RETROSPECTIVE STUDY OF THE PATTERN OF LYMPH NODE METASTASIS IN SUPERIOR SULCUS NON-SMALL-CELL LUNG CANCERS

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Background: By comparing the probability of lymph node metastasis between superior sulcus non–small-cell lung cancers (SS NSCLC) and non-SS NSCLC located in the pulmonary apex, we hope to find out whether there is a unique pattern of lymph node metastasis in SS NSCLC. **Method:** During 2008-2014, a retrospective study was performed on NSCLC patients with lesions located in the pulmonary apex. Patients with lesions invading the peripheral tissue structure were enrolled in the SS NSCLC group, while those without lesions invading the peripheral structure were enrolled in the non-SS NSCLC group. A total of 65 patients in the SS NSCLC group received surgery, and all patients in the non-SS NSCLC group received surgery. According to postoperative pathology and enhanced CT before treatment, the location and number of lymph node metastasis were determined. The chi-square test was used to statistically analyze the difference in the probability of N1, N2 and distant metastasis (DM) between the two groups. **Result:** Compared with the non-SS NSCLC group, the T staging of SS NSCLC group was advanced, but the rate of N1 lymph node metastasis was similar. However, the N2 lymph node metastasis rate of the SS NSCLC was significantly lower than that of the non-SS NSCLC, which was 25.3% and 39.8% respectively (P=0.048). Distant metastasis rates were similar at lower levels in both groups,which was 9.3% and 6.4% respectively (P=0.471).

Table Basic information and results

		SS NSCLC	NOn-SS NSCLC	P value	Chi-square
Gender	male	67	65		
	female	8	28		
Median age		61(37-87)	62(42-82)		
	ad	27	67		
Pathology	squ	32	16		
	others	16	10		
T stage	T3+T4	75(100%)	3(3.2%)	0.000*	156.328
N1		25(33.3%)	33(35.8%)	0.771	0.085
N2		19(25.3%)	37(39.8%)	0.048*	3.902
DM		7(9.3%)	6(6.4%)	0.471	0.519

Ad:adenocarcinoma squ: squamous carcinoma DM:distant metastasis * P<0.05. There were significant differences between the two groups.

Conclusion: Although T staging was very late in SS NSCLC, the N2 lymph node metastasis rate and distant metastasis rate did not increase correspondingly. Therefore, enhanced local treatment, such as neoadjuvant concurrent chemoradiotherapy combined with surgery, may lead to better survival benefits.

Keywords: superior sulcus, NSCLC, Lymph node metastasis

EP1.01-35 CONCURRENT USE OF LOW DOSE ASPIRIN AND VITAMIN D IN ALK, ROS AND EGFR MUTANT NSCLC: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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Background: Tyrosine kinase inhibitors (TKI) are the backbone therapy for EGFR, ALK and ROS positive (pos) non-small cell lung cancer (NSCLC). Pre-clinical data suggest that low vitamin D level facilitates the growth of mutant EGFR NSCLC through Vitamin D receptor (VDR). VDR is highly expressed in EGFR lung cancer cells, and its interaction with activated 1,25 vitamin D3 (1,25D3) promotes epithelial differentiation and apoptosis while inhibiting cellular proliferation and angiogenesis. Thus vitamin D3 supplementation may potentially add anti-cancer activity to conventional therapy in this population. On the other hand, murine models have shown that prolonged use of aspirin reduces the incidence of distant metastases. It is postulated that biosynthesis of prostaglandins generate a permissive intravascular metastatic niche, through platelet aggregation and endothelial activation. Recent meta-analysis published by Feng et al. analyzed seventeen studies and reported statistically significant reduction in risk of lung cancer by 8% when circulating 25-VD is at 10 nmol/L, this benefit was seen in both Caucasian and Asian population. To our knowledge, there have been no studies looking at influence of concurrent vitamin D or aspirin intake on outcomes in ALK, ROS and EGFR pos NSCLC treated with tyrosine kinase inhibitors. We performed a retrospective single institution analysis to study this association. **Method:** Patients (pts) with ALK, ROS EGFR pos NSCLC treated with first line TKI from January 2014 to June 2017 were included. Information on concurrent use and doses of aspirin and vitamin D supplements were studied. Patients were dichotomized based on use of these individual supportive medications. Two sample t-test was used to compare mean PFS and chi-square test to compare proportions of disease control rate (DCR) at 3 months between groups. **Result:** 74 patients were included. PFS in Vitamin D supplementation (n=41, 55%) group was 11 months compared to 10.2 m in those not on Vitamin D (p = 0.21, CI 1.9). For those on aspirin (n=23, 35%), mean PFS was 16m vs 12.5 m (p = 0.7213; 95% CI -5.5812 to 3.8812). DCR for aspirin use was 50% vs 65% (p = 0.1796) and for vitamin D 48.6% vs 43.7% (p= 0.6989). **Conclusion:** Our study did not show any differences in PFS or DCR in EGFR, ROS and ALK positive NSCLC patients who were concurrently taking vitamin D or aspirin compared with those who

were not. Our study was small and was not powered to pick up any significant differences. Given the strong pre-clinical background, further prospective studies would be interesting to evaluate the synergistic benefit of vitamin D and aspirin with concurrent TKI use.

Keywords: vitamin D, Epidermal Growth Factor Receptor (EGFR), Non Small Cell Lung Cancer (NSCLC)

EP1.01-36 QUALITY OF LIFE IN ADVANCED LUNG CANCER PATIENTS IN A DUTCH POPULATION

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Background: In advanced lung cancer chemotherapy is associated with a statistically significant improvement in overall survival (OS) compared to best-supportive care (BSC) alone, by improving survival with 9% at 12 months and median survival by 1.5 months. However, discussion remains whether adverse events of chemotherapy outweigh the relatively modest increase in survival. We aimed to investigate the quality of life (QoL) of patients with uncurable lung cancer treated with systemic therapy or best-supportive care (BSC) alone. **Method:** The European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ-C30) and the EORTC QLQ-LC13 were used to assess patients reported outcome measures (PROMs) at baseline, 3, 6 and 12 months in 235 patients with stage IIIb and IV NSCLC or SCLC diagnosed and treated between 2013 and 2017 in 4 large teaching hospitals in the Netherlands. Comparison between systemic therapy and BSC alone were assessed by using change in SS14 score from inclusion to 12 months. The analysis method used for this correlated longitudinal data was linear mixed modelling. **Result:** Out of 58 of 235 patients who received no systemic therapy, the vast majority did not receive any treatment because of patients refusal of treatment (58.6%), followed by poor performance status (20.7%), comorbidities (5.2%) and rapid deterioration (15.5%). Systemically treated patients had a significantly prolonged OS compared to BSC (median OS of 691 vs 219 days ($p<0.0001$)) and a higher number of patients in the best supportive care arm died during the observation period (62.1% vs 44.6%, $p=0.02$). Over time there was no significant time-treatment interaction in global health, functional or symptom scores between systemic therapy and BSC ($p> 0.05$). **Conclusion:** Although, systemic therapy in advanced lung cancer patients led to significantly longer OS compared to best supportive care, the quality of life decreased in both groups non-differently over time.

Keywords: Best supportive care, systemic therapy, Quality of life

EP1.01-37 PLATINUM-BASED CHEMOTHERAPY (CT) RECHALLENGE IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS (P): A SINGLE INSTITUTION EXPERIENCE

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Background: No phase III trials have been carried out to prove the value of a platinum-doublet rechallenge in p with NSCLC. Currently, the availability of different effective drugs makes the platinum-based salvage therapy unusual. Moreover, the potential cumulative toxicity related to cisplatin or carboplatin can be an issue. However, retreatment with platinum-based CT could be hypothetically proposed for p with a long time to progression (TTP) from the last platinum treatment, in p with a good performance status, who may be symptomatic and with no formal contraindication to receive such treatment We have retrospectively reviewed experience at our institution of platinum-based chemotherapy rechallenge in stage III and IV NSCLC p **Method:** A cohort of 376 p with stage III and IV NSCLC treated with first-line platinum doublets from January 2012 to December 2017 were included. We extracted information on clinical and molecular characteristics, as well as treatment details. Time to progression was evaluated by Kaplan-Meier curves and groups were compared using Log-rank test. **Result:** Overall, 57 p were rechallenged with platinum-based CT (group A). Median age was 57 years (51.5-65) for rechallenged p versus (vs) 62 (56.2-68.8) for the entire cohort (group B)[p=0.001]. Group A include more p with stage III p(54.4% vs. 30.7%; p=0.001), as well as more p with better ECOG Performance Status (PS) (PS 0 70.2% vs. 44.5%; p=0.001). No differences in gender, smoking status, histology and comorbidities were observed between both groups (20.7% and 29.8% were women and 38.6% and 53.9% were smokers in groups A and B, respectively). No differences in molecular profile (EGFR, ALK, ROS1, KRAS, BRAF) were observed. The most common platinum doublet administered in first line setting was cisplatin plus pemetrexed. Group A received more frequently carboplatin plus gemcitabine or vinorelbine. Disease Control Rate (DCR) was 57.9% in p included in group A. No differences in DCR were observed in first line between both groups. Time to progression or death was 9.6 m for gropuo B(5-18.1) vs 20.5 m (14.6-37.3) p <0,001 for p in group A. **Conclusion:** Rechallenge with platinum-based CT doublets could represent an option for NSCLC p with good PS and no contraindications for such therapy.

Keywords: advanced NSCLC, platinum doublets, rechallenge

EP1.01-38 REAL WORLD EXPERIENCE OF 1ST LINE PEMBROLIZUMAB IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: In July 2017, Pembrolizumab, a Programmed Cell Death protein-1 (PD-1) inhibitor was approved in Scotland for first-line treatment of metastatic NSCLC in patients with tumours expressing PD-L1 with tumour proportion score (TPS) of ≥50% and no targetable genetic alterations. Approval was based on findings of the KEYNOTE-024 study. We investigated the survival and toxicities experienced by patients receiving Pembrolizumab in the West of Scotland. **Method:** We identified patients with tumours expressing PD-L1 at TPS ≥ 50% from pathology records from August 2017 to August 2018 and subsequently identified 83 patients receiving first-line Pembrolizumab. We collected baseline and treatment characteristics using electronic patient records. Survival was estimated using the Kaplan Meier method. **Result:** Baseline and treatment characteristics are shown in table 1. Thirty patients had pre-treatment CT head and 8 of them had untreated brain metastases, this would have prohibited KEYNOTE-024 trial entry. Furthermore, there were 10 patients (12%) with active autoimmune co-morbidities which would have been excluded from the trial. After 9.4 months median follow-up, 32 (38.6%) patients had died. Survival at 6 months was 69.6% (95% CI: 58.3 to 78.3%) and 57.1% (95% CI: 42.1 to 69.6%) at 12 months. 39 patients (47%) experienced treatment toxicities, 15 (18.1%) experienced ≥ 2 toxicities. Diarrhoea was commonest (14 patients; 16.9%) followed by hypothyroidism (8 patients; 9.6%), pneumonitis (6 patients; 7.2%) and rash (5 patients; 6%).

Table 1: baseline and treatment characteristics		
	n=83	
Median age (range)	68 years (range: 39-86 years)	
Gender	Male: 42 (51%)	Female: 41 (49%)
Stage of disease	Stage 4 - untreated brain metastases* Stage 3	68 (81.9%) - 8 (11.8%) 15 (18.1%)
Histology	Adenocarcinoma Squamous carcinoma Undifferentiated NSCLC Other histology	54 (65.1%) 17 (20.5%) 9 (10.8%) 3 (3.6%)
Performance status	0 1 2	12 (14.5%) 69 (83.1%) 2 (2.4%)
Active autoimmune co-morbidities*	Psoriasis Interstitial lung disease Fibromyalgia Raynauds phenomenon Rheumatoid arthritis Post-polio syndrome Multiple sclerosis	3 (3.6%) 2 (2.4%) 1 (1.2%) 1 (1.2%) 1 (1.2%) 1 (1.2%) 1 (1.2%)
Median number of cycles = 6 (range: 1-24); 31 patients (37.3%) still continuing treatment**		
Reason for discontinuing treatment (n=52; 62.7%)	Poor PS Disease progression Treatment toxicity: - Colitis - Pneumonitis Death: - NSCLC - Unknown cause Patient choice	19 (22.9%) 14 (16.9%) 10 (12%) - 7 (8.4%) - 3 (3.6%) 7 (8.4%) - 5 (6%) - 2 (2.4%) 2 (2.4%)
*These patients would have been ineligible for KEYNOTE-024 trial ** At time of data analysis - 21 February 2019		

Conclusion: Survival at 6 months for our cohort was less than in the KEYNOTE-024 study (69.6% vs 80.2%) however fewer patients were PS 0 (14.5% vs 35.1%) and several had co-morbidities which would have precluded trial entry. The median number of treatment cycles in our cohort was 6 (range: 1-24) vs 10.5 (range: 1 to 26) trial. Toxicity was more common in this real life cohort with 12% discontinuing treatment due to toxicity vs 7.1% in the pivotal trial.

Keywords: Pembrolizumab, Non-small cell lung cancer (NSCLC), Immunotherapy

EP1.01-39 A RANDOMISED PHASE II TRIAL OF VITAMIN C SYNERGY WITH HYPERTHERMIA IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Intravenous vitamin C (IVC) and modulated electrohyperthermia (mEHT) are widely used by integrative cancer practitioners for many years. However, there are no sufficient data in quality of life (QoL) ,clinical response and survival time of the above treatments in patients with stage III-IV Non-Small Cell Lung Cancer (NSCLC). Our phase I clinical trial proved that IVC simultaneously with mEHT were safe for NSCLC patients. **Method:** A randomised phase II controlled trial was performed to compare supportive care with and without IVC + mEHT concomitant treatment (In the active arm: patients were allocated into 1 g/kg d, 1.2 g/kg d, 1.5 g/kg d dosage groups simultaneously with mEHT, three times a week for 25 treatments in total)on tumour size, progression-free survival (PFS) and overall survival (OS) in advanced Chinese NSCLC patients.Subsequently, 97 patients were analysed at the data cut-off (17th July, 2018). Enhanced chest and abdomen CT scans, brain MRI and bone scans were carried out at baseline, and every 4 weeks for the first 12 weeks from the start of the study. Response measurements were carried out according to RECIST 1.1. 3 month disease control rate(DCR) was measured 3 months after the therapy and defined as the percentage of subjects with complete response (CR), partial response (PR) or stable disease (SD) at 3 months relative to all randomly assigned patients. **Result:** After a median follow up of 10 months, both the PFS and OS were significantly improved by IVC + mEHT compared to control (PFS: 3 month vs. 1.85 months, *P*<0.05; OS: 12 months vs. 7.5 months, *P*<0.05). The average scores for the functioning scales increased continuously, so that the QoL improved in the active arm despite the advanced stage of the disease(P<0.05). 3-month DCR after treatment was 42.9% in the active arm and 16.7% in the control arm (*P*<0.05). Both interleukin-6 and c-reactive protein were significantly decrease after treatments in active arm in comparison with control arm (*P*<0.05). However,there were no significant differences in 3 month DCR, PFS and OS between the three groups with different applied dosages of vitamin C. No significant differences were observed between parameters of adenocarcinoma and squamous cell carcinoma and between EGFR(+) and EGFR(–). **Conclusion:** IVC + mEHT treatment significantly improves QoL, prolongs PFS and OS, and moderates cancer-related inflammation, and so is a feasible treatment for patients with advanced NSCLC. This trial is registered in ClinicalTrials.gov (ID: NCT02655913).

Keywords: modulated electrohyperthermia, Non small cell lung cancer, vitamin C

EP1.01-40 OUTCOME OF EGFR-MUTATED AND NON-MUTATED LUNG ADENOCARCINOMA RECEIVING STANDARD THERAPY - A NEPALESE COHORT

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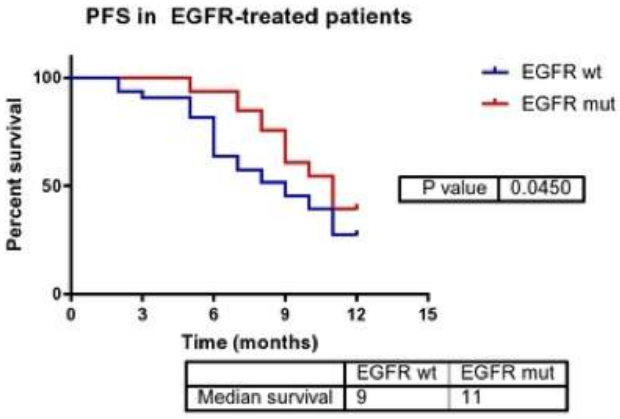
Background: Lung cancer represents major health challenges worldwide including Nepal where patients (pts) often present in advanced stage. The purpose of this study was to compare the objective response rates (ORR), progression free survival (PFS), and quality of life (QoL) of EGFR-mutated (EGFR-mut) and non-mutated (EGFR-wt) pts with adenocarcinoma of the lung (ACL) receiving standard therapy. **Method:** An IRB approved comparative analytical study was performed in pts with ACL. Newly diagnosed stage IV ACL pts were enrolled and ORR, PFS and QoL was compared between EGFR-mut and EGFR-wt (33 pts in each arm) pts. EGFR-mut pts were given gefitinib and EGFR-wt pts were given systemic chemotherapy (pemetrexed/cisplatin or cisplatin/etoposide). Response evaluation was done using RECIST criteria in both arms. PFS was calculated from the date of starting treatment to the date of progression and QoL was evaluated using EORTC QLQ-C30 (version 3) questionnaire and compared between two arms. Adverse effects were assessed using CTCAE criteria. Pts were followed for 1 year. **Result:** Complete response (CR) was achieved in 9.1% vs 3.0 % (p=0.46), and ORR was 27.3% vs 15.2% (p=0.23) in EGFR-mut vs EGFR-wt. The median PFS was 11 and 9 months for EGFR-mut and EGFR-wt respectively (p = 0.045). The mean score of global health status from EORTC QLQ-C30 was 68.1 vs 61.6 in EGFR-mut pts vs EGFR-wt pts (p = 0.036). Skin toxicities were more common in pts receiving gefitinib. One pt had grade 3 skin toxicity. Febrile neutropenia and peripheral neuropathy (either grade 1 or grade 2) were the most common toxicities in pts receiving standard chemotherapy.



Conclusion: EGFR-mut pts treated with EGFR-TKI had improved ORR, PFS and QoL in comparison with EGFR-wt pts treated with chemotherapy. EGFR-mutational analysis and EGFR-directed therapy is feasible and provides survival benefit, also in developing countries as Nepal.

Keywords: Outcome, Advanced Adenocarcinoma Lung, EGFR mutation Nepal

EP1.01-41 FEASIBILITY OF EBUS-TBNA CYTOLOGIES FOR AN EXTENSIVE ASSESSMENT OF PREDICTIVE BIOMARKERS IN LUNG CANCER

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Background: Clinical guidelines support the determination of several driver genes as well as PD-L1 to drive treatment decisions in non-small cell lung cancer (NSCLC). Endobronchial-ultrasound transbronchial needle aspiration (EBUS-TBNA) cytology specimens are useful for the initial diagnosis of NSCLC, although its capacity to provide enough material for a complete genotyping remains controversial. The aim of this study is to determine the yield of EBUS for a comprehensive multiplex genotyping in patients (pts) with suspected NSCLC. **Method:** In this single-center, ongoing, prospective study, samples from mediastinal lymph nodes were obtained from pts undergoing EBUS-TBNA for lung cancer diagnosis/staging. Following malignant confirmation and appropriate cell content by rapid on-site evaluation, the study sample was obtained and formalin-fixed paraffin-embedded (FFPE). Three analytes were evaluated (DNA/RNA/protein). DNA and RNA were extracted and analyzed by Oncomine Solid Tumour panel (22 genes) and a customized nCounter panel (*ALK, ROS; RET, NTRK, METDe14*). Tumor Proportion Score (TPS) for PD-L1 protein expression was evaluated by an expert pathologist and scored into <1% (negative), 1-49% (weakly positive) and 50% (high). **Result:** Twenty-five pts with NSCLC have been included and cytology samples of 20 of them molecularly characterized (5 still in progress). Overall, cytological analysis of EBUS-TBNA yield a complete characterization for the three analytes (DNA/RNA/protein) in 15 pts (75%). EBUS-TBNA sampling was sufficient for both, Nanostring and Oncomine evaluation, in a total of 18 pts (90%): 15 patients (83%) had any alteration detected by oncomine (*TP53* 61% [11/18],*KRAS* 44% [8/18], *EGFRe 19*5.5% [1/18], *BRAF V600E* 5,5% [1/18], *DDR2* 5.5% [1/18], *STK11* 11% [2/18]) and 1 pt (5.5 %) by nanostring (*METDex14*). A total of 19 samples were sufficient for PD-L1 expression scoring (95%). TPS for PD-L1 expression was negative in 8 pts (42%), week in 4 (21%) and high in 7 pts (37%). Overall, half of the pts evaluated (10/20) would be potential candidates for an upfront personalized treatment strategy using targeted agents or immunotherapy. **Conclusion:** EBUS-TBNA is a promising alternative source of material for NSCLC genotyping and allows the identification of pts candidates for personalized therapies.

Keywords: NSCLC, Molecular Testing, EBUS-TBNA

EP1.01-42 IS SERUM LYMPHOCYTE COUNT PREDICTIVE BIOMARKER TO IDENTIFY LUNG CANCER PATIENTS WHO MAY BENEFIT FROM AN IMMUNOTHERAPY?

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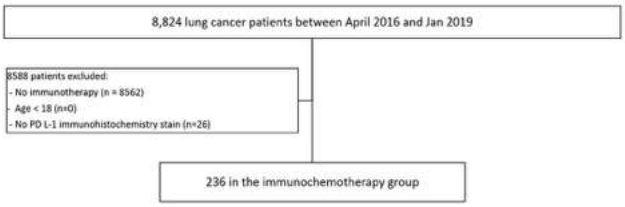
Background: Programmed death ligand 1 (PD-L1) expression is not truly reflected response of immunotherapy. Thus, tumor mutational burden is new biomarker for predict response of immunotherapy. However, sufficient quantity or quality tumor samples must be obtained, so this is limitation. Therefore, we investigated whether high serum lymphocyte is predictive biomarker for immunotherapy response regardless of PD-L1 immunohistochemistry stain among lung cancer patients. **Method:** We retrospectively analyzed the medical charts of lung cancer patients who treated with immunotherapy (pembrolizumab, nivoluamb, ipilimumab, atezolizumab) at Seoul National University Hospital between April 2016 and March 2019. We evaluated correlation the serum lymphocyte count (SLC) with the progression free survival (PFS) using multivariable linear regression. SLC was evaluated when patients **Result:** Total 236 patients treated with immunotherapy for lung cancer. SLC at baseline was not significantly associated with progression free survival (Coeff = -0.00, p = 0.478) after adjustment age, sex, ECOG status, histology and PD L-1 expression status. The 1-year progression free survival rate was 14.8% and patients who survived over 1 year were not revealed difference of SLC compared with those who didn't survive over 1 year. When we divided two group according lymphocyte count as 5000/uL, among patients who were over 5000/uL of lymphocyte related with increased progression probability (hazard ratio for disease progression, 1.68; 95 % CI, 1.03 to 2.77; P=0.04).

Fig1. Flow chart of the study



Conclusion: In this study, we revealed that increased serum lymphocyte count over 5000/uL at baseline when immunotherapy start is associated with decreased progression free survival among lung cancer patients who treated with immunotherapy.

Keywords: immunochemotherapy, Lung cancer, Programmed death ligand 1

EP1.01-43 IMMUNOTHERAPY AND RADIOTHERAPY - A USEFUL COMBINATION?

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Background: Immunotherapy has emerged as a major and effective therapeutic modality in non-small cell lung cancer (NSCLC). With expanding indications for immunotherapy, therapeutic modalities in progressive disease under immunotherapy are needed. **Method:** In a retrospective single center analysis patients treated with immunotherapy and radiation for progressive lesions were identified. Both patients with acquired and primary resistance to immunotherapy were included in the analysis. **Result:** In eight patients (2 adenocarcinoma, 6 SCC) immunotherapy was continued (5 Nivolumab, 1 Pembrolizumab, 2 Atezolizumab) despite disease progression due to good tolerance and missing therapeutic alternatives because of multiple pretreatment regimens and their toxicities. We observed that all 8 patients had a clinical benefit without developing a disseminating disease, we only observed a growth in the previously existing lesions. In 5/8 patients the disease could be stabilized. An abscopal effect could be excluded. In five patients local metastatic growth was treated with radiation to manage pain and local complications. Three additional patients with asymptomatic, progressive lesions were treated with radiotherapy to prevent organ complications. **Conclusion:** Immunotherapy has revolutionized NSCLC treatment. However there are therapeutic modalities questioned in progressive disease under immunotherapy. By maintaining immunotherapy during and after radiotherapy localized progression might be effectively treated. Therefore we summarize that in a number of patients further metastatic evolution might be preventable. Whether peritumoral or systemic prognostic determinants can be identified should be a matter of further research. Either benefits of local ablative techniques or perpetuation of immunotherapy despite of disease progression were recently reported (Gandara et al. 2018, Gettinger et al. 2018). This also suggests a differentiative perspective of local ablative therapy in metastatic NSCLC.

Keywords: Immunotherapy, radiotherapy

EP1.01-44 EARLY AND LONG-TERM RESULTS OF TRACHEAL SLEEVE PNEUMONECTOMY FOR LUNG CANCER AFTER INDUCTION THERAPY

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Background: The role of induction therapy (IT) and its effects on morbidity and mortality of patients receiving tracheal sleeve pneumonectomy (TSP) are unclear. We evaluated early and long-term outcomes of patients who underwent TSP after IT. **Method:** From 1998 to 2018, 32 patients (26 men; median age, 63 years) underwent TSP. Twenty-two patients (69%) received IT (cisplatin-based chemotherapy). The TSPs were all right sided and included three completion pneumonectomies. Superior vena cava resection was combined with TSP in 15 cases. Diaphragmatic and vertebral resection was also associated in 1 case each. **Result:** Operative mortality was nil. Thirty-day mortality was 9% (n = 3). Major complications occurred in 7 patients (21.8%): bronchopleural fistulas in 3; acute respiratory distress syndrome in 2; cardiac hernia in 1; and empyema in 1. The IT had no significant effects on morbidity and mortality. Resection was complete in 31 patients (97%). Pathologic N status was N0 in 2 cases, N1 in 17, and N2 in 13. Nodal downstaging was diagnosed in 13 of 22 patients (59.1%) who received IT (11 passed from N2 to N1, and 2 to N0). Mean survival was 36 months (range, 1 to 181). Overall 5-year survival and disease-free survival were 30.3% and 27.7%, respectively. Patients receiving IT had a poor survival (p = 0.03). At multivariate analysis, nodal downstaging and adjuvant treatment significantly affected survival (p = 0.035 and p = 0.007, respectively). **Conclusion:** Tracheal sleeve pneumonectomy is a feasible but technically challenging surgical procedure and provides acceptable results in terms of early and long-term outcomes. Induction therapy did not significantly affect morbidity and mortality.

Keywords: Advanced lung cancer, pneumonectomy, induction therapy

EP1.01-45 CISPLATIN PLUS GEMCITABINE THERAPY FOLLOWED BY MAINTENANCE GEMCITABINE FOR ADVANCED SQUAMOUS CELL LUNG CANCER (KTORG1302)

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Background: One of the standard treatments in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC) is platinum-containing doublet chemotherapy. Moreover non-squamous NSCLC, patients benefit from pemetrexed maintenance therapy following induction therapy with cisplatin (CDDP) plus pemetrexed. However, no large-scale trial showing the efficacy of maintenance therapy has been reported in squamous cell lung cancer. We evaluated the efficacy and the safety of continuation maintenance therapy with gemcitabine (GEM) after induction chemotherapy with CDDP plus GEM in advanced squamous cell lung cancer. **Method:** This study was a single-arm, multicenter and phase II trial. Main eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1, and the aged of 20 to 74 years old. Patients received an induction phase which consisted of 4 cycles of CDDP (80mg/m2, day 1, q3w) plus GEM (1000mg/m2, day 1, 8, q3w). Patients who did not progress after completion of 4 cycles of induction received continuation maintenance therapy with GEM (1000mg/m2, day 1, 8, q3w) until disease progression. The primary endpoint was progression-free survival (PFS) in the intention-to-treat population. **Result:** Between June 2013 and October 2018, 26 patients were enrolled in this study. Although the scheduled numbers were 60, this study was ended early for poor accrual. The mean age was 65.7 years (range, 47 – 74 years). 18 patients (69.2%) completed 4 cycles of CDDP plus GEM, and 16 patients (61.5%) received continuation maintenance therapy with GEM. At the cutoff date of December 31, 2018, overall response rate was 46.2%, median PFS from induction therapy was 5.3 months (95% confidence interval [CI]: 2.9-7.3), and median PFS from continuation maintenance therapy was 3.8 months (95% CI: 2.3-5.2). Median overall survival from induction therapy was 11.9 months (95% CI: 7.5-26.5). The most common grade 4 adverse events were neutropenia (16%) and thrombocytopenia (12%). Pneumonitis ware seen in 3 cases (grade 1: 1, grade 2: 1, grade 3: 1 case). Adverse events except for hematotoxicity were generally well tolerated. There were no treatment-related deaths. **Conclusion:** This study terminated early because of poor accrual and did not meet its primary endpoint. However, this study indicated continuation maintenance therapy with GEM can be well-tolerated treatment option for patients with advanced squamous NSCLC.

Keywords: Gemcitabine, advanced squamous cell lung cancer, maintenance therapy

EP1.01-46 ACUTE ESOPHAGEAL DAMAGE IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER TREATED WITH CONCURRENT AND SEQUENTIAL CHEMORADIOTHERAPY

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Background: Acute esophageal damage may be dose-limitation factor for application of the full planning radiotherapy dose in patients with inoperable Non Small Lung Cancer-NSCLC. Combination of chemotherapy and radiotherapy may increase esophageal toxicity, however three-dimensional conformal radiotherapy offers better spearing. **Method:** To evaluate the treatment results, study of 75 patients was randomly assigned to one of the two treatment arms. In the sequential arm, 26 (34.7%) patients had previously received sequential chemotherapy with 4 cycles of carboplatin and etoposide followed by conformal radiotherapy (RT). In the second concurrent arm, 49 (65.3%) patients received concurrent chemotherapy of cisplatine and etoposide and conformal RT. We described all phases of the conformal RT. Treatment-related toxicities were assessed according RTOG/EORTC criteria. **Result:** From 2010 to 2013, 73 patients were enrolled in this study. From all included patients, 43 (57.3%) did not present any grade of esophagitis during the treatment. In sequential group 73.1% presented no esophagitis and in concurrent group 49%, respectively. Although there were differences between the two groups, none was statistically significant. The median survival was 13 months for the patients in the sequential arm and 17 months for those in the concurrent treatment arm. The differences were statistically significant (log-rank test p=0.0039). Table 1 and 2 present grade of ezophagitis and the needs of analgesia in the patients of sequential and concurrent treatment arm. The risk of esophagitis was 22%, in patients whose esophageal volume (V50) recieved less than 30% of prescribed dose in comparation, the risk of esophagitis was 71%, in patients whose V50 recieved dose higher than 30% (p=0.0009).

Table 1: Grade of esophagitis according radiotherapy dose

	Sequential arm				Concurrent arm			
	0	1	2	3	0	1	2	3
40 Gy	22 (84.6%)	1 (3.8%)	3 (11.5%)	0	30 (61.2%)	8 (16.3%)	9 (18.4%)	2 (4.1%)
60 Gy	20 (76.9%)	0	6 (23.1%)	0	25 (51.0%)	6 (12.2%)	15 (30.6%)	3 (6.1%)
End of radiotherapy	19 (73.1%)	1 (3.8%)	6 (23.1%)	0	28 (84.6%)	4 (8.2%)	14 (28.6%)	3 (6.1%)

0,1,2,3= grade of esophagitis according RTOG/EORTG

Table 2: Irradiation doses and analgesia

	Sequential arm				Concurrent arm			
	0	1	2	3	0	1	2	3
40 Gy	22 (84.6%)	1 (3.8%)	0	3 (11.5%)	30 (61.2%)	11 (22.4%)	4 (8.2%)	4 (8.2%)
60 Gy	21 (80.8%)	1 (3.8%)	1 (3.8%)	3 (11.5%)	25 (51.0%)	12 (24.4%)	4 (8.2%)	8 (16.3%)
End of radiotherapy	20 (76.9%)	1 (3.8%)	2 (7.7%)	3 (11.5%)	31 (63.3%)	7 (14.3%)	2 (4.1%)	9 (18.4%)

0=no analgesia; 1=anti-inflammatory drugs; 2=opoids; 3=combination of anti-inflammatory and opoids

Conclusion: The reason for good tolerability of the combination of chemotherapy and radiotherapy for patients in this study is using three-dimensional conformal radiotherapy. Further improvements may be obtained with more sophisticated radiotherapy techniques or by using radio protective drags.

Keywords: acute esophageal damage, sequential and concurrent chemo radiotherapy, conformal radiotherapy

EP1.01-47 THYROID RELATED ADVERSE EVENTS PREDICT SURVIVAL IN NSCLC PATIENTS RECEIVING ANTI-PD-1/ PD-L1 THERAPY

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Background: Immune checkpoint inhibitors (ICI) have altered the therapeutic paradigm of advanced non-small cell lung cancer (NSCLC) and produce antitumor effects by activating host immunity, which also causes immune-related adverse events (irAEs). Thyroid irAE is the second most common irAEs after dermatological irAEs following ICI and present in 2%-21% of patients s depending upon the immune checkpoint inhibitors used. It has been reported that irAEs induced by ICI may be associated with possible improvement in survival and better therapeutic outcomes. The aim of this study is to analyze the relationship between PD-1 inhibitors -induced Thyroid irAE and clinical efficacy in advanced NSCLC patients treated at three regional cancer centres. **Method:** Retrospective study was conducted using the Hospitals' Inpatient Enquiry (HIPE) to identify patients with NSCLC stage IV or inoperable stage IIIB who received at least one dose of PD-1 inhibitors (Nivolumab or pembrolizumab) between Januarys 2017 and December 2018. Patients who had no baseline Thyroid function tests (TFTs), abnormal baseline TFT or had a history of thyroid disorder were excluded. Thyroid irAE were identified and classified according to TSH and free T4 (fT4) Efficacy was evaluated with progression free survival (PFS) and median overall survival (OS) according to the development Thyroid IrAEs **Result:** One hundred and eighty-five patients were included, 120 male [64.9%] ,65 female [35.1%] and the median age was median age 66(38-88) years. A total of 38 (20.5 %) patients on PD-1 inhibitors (nivolumab or pembrolizumab) had new-onset Thyroid IrAEs. 76.3% (29/38) of those patients manifested initially with thyrotoxicosis. The remaining 22.6% (9/38) of patients presented with hypothyroidism as the initial presentation. The median times to new-onset Thyroid IrAEs was 46 days. Kaplan Meier survival analysis showed that patients with Thyroid IrAEs had a statistically significant longer median PFS of 9.0 months (95% CI, 9.3–17.1) compared to patients with without Thyroid IrAEs who had a median PFS of 2.0 months (95% CI, 2.0–13.5), hazard ratio = 0.38, (95% CI, 0.20–0.71; P = 0.002). For entire cohort, Thyroid IrAEs was associated with superior survival (median OS 16.0 months for those who developed Thyroid IrAEs compared to 2.9 months of those without Thyroid irAEs ($p < 0.0001$) **Conclusion:** The result of this study emphasizes the association between irAEs and better survival outcomes from anti-PD1 therapy. Development of grade 2 Thyroid IrAEs was a useful predictor of survival outcomes in NSCLC patients treated with ICI. These results support previously published retrospective data. Further prospective studies are required to thoroughly underline the association between ICI induced irAEs, tumor response and long term survival.

Keywords: PD-1 inhibitor, NSCLC, Thyroid

EPOSTERS

EP1.01-48 INVASIVE MUCINOUS ADENOCARCINOMA OF THE LUNG: SERIAL CT FINDINGS, CLINICAL FEATURES, AND TREATMENT OUTCOMES

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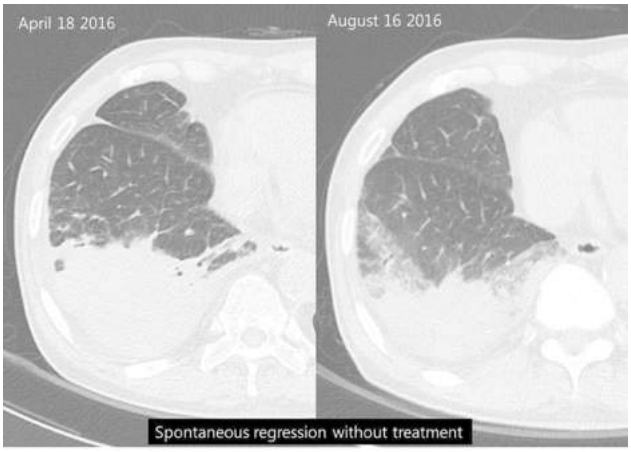
Background: Invasive mucinous adenocarcinoma of the lung is a rare and distinct subtype of adenocarcinoma, previously described as bronchoalveolar carcinoma (BAC). In our daily practice, we have sometimes encountered spontaneous regression without treatment in patients with invasive mucinous adenocarcinomas, but serial CT findings of this cancer have not been described in the literature. We performed an analysis to describe the serial chest CT findings, clinical features, and treatment outcomes of patients with invasive mucinous adenocarcinoma of the lung.



Method: From January 2013 to June 2018, 49 cases of pathology-confirmed invasive mucinous adenocarcinoma of the lung were identified. Initial chest CT and follow-up CTs were available for 48 patients (23 men and 25 women; median age, 69.5 years; range, 26-82 years). Median follow-up period was 19.0 months (range, 0-110 months). Serial CT scans were reviewed, with emphasis on changes over time and in relation to medical or surgical treatment. Patients were classified as either nodule/mass type or consolidation type according to the initial CT. Clinical, radiological, and treatment outcomes were compared between nodule/mass and consolidation types by adopting the χ^2 test, Mann-Whitney U test, and Kaplan-Meier analysis with log-rank tests. **Result:** There were 33 nodule/mass type and 15 consolidation type at initial CT scan. Of 15 consolidation type, 9 patients showed combined GGO. Consolidation type presented with significantly larger lesion size (p<0.001), higher stage (p<0.001), and multifocality (p=0.001) on initial CT and showed spontaneous regression without treatment during follow-up (p<0.001) compared to the nodule/mass type. Six patients died during follow-up, and they were all from the consolidation group (p<0.001). 33 patients underwent surgery and 11 patients received chemotherapy. Patients with the consolidation type showed reduced progression-free survival (PFS) (mean 9.5 months) compared with those with the nodule/mass type (mean 63.9 months) (p<0.001). **Conclusion:** Invasive mucinous adenocarcinomas of the lung appearing as consolidation on initial CT are larger and multifocal, have higher stage, higher mortality, and reduced PFS, and can show spontaneous regression.

Keywords: CT, invasive mucinous adenocarcinoma, NSCLC

EP1.01-49 HISTOLOGY-DEPENDED PATTERN OF PATHO-HISTOLOGICAL RESPONSE AFTER INDUCTION THERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Pathological response after induction therapy (IT) is expected to be associated with favorable outcome in locally advanced non-small cell lung cancer (NSCLC). The pathologic response pattern remains unpredictable. Aim of this retrospective study was to analyze the patho-histologic response according to tumor histology, in order to identify the potential correlation and prognostic impact. **Method:** In 57 patients with locally advanced NSCLC the patho-histologic response to IT were assessed and compared for adenocarcinoma vs. squamous cell lung cancer after curative lung resection. The prognostic differences were estimated by Kaplan-Meier method and compared using log-rank test. **Result:** The IT included chemo-radiation with 50.4Gy (range 45-56.4 Gy) combined with platin-based chemotherapy in 54 patients (94.7%) or only platin-based chemotherapy in 3 patients (4.3%). Perioperative morbidity and 30-days-mortality was 36% and 3.5%, respectively. Complete resection was achieved in 93% patients. Significantly improved long-term survival and recurrence-free survival were associated with <15% viable squamous cells and with <60% viable adenocarcinoma cells (long rank 0.013 and 0.012, 0.04 and 0.05, respectively). The median long-term survival for <15% viable squamous cells was 35.2 months, recurrence-free survival was not achieved; for <60% viable adenocarcinoma cells the median long-term and recurrence-free survival were 87.9 and 35.9 months, respectively. **Conclusion:** The patho-histologic response pattern to IT is correlated to tumor histology and has potential implication on pathologic assessment. Distinct prognostic impact can be further reflected in the clinical practice and multimodal treatment strategies.

Keywords: induction therapy, locally advanced non-small cell lung cancer, pathologic response

EP1.01-50 QUANTITATIVE ASSESSMENT OF SUBSEGMENTAL BRONCHI ON THIN-SECTION CT FOR PULMONARY LYMPHANGITIS CARCINOMATOSA

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Background: CT is the main modality to measure the of the tumor and/or metastasis of solid malignancies to evaluate the change over time due to conservative therapy, especially in chemotherapy. However, the change of lymphangitis carcinomatosa which appears at advanced stage could be evaluated quantitatively, only. The purpose of this study was to evaluate the availability of CT to quantify the lymphangitis carcinomatosa of lung cancer. **Method:** Fifteen consecutive patients (12 males, three females; 51-76 y.o.) with pulmonary lung cancer who were diagnosed as lung cancer with lymphangitis carcinomatosa by CT were enrolled retrospectively. Each patient's lung cancer was diagnosed by using bronchoscope or CT guided biopsy. All patients underwent CT examination before and after the chemotherapy. All CT studies were performed by using MDCT machine (Aquilion Prime or Aquilion Precision; Canon Medical Systems, Otawara, Japan). All CT examinations were performed with 80 or 160-detector row CT scanner with contrast media. CT images were reconstructed with 1mm slice, 1mm interval, 512 x 512 matrix. The long axis diameters of primary tumors were measured on CT before and after the therapy. The wall area of the sub-segmental bronchus affected by lymphangitis carcinomatosa was defined by Synapse Vincent (Fujifilm Medical; Tokyo, Japan) before and after the therapy. The correlation coefficient of tumor reduction rates between the primary tumor diameter and wall area of the affected sub-segmental bronchus was statistically assessed. P value less than 0.05 was considered as significant in statistical analyses. **Result:** The correlation coefficient of tumor reduction rates between the primary tumor diameter and wall area of the affected sub-segmental bronchus was 0.533 (p = 0.041). **Conclusion:** The positive correlation of tumor reduction rates was significant between the primary tumor diameter and wall area of the affected sub-segmental bronchus. The measurement of wall area of affected sub-segmental bronchus on thin-slice CT has the availability to evaluate the quantitative change of lymphangitis carcinomatosa of lung cancer patients.

Keywords: lymphangitis carcinomatosa, CT, bronchus

EP1.01-51 EFFICACY IMPACT OF SERUM VEGF FOR ELDERLY OR POOR PS PATIENTS RECEIVING ANTI-PD-1 ANTIBODY WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Anti-programmed cell death (PD)-1 antibody therapies have shown durable clinical efficacy and manageable toxicity profiles, and have become a standard therapy in advanced non-small cell lung cancer (NSCLC). Because of manageable toxicity profiles, extensive interest in the potential benefits of anti-PD-1 antibody has expanded to high-risk patients such as the elderly or poor performance status (PS) patients. Here, we aimed to investigate predictive markers for the efficacy of anti-PD-1 antibody in elderly patients and poor PS patients. **Method:** The medical records of 75≥ years old or PS2 NSCLC patients treated with anti-PD-1 antibody (e.g., nivolumab and pembrolizumab) at the National Cancer Center Japan between December 1, 2015, and May 31, 2018, were reviewed retrospectively. We evaluated the association between efficacy for anti-PD-1 antibody and gender, smoking status, histology, PD-ligand 1(PD-L1) expression on tumor cells, white blood cell counts, lymphocyte counts, albumin, lactate dehydrogenase, c-reactive protein, and serum vascular endothelial growth factor (VEGF). We divided patients into two groups with the median values. **Result:** A total of 235 patients with advanced NSCLC treated with anti-PD-1 antibody were reviewed. Of these patients, 31 patients were ≥ 75 years old, and 22 patients were PS2. The median PFS was 6.9 months in patients aged ≥ 75 years and 2.1 months in PS2 patients. Cox proportional hazard regression analysis showed that only the low-VEGF was significantly associated with longer PFS in patients aged ≥ 75 years (HR, 0.35; 95% CI, 0.13-0.88; *P* = 0.025) and in PS2 patients (HR, 0.31; 95% CI, 0.10-0.85; *P* = 0.023). The overall response rate of patients with low-VEGF was tend to be higher than that with high-VEGF among patients aged ≥ 75 years (43% *vs*. 20%; *P* = 0.18) and PS2 patients (20% *vs*. 0%; *P* = 0.084). **Conclusion:** Low-VEGF in patients aged ≥ 75 years and PS2 patients was associated with longer PFS. Serum VEGF may thus be a biomarker for the efficacy of anti-PD-1 antibody therapy.

Keywords: Biomarker, vascular endothelial growth factor, immune checkpoint inhibitor

EP1.01-52 PREFERABLE INTRACRANIAL CHEMOTHERAPY FOR LUNG CANCER PATIENTS WITH MENINGEAL METASTASIS HARBORING CIN IN CSF

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Background: Brain metastases occur in about half of the NSCLC patients throughout the course of disease, including brain parenchymal metastasis and meningeal metastasis. It has been reported that compared with plasma detection, next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) from cerebrospinal fluid (CSF) is capable of more comprehensively characterizing the genomic alterations of brain tumor, so as to identify actionable variants. **Method:** We conducted a small sample study consisting of 7 patients with brain metastasis, including 3 lung cancer patients with meningeal metastasis (P314, P316, P318), a lung cancer patient with brain parenchymal metastasis (P323), 2 breast cancer patients with meningeal metastasis (P324 and P328) as well as a gastric cancer patient with meningeal metastasis (P326). Profiling of the specimens from CSF, brain parenchyma and plasma of these 7 patients was performed using NGS along with bioinformatics analysis. **Result:** Among the three patients P314, P316 and P318, high-frequency driver mutations including *ERBB2* p.V659E, *EGFR* p.L858R & *MET* amplification, *EGFR* 19del were detected in the CSF respectively, but all of these variants were not observed in the plasma. Notably, these three patients' brain lesions continued to progress after receiving corresponding targeted agents, while their conditions remained stable in the presence of switching to intracranial chemotherapy. Following bioinformatic analysis revealed the occurrence of chromosome instability (CIN). We wonder if it is a special case or a common phenomenon. To further explore whether there is similar phenomenon in brain parenchymal metastasis, we examined the patient P323. The detection results of his brain parenchyma, CSF and plasma showed that there was no variation of CIN in brain parenchyma and CSF. In view of this, we hypothesized that CIN variants might exist only in lung cancer patients with meningeal metastasis. In addition, our results displayed that no chromosome instability was identified in the CSF of patients P324, P328 and P326. **Conclusion:** In summary, CIN is likely an important genomic feature of lung cancer with meningeal metastasis and is apt to be detected in the CSF. According to our observation, NGS of CSF specimen rather than plasma sample may be more favorable to the selection of appropriate treatment options for lung cancer patients with meningeal metastasis. For such patients with CIN variation, intracranial chemotherapy possibly offers more significant clinical benefit than other treatments such as targeted therapy. It still requires more investigations to verify above hypothesis.

Keywords: lung cancer/meningeal metastasis /chromosome instability (CIN)/intracranial chemotherapy

EP1.01-53 UPDATE OF MUTATION STATUS IN LUNG CANCER. A MULTICENTER LOCAL STUDY

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Background: Advances have been made in the understanding of the biology of NSCLC in relation to the characterization of molecular features such as activations of oncogenes by mutations, translocations and amplifications, which are being used as a targets and predictive biomarkers. Molecular analysis of NSCLC, adenocarcinoma (AC) is now the standard of care for therapy selection. **Method:** We determined the molecular alterations in EGFR, and gene fusion ALK in our Caucasian and Hispanic populations 169 small samples and resection specimens of patients with NSCLC in different institutions of Cordoba were studied during a period (2014 - 2019). In addition to Histopathology Type, we analyzed immunohistochemistry (IHC) characteristics, molecular profiles, and several clinical variables were studied. Different tests were used to detect alterations of EGFR and fusion gene EML4-ALK expression, with the aim to identify our own profile. EGFR mutation was studied by therascreen kit, PCR, in order to detect genetic alterations in exons 18, 19, 20 and 21. ALK translocations were analyzed by FISH (Vysis- Break Apart, Abbott) and IHC (clon D5F3, ventana, Roche). We correlated the molecular profile with different clinical variables (age, gender, and tobacco habits). The statistical method used was the multiple regression logistic model. **Result:** 169 samples were tested for EGFR expression and alk alterations 64% of subjects were men and 89% were smokers. Smoking habit was associated with sex (33% and 67% of smokers were women and men respectively, p=0.009). Smokers were older than non-smokers (p=0.011); to 64.4 (0.98) and 57.5 (2.35) years old for smokers and non-smokers. EGFR alterations were associated with sex (p=0.002, Fig 1). Women had more chance of having positive alterations of the gene (OR 3.57, 95CI:2.04-7.55). Age and smoking habit of patients did not show significant effects (p=0.44, Fig.2, and p=0.09, respectively). Only 1.7% of subjects reported ALK alterations, and were not related to sex (p=0.42), age (p=0.965) and smoking habit (p=0.281). **Conclusion:** Our results showed a comparable frequency in EGFR mutations and gene fusion ALK in relation to the data published in western population. These results allowed a proper diagnosis to provide the most adequate therapy.

Keywords: tobacco habits, Lung cancer, molecular features

EP1.01-54 IMPLEMENTATION OF FINE NEEDLE ASPIRATION OF SUPRACLAVICULAR LYMPH NODE AS A NOVEL MEDIUM FOR GENOMIC PROFILING IN NSCLC

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Background: Supraclavicular lymph node (SLN) metastasis is not rare in non-small cell lung cancer (NSCLC). Palpation or B-ultrasound guided fine needle aspiration (FNA) of SLN is a very simple, rapid, and minimally invasive tool for diagnosis of these patients. With the development next generation sequencing (NGS) which has been

widely used to catalogue genetic mutations in cancer, uncertainty remains if FNA of lymph node could be combined with NGS and applied in clinical practice. The aim of this study was to evaluate the clinical utility of FNA of SLN in patients with NSCLC **Method:** FNA of SLN samples (stored in 10% neutral buffered formalin) and matched plasma samples from 30 patients with NSCLC were collected. Twenty-three patients (both FNA and plasma samples) were sequenced using a panel covering whole exons and critical introns of 520 cancer-related genes and seven patients (both FNA and plasma samples) were profiled using a panel of 168 lung cancer-related genes. **Result:** During the procedure of next-generation sequencing library construction, the amount of extracted DNA and qualification percentage of FNA samples (n=30) from lymph nodes were similar to those of punctured lung biopsy samples (n=100, randomly selected from burning Rock database). Comparative analysis of mutation spectrums revealed that mutations were positively identified in 93.3% (28/30) FNA samples and 90.0% (27/30) plasma samples, while mutations of eight well-established lung cancer-related genes (EGFR, ERBB2, MET, BRAF, KRAS, ROS1, ALK and RET) were detected in 83.3% (25/30) FNA samples, which was higher than that in plasma samples (63.3%, 19/30). Moreover, FNA was significantly superior to plasma in detecting copy number variation (CNV) (detection frequencies, 88.9% vs 0.9%, $p<0.001$), both for CNVs of all genes in NGS panel (99.5% vs 10.0%) and eight well-established genes (96.0% vs 20.0%). **Conclusion:** Samples from FNA of SLNs were found to be equivalent to plasma during NGS library construction. Moreover, FNA of SLNs was superior to plasma in detecting mutations of eight lung cancer-related genes, as well as CNVs in both all genes of NGS panel and the 8 key genes. This study provides knowledge for the potential use of FNA of lymph nodes in sequencing genomic profiles of patients with lung cancer, and further support its utility in clinical practice.

Keywords: fine needle aspiration, supraclavicular lymph node, Next generation sequencing

EP1.01-55 NEOANTIGEN DELETION LEADS TO HYPERPROGRESSIVE DISEASE (HPD) IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH PD-1/PD-L1 INHIBITORS

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Background: Hyperprogressive disease (HPD) is a distinct pattern of progression described in patients with cancer treated with PD-1/PD-L1 inhibitors. The incidence of HPD is reported to be 13.8% in advanced NSCLC. Recently multiple characteristics have been recognized to predict the risk of HPD, however the mechanism underlying have not been systemically studied. **Method:** We report a Chinese patient who developed hyperprogressive disease after 4 cycles of PD-1 blockade treatment. Clinical and demographic data was collected from electronic records. Whole exome sequencing (WES) of the primary tumor was performed to identify tumor mutation burden (TMB) and tumor neoantigen burden (TNB) following the restricted pipeline. Liquid biopsy targeting ctDNA and T cell receptor (TCR) was constructed to monitor the efficacy of immunotherapy. **Result:** A 70-year-old male with smoking history underwent chest CT scan in February 2018 and was found to have a right upper lobe mass with intrapulmonary metastasis in different lobes and multiple lymph nodes. Resection of right lower lung by video-assisted thoracic surgery (VATS) revealed poorly differentiated, squamous cell carcinoma. In July 2018, he progressed after two cycle of chemotherapy and radiation therapy targeting newly bone metastasis of lumbar spine, then he was screened to start Nivolumab at dose of 240mg daily/2 weeks. After four cycle of Nivolumab, he obtained PD and was assigned to palliative thoracic radiation therapy. The PD-L1 expression level of our patient was $1\% \leq TC < 5\%$, next generation sequencing (NGS) didn't show alteration in genes related to HPD, such as MDM2/MDM4 or EGFR. Blood sample retrieved before and after immunotherapy revealed the increase in bTMB (from 7.70 Muts/Mb to 18.00 Muts/Mb), however TNB truly expressed as neoantigens were rather lower compared to TMB, indicating the low immunogenicity of tumor. We also found a sharp fluctuate in the detection of driver genes mutations in ctDNA (TP53,CDKN2A,ERBB3,FBXW7), and the majority of high-frequency TCR dropped significantly during immunotharapy. **Conclusion:** It is reported that NSCLC with a high tumor mutation burden (TMB) may benefit from PD-1/PD-L1 inhibitors treatment, and TMB is considered as the surrogate of tumor neoantigen burden (TNB). However the deletion of neoantigen may occur at different level, including copy number variation at the DNA level, down-regulation of transcription level and inherited variation at the epigenetic level, resulting in the low immunogenicity of primary tumor. Deletion of neoantigen may provide a mechanism of immune evasion which leads to the resistance to PD-1/PD-L1 inhibitors. In this case, treatment of checkpoint inhibitors may activate certain signaling pathway of driver genes to support the hyperprogression disease (HPD). This case report focusing on neoantigen provides a new approach to predict the presence of hyperprogressive disease (HPD) before immunotherapy, and explains the potential mechanism of HPD.

Keywords: hyperprogressive disease, neoantigen, NSCLC

EP1.01-56 CO-PRESENTATION OF ADENOCARCINOMA AND SQUAMOUS CELL LUNG CARCINOMA HARBOURING ALK REARRANGEMENT IN DIFFERENT SITES

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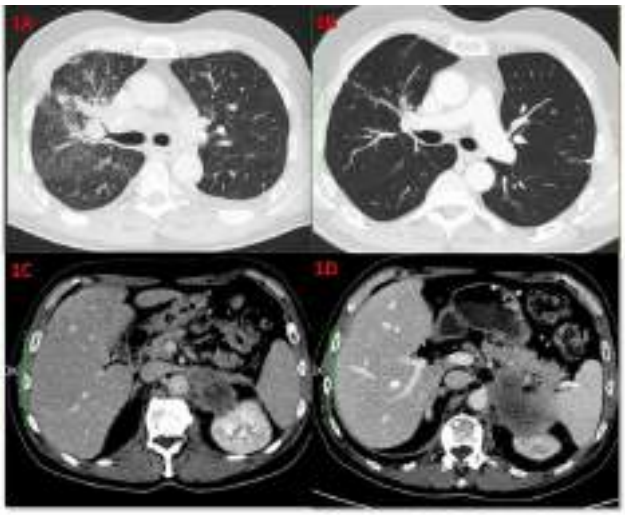
Background: Approximately 4% to 9% of Non Small Cell Lung Carcinoma (NSCLC) contain mixed adenomatous on squamous pathologies (adenosquamous cell carcinoma). The lung ADC to SCC transdifferentiation as a drug-resistance mechanism has been recently described. While the histological transformation mainly described in ALK-positive patients is from NSCLC entity to SCLC, only one case of histologic transformation of ALK rearranged ADC to SCC after treatment with an ALK inhibitor has been reported. Importantly, transformed samples retain the initial genomic alteration, supporting the lineage transition as a novel resistance mechanism.We describe an unique case of co-presentation of ADC and SCC in two different disease sites, both harbouring ALK rearrangement. **Method:** A 57-year-old male never smoker presented with a left adrenal mass. CT Scan showed a right superior lobe mass, bilateral pulmonary nodules (Fig. 1 A), and bone metastases. The lung biopsy documented ADC with moderate differentiation and ALK rearrangement by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC).



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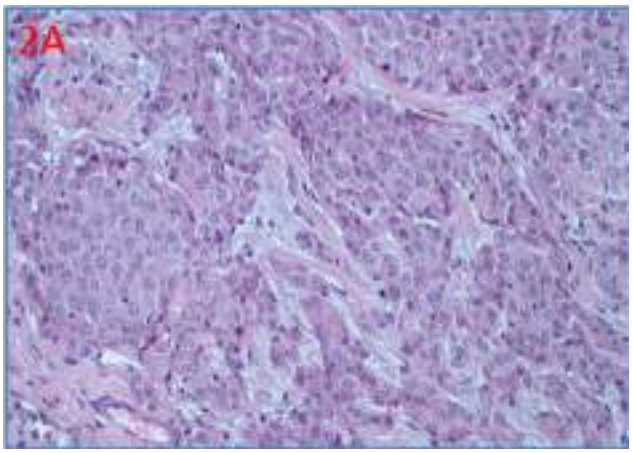

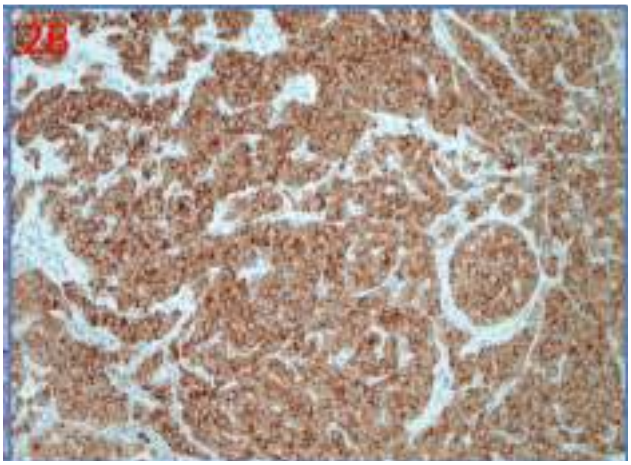

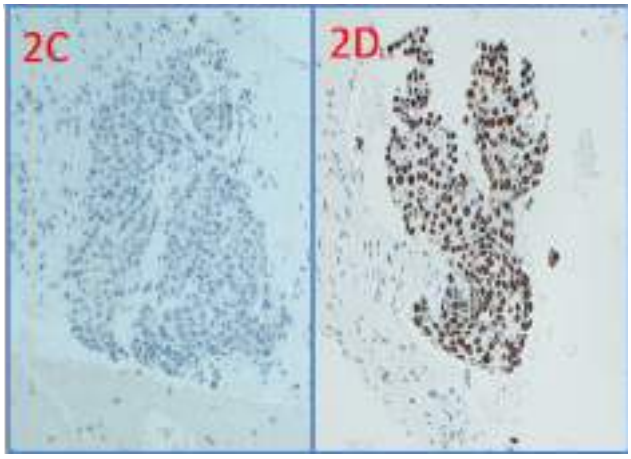

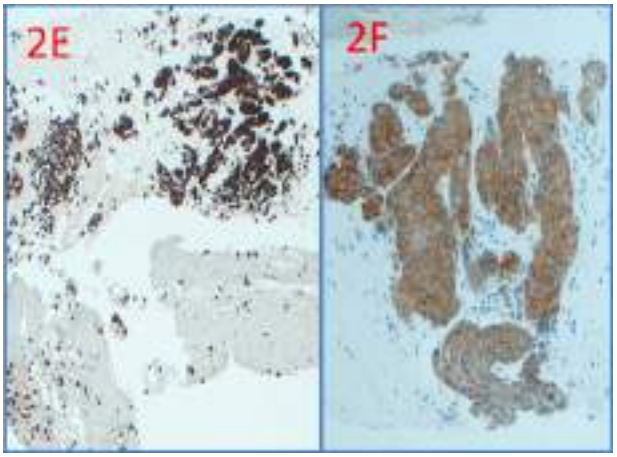

Result: The patient was treated with Crizotinib but, after 4 months, the CT showed a near complete response of the pulmonary disease (Fig. 1 B), while a progression of the left adrenal metastasis was observed. (Fig. 2 A, Fig. 2B). A left adrenal biopsy showed a SCC histology, with ALK rearrangement confirmed both by IHC and FISH. The treatment was switched to alectinib without respoinse so the patient received chemotherapy. **Conclusion:** The absence of an initial biopsy of the adrenal mass doesn't allow to distinguish between a lung ADC to SCC transdifferentiation with a consequence of the treatment-induced selection pressure, so a preexisting SCC at the time of diagnosis would exhibit tumor dominance after elimination of the ADC. However, the presence of the ALK rearrangement in the adrenal biopsy suggest a possible ADC to SCC transdifferentiation in the early phase of metastases development as a new potential mechanism of drug resistance

Keywords: Adenosquamous NSCLC, ALK translocation

EP1.01-57 CLINICAL PROFILE AND TREATMENT OUTCOMES OF NSCLC IN ELDERLY SUBJECTS WITH POOR PERFORMANCE STATUS FROM INDIA

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Background: Elderly population and subjects with poor performance status (PS) are generally excluded from Lung cancer (LC) trials evaluating various treatment modalities, and their outcome is unclear. Herein, we report the clinical profile, treatment and overall survival (OS) of elderly non-small cell LC (NSCLC) subjects with poor PS. **Method: Method:** We retrospectively reviewed our database (from Jan 2016-Dec 2017) to identify NSCLC subjects aged ≥65 years and having an Eastern cooperative oncology group PS (ECOG-PS) ≥2 at presentation. Demographic profile, treatment details, PS after treatment and OS (as on 15th November 2018) were retrieved. We also report the incidence of grade 3 or 4 adverse events (AE) following chemotherapy. **Result:** 122 patients with a median (interquartile range [IQR]) age of 72.5 (65-88) years were included. Majority were men (86.1%) and smokers (79.5%). ECOG-PS was 2, 3 and 4 in 64.8%, 27.9% and 7.4% patients. Squamous cell carcinoma (53, 43.4%) and adenocarcinoma (51, 41.8%) were the most common histologic subtypes. 69% had TNM (8th edition) stage IV (A in 41%, B in 28%) and 26% had stage III (IIIA 8%, IIIB 10% and IIIC in 8%). Chemotherapy with or without radiotherapy (86%), tyrosine kinase inhibitors (6%) and immunotherapy (1%) were the common treatment modalities, while 10 patients did not receive any treatment. In whom response could be assessed (n=61), the best response achieved was partial response in 38%, stable disease in 49%, complete response in 5% and progressive disease in 8%. Of the subjects undergoing chemotherapy (n=102), 33 experienced grade 3 or 4 AE and 14 subjects had to discontinue chemotherapy before 4 cycles. ECOG PS improved to 0/1 in 22 (19.6%) subjects who underwent any form of treatment. The median survival of the study cohort was 250 days. On a multivariate analysis, the presence of brain metastases was associated with poor OS (HR [95% CI] 7.6 [1.4-41.6]) **Conclusion:** Conclusions: Most of the Elderly patients with NSCLC and poor PS had an advanced stage at presentation. Majority tolerate chemotherapy well and some have an improvement in their PS. The presence of brain metastases is associated with a poor survival.

Keywords: NSCLC, Elderly, Chemotherapy

EP1.01-58 IMPACT OF TUMOUR SIZE ON THE MANAGEMENT AND OUTCOME OF STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: We aimed to evaluate the difference in clinical/radiological presentation and patient management according to tumour size in stage III NSCLC. We also reported its impact on patient's outcome. **Method:** We retrospectively studied 88 patients with stage III NSCLC treated between 2010 and mid-2017 in our oncology department. Various cut-off values for tumour diameter were evaluated. We selected a cut-off value of 4 cm, and considered two groups: tumour size≤4 cm and >4 cm. Epidemiological, anatomo-clinical parameters were collected and compared. Kaplan-Meier method was used to evaluate survival. **Result:** Differences in characteristics of the two groups were described in table 1. Initial

therapeutic strategy was significantly correlated with tumour size; in tumour≤4 cm therapy was concurrent chemoradiation in 0%, neoadjuvant chemotherapy in 53%, upfront surgery 47% vs 25%, 61%, and 14% respectively for tumour size>4 cm group (p=0.003). Among patients receiving neoadjuvant chemotherapy, response was not correlated to tumour size; in≤4 cm group we observed (Partial response (PR) 89%, stable disease (SD)11%, Progressive disease(PD) 0%), in >4cm group response was (PR 39%, SD 36%, PD 25%)(p=0.6). Surgery (upfront or after neoadjuvant chemotherapy) was significantly higher in tumour ≤4cm (65% vs 20%) (p=0.0001). Definitive chemoradiation was more indicated in larger tumours, without statistical significance (75% vs 46%)(p=0.4). Therapeutic discordance between the planned and the administered treatment was significantly higher in larger tumours (68% vs 18%) (p=0.0001). Progression free survival was longer in smaller tumours (18±9.3 vs 11±12.1 months) without being statistically significant. However, median overall survival was significantly correlated with tumour size (41.7± 5.1 in ≤4 cm, 32.8±4.6 months in > 4 cm) (p=0.04). The pattern of recurrence was not correlated to tumour size; it was locoregional in 30%, distant in 20% and both locoregional/distant in 50% in≤4 cm group vs 42%, 24%, and 34% respectively in tumour size> 4 cm (p=0.6). Table 1: Characteristics of patients in the two preselected groups.

Patient characteristics	Tumour size ≤4 cm (n=17)	Tumour size> 4 cm (n=71)	P
Age at diagnosis Median ± SD (years) Elderly (≥70 years),% Young (<70 years),%	. 59±9.1 6% 94%	. 62.27±10.8 28% 72%	0.25 0.05
Gender, % Male Female	. 59% 41%	. 87% 13%	0.006
Performance Status, % 0 1 2	. 6% 94% 0%	. 1% 83% 16%	0.02
Weight loss, %	18%	42%	0.06
Histological type, % Adenocarcinoma Squamous cell carcinoma large cell carcinoma	. 88% 12% 0%	. 47% 52% 1%	0.008
Histological grade, % Well differentiated Moderately differentiated Poorly differentiated	. 18% 76% 6%	. 24% 48% 28%	0.075
T Status, % T1 T2 T3 T4	. 24% 29% 29% 18%	. 0% 7% 18% 75%	0.0001
N Status,% N0 N1 N2 N3	. 6% 6% 71% 17%	. 10% 15% 58% 17%	0.67
Stage,% IIIA IIIB	. 77% 23%	. 44% 56%	0.015

Conclusion: When taking 4 cm as a cut-off value, tumour size influenced clinical presentation and management modalities. It may be considered as a prognostic factor in stage III NSCLC.

Keywords: Tumour size, prognosis, locally advanced NSCLC

EP1.01-59 THE EFFECTIVENESS OF OSIMERTINIB IN A NSCLC PATIENT WITH COMPLEX UNCOMMON EGFR MUTATIONS OF G719X AND S768I: A CASE REPORT

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Background: With the deeper and wider application of gene detection technology in lung cancer, an increasing number of genetic alterations have been identified, especially in the epidermal growth factor receptor (EGFR) gene, including uncommon and complex types of EGFR gene mutations; however, the efficacy of the targeted therapy in these gene mutation types is not clear. **Method:** We report the genetic test results from the analysis of postoperative specimens from a lung adenocarcinoma patient that suggest complex EGFR mutations of G719X and S768I. **Result:** After tumor recurrence, the patient was treated with osimertinib and achieved an excellent and long-lasting clinical response. The patient has taken osimertinib for 18.2 months with an efficacy evaluation partial response (PR), and her follow-up is still ongoing.

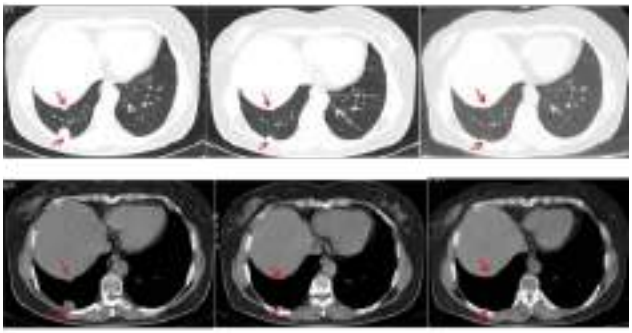

Figure 1. Patient's relevant imaging pictures during treating with osimertinib

Conclusion: Complex uncommon EGFR mutations of G719X and S768I have a good response to osimertinib.

Keywords: uncommon EGFR mutation, Non-Small Cell Lung Cancer, Osimertinib

EP1.01-60 LENT PROGNOSTIC SCORE FOR LUNG CANCER IN THE PRESENCE OF MALIGNANT PLEURAL EFFUSION

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Background: LENT scoring system is the first validated prognostic score in non-selected malignant pleural effusion (MPE), although its significance in MPE secondary to lung cancer remains unclear. **Method:** 85 consecutive patients (59% male, mean age 67±12yrs) with MPE secondary to lung cancer were enrolled. First episode of MPE presented a new cancer diagnosis in 71% of cases, 29% of MPE were diagnosed on disease progression. Histology types were: adenocarcinoma – 71 (83.5%), small cell carcinoma – 10 (11.8%), NOS – 4 (4.7%). LENT score was calculated on the day of MPE diagnosis confirmed. **Result:** 53 (62%) patients presented moderate risk category by LENT score, and 32 (38%) – high risk category. Mean LENT score was 4 (2–6), median (IQR) survival – 70 (32–281) days. The patients with a moderate risk LENT score had a median (IQR) survival of 147 (70–423) days, those with high risk LENT score – 34 (31–41) days. The ROC analysis showed no significant difference between LENT score and ECOG PS at 1, 3 and 6 months at predicting survival time (p>0.05). MPE group that presented primary cancer diagnosis had a median (IQR) survival of 75 (31-318) days and MPE group that presented disease progression had a median (IQR) survival of 63 (37–185) days, there were no significant difference between these groups. **Conclusion:** Our study meets literature data for LENT score predicting survival prognosis in malignant pleural effusion. However, our study showed no superiority of LENT score over ECOG PS.

EP1.01-61 ISEND MODEL AS A PREDICTOR OF EFFICACY IN IMMUNE CHECKPOINT INHIBITORS FOR NON-SMALL CELL LUNG CANCER: FUKUSHIMA COHORT

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Background: The expression of PD-L1 in tumor tissue and the number of gene mutations (TMB) in tumor tissue have been investigated as predictors of the efficacy of PD-1/PD-L1 inhibitors in non-small cell lung cancer. However. In actual clinical practice, it is difficult to perform these tests in all cases. Therefore, we are searching for an effect prediction marker that can be done easily and inexpensively. Wungki Park et al. constructed the iSEND model as a therapeutic effect predictor and showed its usefulness. We examined the usefulness of iSEND model for non-small cell lung cancer patients who received PD-1 / PD-L1 inhibitor at our institution. **Method:** We retrospectively examined the usefulness of the iSEND model in 56 patients with non-small cell lung cancer who were treated with PD-1/PD-L1 inhibitor in our department after the second treatment. The iSEND model uses patient background and blood tests. Calculated and scored using gender, ECOG performance status, NLR before treatment and after treatment (Neutrophi-to-Lymphocyte Ratios), and divided into three group. For each group, we statistically compared the clinical course such as overall survival and recurrence-free survival. **Result:** In the analysis by Wungki Park et al., The iSEND Poor group has a median overall survival of 4.0 months and 15.9 months, respectively, compared with the iSEND Good group (p = 0.0002), and the median recurrence free period is 1.6 months and 2.6 months, respectively. Months (p = 0.0045), and each showed a significant difference. In our study, no statistically significant difference was found, but a trend similar to the analysis of Wungki Park et al. **Conclusion:** In this study, it is suggested that the iSEND model may be useful as a predictor of the effect of PD-1/ PD-L1 inhibitor.

Keywords: Immune Checkpoint Inhibitors, Non-Small Cell Lung Cancer, iSEND

EP1.01-62 THE SAFETY PROFILE AND PRELIMINARY EFFICACY OF CERITINIB 450MG WITH FOOD IN CHINESE ALK/ROS-1 POSITIVE NSCLC PATIENTS

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Background: Ceritinib have shown potent efficacy in both ALK and ROS-1 rearranged NSCLC. However, high rate of treatment interruption was suffered due to gastrointestinal or liver toxicity using Ceritinib 750mg fasting in previous study. Recently, ASCEND-8 study reported an improved tolerance and a trend to better efficacy with 450mg with food, but little data is available in Chinese patients. This first-time real-world study aims to assess the safety profile and preliminary efficacy of Ceritinib 450mg with food in Chinese patients. **Method:** From Oct 2018 to March 2019, 51 ALK or ROS1 positive NSCLC patients received ceritinib were enrolled from 8 centers in Sichuan province. Safety profile and preliminary efficacy were retrospectively analyzed. The follow-up was to 31st March 2019. **Result:** The baseline characteristics of enrolled patients are listed in Table 1. The median time from diagnosis to Ceritinib treatment is 15.93 months(Range:1.37- 89.97), the median treatment duration is 2.63 months (Range:0.2-5.73)by the time of data cut off. 50 out of 51 patients were assessable for toxicity. The adverse event (AE) rate is 76%, majority of which are grade 1/2. Only 2 patients reduced to 300mg due to AE and no patient dead or terminated treatment due to Ceritinib related AEs. Details are in the Table 2. By the data cut-off, 15 patients have stopped treatment due to disease progression(33.3%),death (53.3%) or other reasons(13.3%. Among the 39 patients underwent radiological assessment,the ORR was 41.0% and DCR was 87.2%.

Table 1. Baseline characteristics of the 51 patients

Characteristics	N (%)
Patient number	51
Age- Medium (Range)	53 (29-78)
Gender	
Male	25 (49.0)
Female	26 (51.0)
ECOG	
0-1	22 (43.1)
≥2	29 (56.9)
Smoking history	
Yes	9 (17.6)
No	42 (82.4)
Histology	
Adenocarcinoma	48 (94.1)
Squamous	2 (3.9)
Adenosquamous	1 (2)
Gene mutation type	
ALK	47 (92.2)
ROS-1	4 (7.8)
Stage	
IIIB	1 (2)
IV	50 (98)
Metastasis site	
Brain	34 (66.7)
Bone	15 (29.4)
Liver	7 (13.7)
Previous Crizotinib treatment	
Yes	50 (98)
No	1 (2)
Previous chemotherapy	
Yes	16 (31.4)
No	35 (68.6)
Previous radiotherapy	
Brain RT	18 (35.3)
Other sites	7 (13.7)
Ceritinib treatment line	
First-line	4 (7.8)
Second-line	35 (68.6)
≥Third-line	12 (23.5)

Table 2. Adverse events of Ceritinib 450mg with food in 50 patients

AE	All grade N (%)	Grade 1/2 N (%)	Grade 3/4 N (%)
Any AE	38 (76)	31 (62)	7 (14)
Fatal AE	0	0	0
AE leading to treatment discountinuation	0	0	0
AE leading to dose reduction	2 (4)	0	2 (4)
Diarrhea	21 (42)	21 (42)	0 (0)
GGT elevation	12 (24)	7 (18)	5 (10)
ALT elevation	11 (22)	10 (20)	1 (2)
AST elevation	11 (22)	10 (18)	1 (2)
Decreased appetite	11 (22)	10 (20)	1 (2)
Vomiting	10 (20)	9 (18)	1 (2)
Nausea	8 (16)	8 (16)	0 (0)
Rash	8 (16)	8 (16)	0 (0)
Fatigue	6 (12)	6 (12)	0 (0)
Abdominal pain	6 (12)	5 (10)	1 (2)
Non-cardiac chest pain	5 (10)	5 (10)	0 (0)
Weight loss	3 (6)	2 (4)	1 (2)
Back pain	2 (4)	2 (4)	0 (0)
Anemia	2 (4)	2 (4)	0 (0)
Blood creatinine increased	2 (4)	2 (4)	0 (0)
Dyspnea	1 (2)	1 (2)	0 (0)
Headache	1 (2)	1 (2)	0 (0)
Neutropenia	1 (2)	1 (2)	0 (0)
Peripheral edema	1 (2)	1 (2)	0 (0)

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Conclusion: Ceritinib 450mg with food demonstrated a good safety profile and efficacy with lower AE incidence rate and better compliance rate compare to ASCEND-8 data for Chinese patients in real-world setting.

Keywords: Ceritinib, non-small-cell lung cancer, Safety

EP1.01-63 THE USEFULNESS OF "SERUM" SAMPLES TO DETECT EGFR T790M MUTATION IN EGFR-TKI-RESISTANT NON-SMALL CELL LUNG CANCER

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Background: Osimertinib, a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor, exerts remarkable effects against *EGFR* T790M resistance mutation-positive NSCLC. Identifying T790M mutation by re-biopsy is essential before prescribing osimertinib. Tissue biopsy is the golden standard for this purpose, but several factors limit its success rate. The liquid biopsy with blood, using circulating tumor DNA, has been an alternative method. However, the true biological meaning and equivalence of liquid biopsy and tumor biopsy are still under investigation. Especially, the usefulness of serum samples to detect T790M mutation is not yet been known. **Method:** We prospectively evaluated the sensitivity, specificity, and parallelism of the detection of *EGFR* mutations in tissue re-biopsy and liquid biopsy (plasma and serum), simultaneously, from June 2016 to May 2017. *EGFR*-mutations in tumor re-biopsy were evaluated by COBAS ver2 and peptide nucleic acid/locked nucleic acid PCR clamp method, and those in liquid biopsy were evaluated with COBAS ver2. **Result:** Fifteen patients were enrolled. In ten patients whose *EGFR* mutation was detected in liquid biopsy, the original *EGFR* mutation (exon 19 del or L858R) was detected in all patients. The detection rate of T790M was lower than that of the original *EGFR* mutation in liquid biopsy compared to that in tissue re-biopsy. The detection of T790M in serum exhibited a higher specificity (67%) and positive predictive value (50%) than that in plasma (50% and 40%, respectively). The detection sensitivity was similar in plasma and serum. Nine patients were treated with osimertinib. The RR was 77.8% and DCR was 100%. One patient who presented a response was positive for T790M in liquid biopsy (both plasma and serum) and negative in tissue re-biopsy. **Conclusion:** We suggest serum samples to be more useful than plasma samples for determining the effectiveness of osimertinib against relapse tumor sites because they were more reliable in the detection of T790M mutation at the relapse tumor tissue sites. Repeated tests with different samples and different methods may improve accuracy of T790M detection and will lead to the maximum benefit for the patient.

Keywords: T790M mutation, liquid biopsy, Osimertinib

EP1.01-64 EFFECT OF AMRUBICIN IN PATIENTS WITH PREVIOUSLY TREATED NON-SMALL-CELL LUNG CANCER

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Background: Although the prognosis of non-small cell lung cancer (NSCLC) has been rapidly improved due to the appearance of various tyrosine kinase inhibitors and immune checkpoint inhibitors, cytotoxic chemotherapy are still important treatment for patients who can't receive these drugs or are ineffective for these drugs. Amrubicin (AMR) couldn't significantly improve the progression free survival compared with docetaxel in a randomized phase III trial of Japanese previously treated NSCLC patients, but median progression free survival (PFS) and overall survival (OS)were comparable in the amrubicin and docetaxel groups. The purpose of this study is to clarify the use of amrubicin in clinical practice. **Method:** From January 2014 to March 2019, 479 progressive or recurrent NSCLC patients received chemotherapy or radiotherapy. Only 27 patients received AMR. We retrospectively evaluated these 27 patients. **Result:** None of the NSCLC patients who received AMR had epidermal growth factor recepter gene mutations nor anaplastic lymphoma kinase gene translocations. Median number of prior chemotherapy regimens was four, and median PFS was 62 days and OS was 229 days. Overall response rate was 7.4% and disease control rate was 37.0%. **Conclusion:** AMR was often used for patients considered to have a poor prognosis, and its effect was limited.

Keywords: Amurubicin, NSCLC, cytotoxic chemotherapy

EP1.01-65 THE RELATIONSHIP BETWEEN PRELIMINARY EFFICACY AND PROGNOSIS AFTER FIRST-LINE EGFR-TKI TREATMENT OF ADVANCED NSCLC

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Background: Nowadays, patients with *EGFR*-TKI-sensitive advanced non-small cell lung cancer (NSCLC) receive *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) as first-line treatment. We aimed to analyze the relationship between preliminary efficacy (tumor shrinkage within 1 month) and progression-free survival (PFS) after first-line *EGFR*-TKI treatment. **Method:** A total of 82 patients with *EGFR*-TKI-sensitive advanced NSCLC confirmed by histopathology from January 2013 to January 2017 were retrospectively analyzed. All patients received first-line *EGFR*-TKI treatment and follow-up at Shanghai Chest Hospital. **Result:** Of 82 patients, 42 (51.2%) patients achieved partial response (PR) within 1 month, and 40 (48.8%) patients achieved stable disease (SD: -30%~0) within 1 month. The median PFS among all patients was 10 months. The median PFS in patients achieving PR within 1 month was 10 months. The median PFS in patients achieving SD (-30%~0) within 1 month was 9.3 months. There was no statistically significant difference between PR within 1 month and SD (-30%~0) within 1 month (P=0.620). In the *EGFR*-sensitive mutation subgroup, there was also no statistically significant difference between PR within 1 month and SD (-30%~0) within 1 month. Univariate and multivariate analysis of first-line *EGFR*-TKI treatment showed that age, *EGFR* mutation type, and T staging had effects on PFS. Patients who were more than 65 years old, had *EGFR* 19del mutation, along with a T staging less than 4, had a longer PFS; these differences were statistically significant. Liver metastasis, bone metastasis, and brain metastasis were not shown to be related to PFS. **Conclusion:** For patients with *EGFR*-TKI-sensitive advanced NSCLC, there is no correlation between preliminary efficacy (tumor shrinkage within 1 month) and PFS after first-line *EGFR*-TKI treatment.

Keywords: Non-Small Cell Lung Cancer, EGFR tyrosine kinase inhibitor, first-line treatment

EP1.01-66 DETECTION OF GENOMIC MUTATIONS IN BLOOD AND URINE CTDNA IN LUNG ADENOCARCINOMA WITH EGFR MUTATION ON TISSUE – AN INTERIM PROGRESS REPORT

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective therapy for stage IIIB/IV EGFR-mutation positive (EGFRm+) NSCLC. Despite initial response, clinical progression occurs, often with development of a second TK mutation. Mutation analysis is performed at time of diagnosis usually on single tissue biopsy. Samples can be difficult to obtain and may not represent neoplastic tissue at other sites due to heterogeneity. On progression, patients rarely undergo repeat tissue biopsy. Therapy is no longer truly personalised. CtDNA may be an alternative to tissue biopsy for mutation analysis. It may be more representative, and provide real time assessment of disease status, maintaining individualised therapy. Published retrospective data are available on detection of EGFR mutations in plasma ctDNA, and evidence that urine can be used is emerging. Clinical use has been limited by lack of evidence for detection methods and concordance with tissue. Retrospective data suggest that on response to TKI, TK mutation load reduces, and on progression, mutation load increases and/or a new mutation emerges. This has not been validated prospectively. **Method:** A prospective pilot study: 20 patients, 2 UK sites; with

stage IIIB/IV EGFRm+ NSCLC on tissue sample, TKI-treatment naïve. Plasma and urine collected prior to TKI treatment and monthly on treatment. CtDNA is extracted from plasma and urine using Quigen kit, and analysed using digital droplet PCR for the 3 most common EGFR mutations – del19, L858R and T790M. Objective: To investigate if urine/plasma ctDNA may be used to prospectively detect and monitor EGFR mutational status at baseline and during TKI therapy Primary Endpoint: To assess if ctDNA from urine/plasma could be a reliable source of EGFR testing Secondary Endpoint: To assess if changes in levels of baseline mutation or development of new mutations in ctDNA correlates with disease response/progression during TKI therapy Outcome: To inform development of a larger study to further investigate and validate the role of liquid biopsy in treatment of EGFRm+ NSCLC **Result:** CtDNA analysis performed on samples from 14patients to date. On baseline tissue, 8 (57%) had del19 mutation, 5 (36%) had L858R mutation, and 1 (7%) had L861Q mutation. Representative of population distribution of EGFR mutations. In those with tissue del19 mutation, del19 mutation was identified on baseline ctDNA in 8/8 (100%) plasma samples and 6/7 (86%) urine samples (one patient did not provide baseline urine sample). None had L858R mutation in plasma/urine. In one plasma ctDNA sample, very low levels of T790M mutation were identified, but no T790M mutations were found in urine ctDNA. In those with tissue L858R mutation, L858R mutation was identified on baseline ctDNA in 3/5 (60%) plasma samples and 4/5 (80%) urine samples. All were found to have del19 mutation on baseline plasma ctDNA, 3/5 had del19 mutation in urine ctDNA. None had T790M mutations in plasma/urine ctDNA. **Conclusion:** Sensitivity is high for identifying baseline EGFR mutations in plasma/urine ctDNA. Very hard to comment on specificity. It's known that del19 and L858R mutations can co-exist. It's possible that mutation analysis performed on DNA extracted away from primary tumour site may carry additional mutations due to heterogeneity.

Keywords: ctDNA, EGFR

EP1.01-67 MOLECULAR PROFILING OF K-RAS AND ITS SUBTYPES IN NSCLC PATIENTS WITH LIVER METASTASIS

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Background: Non-small cell lung cancer (NSCLC) tend to have a poor prognosis in the presence of liver metastasis. Molecular profiling of NSCLC has played a major role in identifying a number of oncogenic targets that have led to novel targeted therapies. KRAS is a frequently mutated gene in NSCLC, occurring in approximately 30% of lung adenocarcinomas and most commonly manifesting as the transversion mutations G12C, G12V, G12A. there are presently no targeted therapies approved for *KRAS*-mutant NSCLC. Immunotherapy has emerged as a standard of care for first-line treatment of advanced NSCLC, specifically through targeting the programmed cell death protein-1 (PD-1/PD-L1). Given the aggressive nature of *KRAS*-mutant NSCLC with liver metastases and the lack of approved therapies targeting the KRAS pathway, checkpoint blockade immunotherapy may represent an impactful primary therapeutic option for these patients. **Method:** The CARIS database from 2016 - 2018 was queried and patients with NSCLC were identified. PD-L1 antibody 22c3 ≥1% was considered positive. PD-L1 expression as well as k-ras and TP53 mutation status were analyzed and correlation between different variables were identified using ANOVA **Result:** We identified 361 patients with NSCLC having Liver metastasis. Median age was 67. Gender distribution was equal (51.4% males, 49.7% females). Of the 361 patients, we identified 74 patients with mutated K-ras. Thirty nine out of the 74 patients had PD-L1 expression (52.7%). Twenty one patients had the G12C subtype (28%) with 14 patients (66%) having positive PD-L1 expression. Of the 287 patients with wild type K-ras, 115 patients had PD-L1 positive expression (40%) with no statistical significance (P=0.134) in comparison to the k-ras mutant population.We also studied 2237 K-ras mutant patients without liver metastases where 882 patients had the G12C subtype (39.4%). On the other hand, only 21 patients were positive for G12C k-ras subtype out of the 74 k-ras mutant patients with liver metastases.Among patients with liver metastases, adenocarcinoma was the most common histological subtype (223 patients), Carcinoma NOS was the second common histological subtype (61 patients).Patients with no liver metastasis had median age of 68. Gender distribution was equivocal. **Conclusion:** Patients with k-ras mutant G12C subtype were associated with more frequent PD-L1 expression and less occurrence of liver metastases.

EP1.01-68 IMPACT OF EGFR GENOTYPE ON THE EFFICACY OF OSIMERTINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

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Background: A T790M of the epidermal growth factor receptor (EGFR) is the most frequently encountered mutation occurring acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). The aim of this study was to assess the differential clinical outcomes of osimertinib therapy in NSCLC patients with T790M according to the type of active *EGFR* mutation, i.e. exon 19 deletion or L858R point mutation. **Method:** We conducted a prospective observational cohort study to evaluate the efficacy and safety of osimertinib in patients with major EGFR mutation and T790M-positive advanced NSCLC who had disease progression after first-line EGFR-TKI therapy. The efficacy of osimertinib was evaluated according to the type of *EGFR* mutation. **Result:** A total of 51 patients were included in this study. The exon 19 deletion was found in 33 (65%) patients, and the L858R point mutation in 18 patients (35%). An objective response was obtained in 29 patients, indicating an objective response rate of 58.8%. The response rate was 69.7% in patients with exon 19 deletion and 38.9% in patients with L858R point mutation, indicating a statistically significant difference (*P* =0.033). The median progression-free survival (PFS) and overall survival (OS) of the entire patient population were 7.8 and 15.5 months, respectively. Median PFS in the exon 19 deletion and L858R point mutation groups was 8.0 months and 5.2 months, respectively, indicating a statistically significant difference (*P* =0.045). Median OS in the exon 19 deletion and L858R point mutation groups was 19.8 months and 12.9 months, respectively, indicating a statistically significant difference (*P* =0.0015). Multivariate analysis identified exon 19 deletion as a favorable independent predictor of PFS and OS. **Conclusion:** Investigators should consider the proportions of sensitive *EGFR* mutation types as a stratification factor in designing or reviewing clinical studies involving osimertinib.

Keywords: EGFR genotype, Non-small cell lung carcinoma, Osimertinib

EP1.01-69 SAFETY AND EFFICACY OF PERCUTANEOUS COMPUTED TOMOGRAPHY-GUIDED THERMAL ABLATION OF NON-SMALL CELL LUNG CANCER METASTASES

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Background: Percutaneous computed tomography-guided (CT-guided) thermal ablation is a minimally invasive method for the treatment of adrenal metastases, painful bone metastases and liver metastases originating from non-small cell lung cancer (NSCLC). We aimed to further evaluate the safety and efficacy of CT-guided radiofrequency ablation (RFA) and microwave ablation (MWA) in the management of metastases in a real-life cohort of NSCLC patients. **Method:** The medical records of 142 patients with metastatic NSCLC (71, 32 and 40 patients with adrenal metastases, painful bone metastases and liver metastases, respectively) treated with CT-guided RFA or MWA were retrospectively studied. The efficacy of thermal ablation was evaluated by post-ablation imaging. For painful bone metastases, palliation was assessed by the Brief Pain Inventory (BPI) score. **Result:** Technical success of CT-guided thermal ablation was 100%. No major complications occurred. Among patients with adrenal metastases treated with RFA or MWA, local recurrence was observed in 17.1% and 19.4% of cases at 1-year follow up, respectively. In patients with painful bone metastases, significant pain relief was noted after thermal ablation (p<0,001). Local recurrence was

observed in 3.3% of cases with liver metastases at 1-year follow-up. **Conclusion:** CT-guided RF and MW ablation is a safe and effective local treatment for the management of adrenal, bone and liver metastases from NSCLC. For painful bone metastases RF ablation provides significant pain relief.

Keywords: percutaneous, computed tomography-guided thermal ablation, Non-Small Cell Lung Cancer

EP1.01-70 REIRRADIATION FOR LOCOREGIONALLY RECURRENT LUNG CANCER: OUTCOMES IN NON-SMALL CELL LUNG CARCINOMA

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Background: Locoregional failure in non-small cell lung cancer (NSCLC) remains high often leading to symptoms like hemoptysis and chest pain and the management for recurrent disease in the setting of prior radiotherapy is difficult. We retrospectively analyzed the outcomes for re-irradiation (reRT) for locoregionally recurrent lung cancer when used with intention of symptomatic relief in NSCLC. **Method:** This is a retrospective analysis of treatment of thirty-four patients of NSCLC who received re-irradiation to the thorax. All received re-irradiation by intensity-modulated radiotherapy. Palliative responses, survival outcomes, and prognostic factors were analyzed. **Result:** Median age of the group was 63 years, all but seven patients were males. All patients received a dose of 30.6 Gy in 17 fractions. Median survival of the group was 4.7 months, median KPS was 70. Relief of haemoptysis could be obtained in 31/34 assessable cases (91%), treatment was less effective for coughing 19/34 (56%) and dyspnoea 11/34 (32%). However, acute toxicities and new disease symptoms limited the duration of palliative benefit in the symptomatic NSCLC patients to a median of 2.3 months. No fatal complications were noted. Grade 2 or greater esophagitis was seen in 3/34(8%) cases. **Conclusion:** Reirradiation to the thorax for locoregionally recurrent NSCLC can provide palliative benefit. Select patients may experience meaningful survival prolongation after reirradiation. Careful selection of patients is necessary to avoid acute toxicity in already symptomatic patients. This experience demonstrates that repeated courses of radiotherapy can be given successfully and safely despite previous radical dosage.

Keywords: Re-irradiation, Non-Small Cell Lung Cancer, Palliative RT

EP1.01-71 THYMIDYLATE SYNTHASE AND FOLATE RECEPTOR ALPHA EXPRESSION AS POTENTIAL BIOMARKERS FOR EFFICACY OF PEMETREXED IN NSCLC

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Background: Predictive biomarkers for chemotherapy in advanced non-squamous NSCLC are lacking. Thymidylate synthase (TS) and folate receptor alpha (FRA) are target enzymes for pemetrexed. Here we investigated TS and FRA expression and their role as a prognostic and predictive biomarker for efficacy of pemetrexed-based chemotherapy. **Method:** We performed immunohistochemistry on pre-treatment tumour specimens for TS and FRA expression and correlated it with patient's demographic and clinical characteristics, treatment responses and survivals in a retrospective training cohort of patients with advanced non-squamous NSCLC treated with pemetrexed-based chemotherapy. Similar analysis for validation was performed in a prospective cohort of patients participating in a randomized control trial "to compare efficacy and safety of pemetrexed-carboplatin versus paclitaxel-carboplatin as induction regimen in advanced non-squamous NSCLC". Chi-square test was used to co-relate TS and FRA expression with clinico-pathological characteristics. Kaplan-Meier methods, Log-rank test and Cox proportional-hazards model were used for survival analysis. **Result:** In the retrospective training cohort median age was 57 (26-70) years with male predominance (ratio=2:1). TS and FRA expression were evaluable in 55 and 47 patients respectively. In this cohort TS and FRA expression didn't co-relate with best overall response rates (ORR), however, low TS expression and positive FRA expression were associated with improved progression free survival (PFS), albeit non-significant. In the prospective validation cohort median age was 52 (28-65) years with 70% males. In this cohort TS and FRA expression were analysed in 113 and 97 patients respectively. High TS expression was significantly associated with better ORR in patients treated with paclitaxel-carboplatin (p=0.04) but there was no co-relation of TS expression with response rates in pemetrexed-carboplatin group. Younger patients (age<40 years) had more TS 'low or negative' status (p=0.04). High TS expression was associated with ALK positivity (p=0.02), bone metastases (p=0.01) and brain metastases (p=0.002). Positive FRA expression was associated with EGFR positivity (p=0.004) and liver metastases (p=0.020). Positive FRA expression was associated with improved PFS in patients treated with pemetrexed-carboplatin (median: 9.23 versus 4.27 months, p=0.01), paclitaxel-carboplatin (median: 10.87 versus 6.47 months, p=0.08) as well as improved OS (median: OS not reached versus 10.13 months, p=0.01), especially in patients treated with pemetrexed-carboplatin (median: 18.73 versus 10.46 months, p=0.08). **Conclusion:** In conclusion, the results from this study suggest that TS or FRA expression doesn't predict efficacy of Pemetrexed, however, high TS expression may predict better ORR in patients receiving paclitaxel-carboplatin. FRA expression may serve as a prognostic factor in patients receiving chemotherapy irrespective of the regimen.

Keywords: advanced NSCLC, Thymidylate Synthase and Folate Receptor Alpha, predictive biomarker

EP1.01-72 TREATMENT OUTCOME OF 2ND GENERATION EGFR-TKI FOR NON-SMALL CELL LUNG CANCER

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Background: Efficacy of EGFR-TKI has been demonstrated in 1st line treatment for EGFR mutation positive NSCLC. Afatinib, 2nd generation EGFR-TKI inhibits HER2 (ErbB2) or ErbB4 in addition to the EGFR (ErbB1), is expected more effective compared to the 1st generation EGFR-TKI. In this study, we investigated retrospectively on the treatment outcome of the cases that received 2nd generation EGFR-TKI treatment at our institution. **Method:** The subjects were 70 patients treated with a 2nd generation EGFR-TKI afatinib for the period from May 2014 to April 2018. Age, gender, smoking history, performance status (ECOG), EGFR mutation type, starting dose, dose reduction during treatment period, objective response, presence of brain metastasis, EGFR-TKI treatment line and T790M mutation result were retrospectively analyzed the association with the time to treatment failure and survival. **Result:** Among the 70 patients, male 28 cases and female 42 cases, and 42 never smoker included. Median age was 65 years old (43-88 years old). EGFR mutation type included exon 19 deletion 42 cases, exon 21 L858R 13 cases, uncommon mutation 13 cases and compound mutation 2 cases. 18 cases were administered with 40mg initial dose, 28 cases were 30mg and 24 cases were 20mg. 68 cases were good performance status (0 or 1), and 33 (47%) cases had brain metastasis. Dose reduction were performed in 43 (61%) cases, and partial response were observed in 34 (49%) cases. 36 (51%) cases were no pretreatment with EGFR-TKI (afatinib as first EGFR-TKI). Of the 70 cases, 33 (47%) cases were performed re-biopsy, and 15 cases of those were proved T790M acquired resistant mutation. **Conclusion:** Good performance status, dose reduction, good objective response, no brain metastasis, early EGFR-TKI treatment line and T790M mutation positivity were significantly associated with prolongation of the time to treatment failure, but no significant characteristics were associated with prolongation of the survival.

Keywords: EGFR mutation, 2nd generation EGFR-TKI, Non-Small Cell Lung Cancer

EP1.01-73 TROUSSEAU'S SYNDROME ASSOCIATED WITH PULMONARY PLEOMORPHIC CARCINOMA SHOWING AGGRESSIVE FEATURES: A CASE REPORT

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Background: Trousseau's syndrome is characterized as an unexpected cancer-related thrombotic event, such as a cerebral infarction or a deep vein thrombosis/pulmonary embolism. The histology of most reported cases of lung cancer with Trousseau's syndrome involves adenocarcinoma. We describe the first reported case of Trousseau's syndrome with pulmonary pleomorphic carcinoma and aggressive features. **Method:** A 74-year-old man, a current heavy smoker (38 pack-years), presented with a well-circumscribed peripheral mass (diameter: 38 mm) in the lower lobe of the left lung. A fluorine-18-fluorodeoxyglucose (FDG) positron-emission tomography scan showed a strong accumulation of FDG in the mass. Serum carcinoembryonic antigen (CEA) and D-dimer levels were 16.0 ng/mL and 0.6 μg/mL, respectively. A left lower lobectomy with systemic mediastinal lymph node dissection revealed the tumor was pleomorphic carcinoma with extensive lymph node involvement and was graded as pT3N2M0, pStage IIIB (pm1, pl1, ly1, v1, br+). The tumor mainly comprised giant cells with high-grade pleomorphism, admixed with a solid adenocarcinoma component and papillary growth pattern. The adenocarcinoma component was positive for periodic acid-Schiff (PAS) stain and resistant to diastase, suggesting mucin production. Moreover, most of the tumor cells were strongly positive for tissue factor (clone TF (H-9)). **Result:** Three months postoperatively, diffuse infiltration rapidly appeared in plain chest radiographs of the left lung, which was identified as lymphangitic carcinomatosis via bronchoscopy. Prior to treatment for cancer recurrence, the patient suddenly presented with dysarthria and left hemiplegia. Magnetic resonance imaging revealed acute ischemic stroke in the right hemisphere accompanied with subacute small infarcts in the left hemisphere and bilateral cerebellum. Magnetic resonance angiography revealed a right middle cerebral artery M2 segment occlusion. An echography and a chest CT showed no evidence of atherosclerotic thrombus or cardiac thrombus in the left atrium or in the stump of the resected pulmonary vein. Plasma D-dimer level was elevated at 17.6 μg/mL, as were the CEA and carbohydrate antigen 125 (CA125) levels (73.4 ng/mL and 331 U/mL), respectively. He underwent mechanical thrombectomy with a stent retriever, and partial recanalization was achieved. The pathology of the retrieved thrombus showed that almost all parts consisted of fibrin without red blood cells. These findings and pathological findings of the primary lung cancer suggested Trousseau's syndrome as the etiology of the cerebral infarction. **Conclusion:** A hypercoagulable state, due to aggressive recurrence of pulmonary pleomorphic carcinoma accompanying with cancer cell production of mucin and tissue factor, may be a potential mechanism for cancer-related thrombosis.

Keywords: Trousseau's syndrome, cerebral infarction, pulmonary pleomorphic carcinoma

EP1.01-74 IMPLANTATION OF PERMANENT PLEURAL CATHETER (PPC) FOR MALIGNANT PLEURAL EFFUSION (PE) IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Pleural effusion (PE) is a frequent complication in patients (p) with advanced NSCLC that causes refractory symptoms such as pain and dyspnea. These patients frequently need repeated thoracocentesis to relieve symptoms. Implantation of PPC can avoid repeated thoracocentesis. **Method:** Thirty consecutive patients of our hospital with advanced NSCLC who overwent to PPC implantation from May 2008 to September 2018 were retrospectively evaluated. Baseline characteristics, acute and late complications and outcome were retrospectively collected. Overall survival (OS) was calculated from the date of the PPC implantation to the date of death. **Result:** Thirty patients were evaluated, 20 were male and 10 female. All the patients were death at the cut-off date, the 1st October 2018. Median age at PPC implantation was 66y (range: 47-91) and 80% presented ECOG PS 2. Adenocarcinoma was the most frequent histology (22p). Mean hospital stay was 7 days (range 1-28). Average catheter duration was 60 days (range 3-181). Four patients (13%) suffered an acute complication: 1 pleuro-cutaneus fistula, 1 empyema, 1 hematoma and 1 needed surgical intervention because the catheter guided was at pleural cavity. After hospital discharge, one patient presented a complication, with pleural liquid exit from pericatheter. Twenty-five patients (83%) presented clinical relief and 11p (37%) received chemotherapy after PPC implantation. Citology of pleural liquid was performed in 23p (77%) and resulted positive for malignancy in 14p. Median OS was calculated from PPC implantation to death and resulted of 14.3 weeks (IC 95%, range 1.3-59.1). **Conclusion:** PPC implantation is a safe technique that can cause symptomatic relief in selected patients with malignant pleural effusion. However, average catheter duration and median survival after PPC implantation are low. Therefore a better selection of patients is mandatory in our centre.

Keywords: Lung cancer, Pleural effusion, Pleural Catheter

EP1.01-75 PALLIATIVE THORACIC RADIOTHERAPY FOR LUNG CANCER: WHAT IS THE MOST APPROPRIATE FRACTIONATION?

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Background: Radiotherapy is the one of the most effective modalities to palliate the symptoms (hemoptysis, pain, breathlessness) of poor-prognosis patients with advanced non-small-cell lung cancer. Most appropriate dose schedule however remains debatable. We conducted a retrospective analysis that compared the efficacy of radiotherapy schedules consisting of 5 fractions of 4 Gy (5 x 4 Gy) versus 10 fractions of 3Gy (10 x 3 Gy) in advanced Non Small Cell Lung Cancer (NSCLC). The end point evaluated was symptomatic relief. **Method:** Between July 2016 and September 2017, 60 patients with advanced NSCLC were randomised to either 5 fractions of 4 Gy (5 x 4 Gy):Arm A or 10 fractions of 3Gy (10 x 3 Gy):Arm B. The eligibility criteria was histologically or cytologically confirmed NSCLC, age $\geq$ 30, stage III or IV disease, Karnofsky performance status (PS) $\geq$ 40, expected survival $\geq$ 3 months. The quality-of-life was assessed using the patient records :European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the lung cancer–specific module QLQ-LC13. The primary study end points was control of symptoms viz cough, hemoptysis, pain and dyspnea, and the secondary end point was to evaluate Overall Survival (OS). **Result:** 52 out of 60 patients were males, 18/60 had lost to follow up. Majority of patients presented in 5th and 6th decade of their lives, mean age of presentation was 58.87 (Range31-80). Majority (69%) of patients had presented with poor KPS 70 or less. Most common presenting symptom was cough with expectoration (74.66%) followed by hemoptysis (47.33%). Post treatment 36% reported reduced cough, 44% reported reduced dyspnea, 57% reported reduced pain and 90% reported reduced hemoptysis within 20 weeks from start of treatment, with no statistical difference among the groups. Except for improved hemoptysis at week 5 in Arm A (P =0.03), there was no difference among the groups. Furthermore, the palliative effect of symptoms seemed to last throughout the planned follow-up period. Overall survival for all patients (n=42) revealed no significant survival difference among the treatment groups (P = 0.2). The median survival was 6.2 and 6.7 months in arm A and B, respectively. **Conclusion:** Hypofractionated regimen of 20Gy/5 fractions is atleast as effective at providing symptomatic relief and yields equivalent survival as 30Gy/10 fractions in patients with advanced non-small cell lung cancer and thoracic symptoms besides having the advantage of fewer visits to hospital as well.

Keywords: advanced NSCLC, Hypofractionated RT, Palliative RT

EP1.01-76 ONCOMINE TUMOR MUTATION LOAD ASSAY IN NSCLC PATIENTS FROM ARGENTINA: STUDY DESIGN AND FEASIBILITY

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Background: High throughput next generation sequencing has improved the understanding of the genomic landscape of cancer. Somatic mutations throughout the exome derive in novel peptide sequences that can be recognized by the host immune system and drive immune responses in patients. The tumor mutational load (TML) is the number of somatic mutations per megabase of DNA and is an emerging biomarker to predict response to immune checkpoint inhibitors. **Method:** The objective of this study was to evaluate the feasibility of assessing TML in tumors from patients with advanced NSCLC, treated with Nivolumab in second with Ion Torrent™ Oncomine™ TML Assay and compare it with TML from WES. The Oncomine TML is a targeted NGS assay that provides quantification of somatic mutations, from limited formalin-fixed, paraffin-embedded (FFPE) samples. **Result:** DNA was purified with QIAamp DNA FFPE Tissue Kit (QIAGEN). We used a new Ion AmpliSeq targeted panel, derived from the Comprehensive Cancer Panel which covers approximately 1.7 Mb of genomic DNA and 409 genes, OTML in S5, Ion Proton (Life Technologies); and WES were performed in NovaSeq 6000 Sequencing System (Illumina). We included 40 patients with advanced NSCLC. 27 (68%) of patients had both, tumor and normal tissue to perform WES. FFPE samples were obtained from lungs (N=21), lymph nodes (N=11), pleura (N= 3), brain (N=1), skin (N= 1), bone marrow (N = 1), soft tissue (N=1). We used 20 ng of DNA to develop the manual library and templating. We covered a large genomic footprint to accurately measure somatic mutations, replacing the need for whole-exome sequencing (WES). Pipeline for analysis of the NGS output will be presented. **Conclusion:** TML estimation with low DNA input requirements from FFPE samples is feasible. Up to 8 samples can be sequenced in a Ion 540™ Chip. Mutation load assessment can be done within 2–3 days. This assay was highly reproducible in FFPE samples. A detailed report provides normalized mutation count per MB as well as mutation signatures.

EP1.01-77 LOCALLY ADVANCED NON SMALL CELL LUNG CANCER - TREATMENT OUTCOME IN REAL WORLD SETTING

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Background: Lung cancer is one of the leading cancers in India. About two-thirds present in advanced /metastatic stage. The mainstay therapy for advanced non small cell lung cancer (NSCLC) is concurrent chemoradiation. Locoregional failure constitutes the predominant failure pattern. A larger proportion of the patients are treated with palliative intent. The current study evaluates the demographic profile, treatment pattern, and outcome and radiation practice for palliative treatment at a tertiary care academic medical institution. **Method:** Medical records of patients treated between June 2016- June 2018 were evaluated Clinical presentation, treatment details and outcome was recorded. Case records with incomplete workup or treatment was excluded. **Result:** A total of 181 patients of NSCLC were registered of which 108 were metastatic at presentation 96 patients received palliative radiotherapy and are analysed. 11 patients has pulmonary metastasis and 85 had extrapulmonary metastasis of which 21 patients had multiple extrapulmonary disease. Ninety-six patients received palliative radiotherapy. 84 patients had ≤ 1comorbidity. Most of the patients were aged ≤65years (80%) with a female preponderance. Cough, chest pain and dyspnea each were present in one-third of patients. Twenty-six patients had bony pain, 18 had symptoms of raised intracranial pressure and 7 patients had SVCO. Adenocarcinoma was the commonest histology observed in 86.4% patients. Bone was the most common site of metastasis, seen in 65(65.7%) patients; followed by brain in 23(24%). Palliative radiotherapy was given to primary in 13(13.5%), brain in 27(28%), bone in 56(58%). Palliative radiotherapy to weight bearing sites was treated with 8Gy in single fraction. Whole brain radiotherapy was treated with 20Gy in 5 fractions. 65% of patients received palliative chemotherapy. Platinum- taxane and platinum-pemetrexed regimens were the most common regimen practiced for among squamous and adenocarcinoma histology respectively. Median follow up was 6.6 months (2 to 37 months). Median time for oncological intervention was 1.2 months (0.1 to 5.4months). Median PFS was 6months (IQR 3- 11.2months) **Conclusion:** The study concludes that a large proportion of patients present in advanced/metastatic disease. In the metastatic setting bone metastasis was the most common site followed by brain. The outcome is dismal and newer treatment techniques /modalities may result in improved outcome in this group of patients.

Keywords: Radiation therapy, palliative, Advanced lung cancer

EP1.01-78 T4 LUNG CANCER INVADING THE DESCENDING THORACIC AORTA: A CASE SUCCESSFULLY TREATED WITH SURGERY BY A MULTIDISCIPLINARY TEAM

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Background: T4 lung cancer invading the great vessels was usually considered a relative contraindication for radical surgery, because of technical difficulties and intra/postoperative bleeding complications. Recent studies have proved radical pneumonectomy or lobectomy together with aorta endograft positioning to have low mortality and morbidity rate and fairly good overall survival; however, only few cases have been reported in the literature. We report a case of T4 lung cancer invading the descending thoracic aorta (DTA) successfully treated with surgery by a multidisciplinary thoracic and vascular team. **Method:** A 60-year old male patient was admitted to our Department with a left upper lobe pulmonary tumor of 9 cm invading the DTA, as shown by preoperative computed tomography (CT) scan and magnetic resonance imaging (MRI). 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT total body scan revealed an uptake only at tumor site (SUV max 26.28) with no lymph nodes positivity. Preoperative spirometry values were FEV1 79%, FVC 82% and DLCO 72.5%. Pulmonary perfusion scintigraphy showed 65% for the right lung and 35% for the left one. We performed left pneumonectomy and hilar-mediastinal lymphadenectomy by posterolateral thoracothomy approach, observing about 5 cm long abventitial infiltration of DTA, 3 cm after left subclavian artery origin. An aortic endograft (GORE TAG Comformable Thoracic Stent Graft with ACTIVE CONTROL System) via left femoral artery was disposed 2 cm distal to the subclavian artery origin, then the infiltrated abventitial aortic wall (40% of the aortic circumference) was removed, leaving only the macroscopic healthy endothelium and protecting it with a Goretex mesh (BARD COMPOSIX E/X MESH). **Result:** The patient spent one night in intensive care unit (ICU), transfusing blood once. The only postoperative complication was a transitory atrial fibrillation pharmacologically treated. He was discharged 9 days after surgery. Pathologic analysis showed a non-mucinous lung adenocarcinoma invading the visceral pleura with a metastatic bronchial lymph node (pT4N1M0), with margins free of tumor. Chemotherapy and radiotherapy were administered and the patient is alive and in good condition 6 months after surgery, free of relapse. **Conclusion:** In selected cases, in young patients with good performance status, surgery for T4 lung cancer invading the DTA can successfully be accomplished, without complications, by an experienced multidisciplinary thoracic and vascular surgeons team, in high volume centers.

Keywords: advanced lung cancer, surgery, multidisciplinary team

EP1.01-79 CHEMORADIOTHERAPY IN ADVANCED NON SMALL CELL LUNG CANCER

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Background: Advanced NSCLC is a frequent cancer among our patients. Delay in diagnosis and treatment leads to advanced stages that require complex treatment modalities and poor prognosis. We report our experience in term of epidemiological, diagnostic, therapeutic and prognostic aspects of this disease in our department. **Method:** This is a retrospective study of 38 cases of advanced NSCLC treated with concurrent chemoradiotherapy,

collected in the radiotherapy department in the University Hospital Hassan II in Fez, between January 2012 and January 2017. All cancers were prooved histologically by biopsy. The standard treatment was concurrent chemoradiotherapy alone or after induction chemotherapy mostly due to a large tumor volume where radiotherapy is not feasible upfront. Chemotherapy drugs were mainly cisplatin-based with vinorelbine or paclitaxel and in some cases carboplatin if renal function is not correct. Radiotherapy was delivered through 3D conformal technique after CT-simulation and image fusion with CT or in rare cases PET-CT. After completion of treatment, no patient received adjuvant chemotherapy. Immune therapy was not affordable due to the high price. Follow-up was done clinically and with control CTscan. Tobacco control counseling was recommended to all our patients. **Result:** The average age was 59 years (38 to 81 years). The patients were all males and chronic smokers. Significant clinical symptoms were mainly chest pain, dyspnea and hemoptysis. There were 21 cases of adenocarcinoma, 17 cases of squamous cell carcinoma. 18 cases were classified as stage IIIA, 20 cases as stage IIIB. Neoadjuvant chemotherapy was received in 23 cases from 2 to 4 cycles. All patients received radiotherapy with doses to PTV between 60-70Gy with concomitant chemotherapy including cisplatin or carboplatin. After an average follow-up of 12 months, the evolution was marked by the occurrence of 2 deaths, distant metastasis in 14 patients (6 cases of cerebral metastasis and 8 cases of bone metastasis), 2 cases of progressive disease, 14 patients in complete clinical remission and are always followed, and 6 patients were lost to follow-up, **Conclusion:** It is now proven that the survival of patients with locally advanced lung cancer is better if chemotherapy is combined with radiotherapy. The survival gain obtained is essentially related to better control of micro-metastases even though the local control remains very poor. Some irradiation techniques seem to be able to improve this local control: conformal radiotherapy with intensity modulation, hypofractionation. Immue therapy concomitant to radiation might be the future but still needs randomized clinical trials to approve it.

Keywords: Advanced NSCLC - Chemotherapy - Radiotherapy

EP1.01-80 PROGRESSIVE DISEASE WITH T790M MUTATION VS NON-T790M MUTATION IN EGFR POSITIVE PATIENTS TREATED WITH TYROSINE KINASE INHIBITORS

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Background: Patients with metastatic non-small cell lung cancer (NSCLC) with a sensitizing EGFR mutation are candidates for treatment with a tyrosine kinase inhibitor (TKI), but acquired resistance is inevitable. The most frequent mechanism of acquired resistance to TKI is the T790M mutation. **Method:** Retrospective analysis of patients with EGFR mutation treated with TKI who progressed from November 2016 to July 2018, for whom the T790M mutation testing was done through liquid or tissue biopsy. **Result:** Progression disease was observed in 18 patients. The mean age was 67.1 ± 14.4 years. Twelve patients (66.7%) were female. Ten patients (55.5%) presented the T790M mutation as a resistance mechanism to TKI.

	T790M positive	T790M negative	p value
Non-smokers Ever smokers	9 (90%) 1 (10%)	2 (25 %) 6 (75 %)	0.005
EGFR mutation Exon 18 Exon 19 Exon 21	0 (0%) 8 (80%) 2 (20%)	1(12.5%) 5(62.5%) 2 (25%)	0.604
Initial TKI Gefitinib Afatinib Erlotinib	2 (20%) 0 (0%) 8 (80%)	2 (25%) 3(37.5%) 3(37.5%)	0.146
Response evaluation Stable disease Partial response	3 (30%) 7 (70%)	6 (75%) 2 (25%)	0.119
PFS with initial TKI - months (mean ± SD)	11 ± 5.3	10 ± 6.9	0.586
Months treated with initial TKI after disease progression due to clinical benefit (median - IQR)	2 - 5	4 - 3	0.409
Progressive disease Increase of primary lesion size Increase of metastasis size New intrathoracic lesions New extrathoracic ± intrathoracic lesions	3 (30%) 3 (30%) 2 (20%) 2 (20%)	3(37.5%) 2 (25%) 0 (0%) 3(37.5%)	0.465

Conclusion: The T790M mutation was the most frequent mechanism of TKI resistance. Non-smokers developed the mutation more often than ex-smokers, although this result was not statistically significant. In the other analyzed variables there were no statistically significant differences.

Keywords: Lung cancer, T790M, TKI

EP1.01-81 RESECTION OF TUMORS WITH CARINAL INVOLVEMENT AFTER INDUCTION THERAPY

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Background: Tumors involving the carina may be treated with resection of trachea-bronchial bifurcation with or without lung resection. The role of induction therapy (IT) and its effects on morbidity/mortality are unclear. We evaluated surgical and long-term outcomes of patients who underwent carinal resection after IT. **Method:** From 1998 to 2018, 45 patients (35 men; median age, 62 years) underwent carinal resection. Twenty-nine patients (64.4%) received IT (24 chemotherapy and 5 chemo-radiation). Histology included 41 non-small cell lung cancers, 3 adenoid cystic carcinomas, 1 carcinoid. Carinal pneumonectomy was performed in 32 cases (all right sided), carinal resection plus right upper lobectomy in 9, carinal resection plus upper bilobectomy in 1, and carinal resection without pulmonary resection in 3. Superior vena cava resection was associated in 22 cases. **Result:** Operative mortality was nil. Thirty-day mortality was 8.8% (n=4). Major complications occurred in 9 patients (20%): 5 bronchopleural fistulas, 2 ARDS, 2 cardiac hernias. IT did not influence morbidity rate (p=.7371). Pathological N status included 6 N0, 22 N1, and 17 N2. Follow-up was completed for all patients. Median survival was 16 months (range, 1 to 181 months). Overall 5-year survival rates was 35.8%. Overall, 5-year freedom from recurrence was 49.8%. Patients receiving IT had a poor survival (22.6% versus 60%) but it was not statistically significant (p=.0596). Histology, extended resection, and N status, did not influence survival. **Conclusion:** Carinal resection is a feasible but challenging procedure providing acceptable mortality and long-term outcomes. IT did not influence morbidity, mortality, and overall survival.

Keywords: carina, induction therapy, Advanced lung cancer

EP1.01-82 10 YEARS SINGLE CENTER EXPERIENCE WITH RESECTION OF THE SUPERIOR VENA CAVA IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: In patients with locally advanced T4 non-small cell lung cancer (NSCLC) invading the superior vena cava (SVC), combined multimodality treatment including surgery is indicated. However, this treatment approach warrants careful patient selection and adequate postoperative management. We aim to review our institutional experience with SVC resection in advanced NSCLC. **Method:** Between 2006 and 2017, surgery for NSCLC including SVC resection has been performed in 21 patients at our department. We defined "SVC resection" as resection of the SVC and replacement with ring-enforced tube grafts and "SVC reconstruction" as partial resection with direct closure or reconstruction with a bovine pericardial patch. Clinical parameters and long-term outcome were analyzed. **Result:** Overall, 15 male and 6 female patients have been included. Induction treatment was performed in 16 patients, 8 patients received chemoradiation therapy and the other 8 patients had chemotherapy alone. Pulmonary resection included 8 sleeve pneumonectomies, 4 pneumonectomies, 3 lobectomies and 4 sleeve-lobectomies of the right upper lobe, 1 extraanatomical resection of the right upper lobe and one mediastinal tumor debulking. Two patients required cardiopulmonary bypass during surgery. An additional extended resection including chest wall (n=1), phrenic nerve (n=3), pericardium or right atrium (n=4) was performed in 8 patients. Overall 5 patients underwent SVC reconstruction whereas 16 patients had complete SVC resection and replacement. The 90-day-mortality rate was 4.8% (n=1). Major complications occurred in 8 patients (38%) with no difference between patients undergoing SVC resection or reconstruction. Oncological long-term outcome will be presented at the conference. **Conclusion:** Our results suggest that an extended resection including SVC replacement or reconstruction is a feasible and safe procedure for carefully selected patients with NSCLC and SVC involvement with acceptable postoperative morbidity and mortality rates.

Keywords: surgery, locally advanced lung cancer, SVC

EP1.01-83 EFFICACY AND SAFETY OF EGFR-TKI RECHALLENGE TREATMENT IN ELDERLY PATIENTS WITH ADVANCED NSCLC HARBORING SENSITIVE EGFR MUTATIONS

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Background: Epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR–TKI) is effective as first-line chemotherapy for patients with advanced non-small-cell lung cancer (NSCLC) harboring sensitive EGFR mutations. However, whether the efficacy of second-line EGFR–TKI treatment after first-line EGFR–TKI treatment was poorly studied in elderly patients aged ≥ 75 years harboring sensitive EGFR mutations. Therefore, we aimed to investigate the efficacy and safety of EGFR-TKI re-administration after first-line EGFR–TKI treatment in elderly patients with NSCLC harboring sensitive EGFR mutations. **Method:** Between October 2002 and December 2015, 22 elderly patients with advanced NSCLC harboring sensitive EGFR mutations who were initiated on EGFR–TKI Rechallenge at four Japanese institutions were included in this study. The eligibility criteria were histologically or cytologically confirmed NSCLC, unresectable stage III/IV disease, and a drug-sensitive EGFR mutation (exon 19 deletion or exon 21 L858R). All patients were initially treated with gefitinib (250 mg/day) or erlotinib (150 mg/day) and after recurrence, re-administration of EGFR-TKIs (gefitinib, erlotinib, afatinib) was performed as a secondary chemotherapy **Result:** Ultimately, 22 cases of this study were studied. The median age was 77.5 years (range 75-87 years). Although it was a retrospective analysis, even with re-administration of EGFR-TKI rechallenge, the response rate was 23%, PFS 5.26 months, OS (after EGFR-TKI rechallenge) 14.4 months (the administration lines were 2, 3 and 4 lines). **Conclusion:** Until now it was said that EGFR-TKI rechallenge does not contribute to OS in LUX-LUNG 1 and so on. On the other hand, there are also reports on the usefulness of EGFR-TKI rechallenge. From the results of this study it can be said that it can be one of the options among the limited treatment options for elderly EGFR positive lung cancer.

Keywords: EGFR–TKIs, Elderly patients, Readministration

EP1.01-84 SECOND LINE TREATMENT WITH DOCETAXEL/ NINTEDANIB IN PATIENTS WITH METASTATIC NON SMALL CELL LUNG ADENOCARCINOMA-PRELIMINARY RESULT

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Background: The treatment landscape of non small cell lung cancer (NSCLC) has changed dramatically during the last years involving targeted therapy, chemotherapy ± immunotherapy or/ and antiangiogenic agents, based mainly on patients' molecular characteristics. Not all patients respond well to immunotherapy, so there is an essential need for other effective treatments. **Method:** The aim of this prospective study is to estimate and record, the efficacy of the combination of Docetaxel with Nintedanib as a second line therapy in metastatic NSCLC. There were 20 patients, 16(80%) men, 4(20%) women, median age 62(52-73) years and median ECOG 1(0-3), without driver mutations, consecutively admitted in Evangelismos Oncology Department in Athens, Greece from 27/11/2017-23/02/2019. **Result:** All patients had received Cisplatin/Pemetrexed/ Bevacizumab as first line treatment for their disease, with a median duration of 104(45-255) days. Progressive disease sites were found in lung, liver, and bones in :18/20(90%), 8/20(40%) and 4/20(20%) patients respectively. All received as second line treatment Docetaxel 75mg/m^2 q3weeks plus Nintedanib 400mg p.o., d 2-20 in 21 days cycles. CEA, CA125, NSE, CA19.9, CA72-4 and Cyfra 21.1 tumor markers were monitored according to our clinical protocol. Increased values of these markers were documented at initiation of therapy in 18, 14, 10, 14 ,0, 2 patients respectively. After 3 cycles of treatment all patients were reevaluated and in 2 of them partial response (P.R.) was documented, with 40-50% reduction of CEA, CA125, CA19.9 και Cyfra 21.1, while 12 patients had stable disease (S.D.) with no more than 20% change in the aforementioned tumor markers. Six patients with progressive disease (P.D.) showed significant increase of CEA, CA 125, NSE, CA 19.9 and CA 72-4. The responders (P.R.+ S.D.) continued therapy for a median of 5(3-8) cycles. Among 96 cycles of chemotherapy, any toxicity grade ≥ II occurred in 14 (7%) of them. Anaemia in 7(50%), stomatitis in 4(28.5%), diarrhea in 5(36%) and AST/ALT elevation of >2.5 fold in 3(21%) cycles respectively. All patients were treated symptomatically, without dose reduction in any patients **Conclusion:** The combination of Docetaxel/Nintedanib in metastatic NSCLC adenocarcinoma, following progressive disease post Cisplatin/ Pemetrexed/ Bevacizumab treatment, showed 70% response rate. Although the number of the patients included in the study is small, we concluded that the tumor markers examined, had a clear correlation with the disease outcome. No major toxicity issues were documented. Larger studies are needed in order to make more solid conclusions.

Keywords: NSCLC, second line, NINTETANIB

EP1.01-85 PROGNOSIS OF PATIENTS WITH RECURRENT OR ADVANCED LUNG CANCER ACCORDING TO THE STATUS OF EPIDERMAL GROWTH FACTOR RECEPTOR

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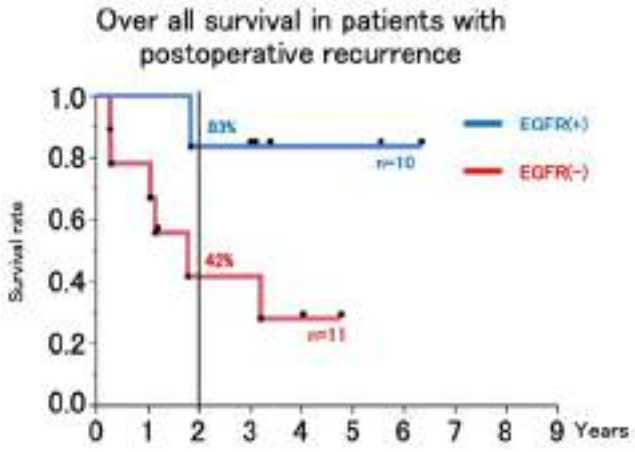
Background: We report the 9-year experience of the therapy and prognosis of the patients with postoperative recurrence or advanced lung cancer according to the status of epidermal growth factor receptor (EGFR) status in a single institution. **Method:** We retrospectively evaluated the prognosis of the patients who received the therapy in a single institution from April 2009 to March 2018. Patients who relapsed after surgery and patients with inoperable advanced lung cancer (c-stage IIIB, stage IV) were enrolled. The EGFR gene mutation was examined using surgical specimens in relapsed patients and biopsy specimens at diagnosis in patients with advanced lung cancer. At first treatment, we administered EGFR-tyrosine kinase inhibitors (TKIs) to EGFR gene-positive patients and platinum doublet agents to EGFR gene-negative patients. At the time of progression or the intolerable adverse effects, we went on to the secondary treatment. **Result:** In patients with postoperative recurrence, the 2-year survival rate in EGFF gene-positive patients (83%, n=10) was significantly higher than that in EGFR gene-negative patients (42%, n=11). The locations of recurrence were 14 in the lung, 7 in lymph nodes, 2 in bones, 1 in the brain, adrenal glands, and kidney. In patients with advanced lung cancer, the 2-year survival rate in EGFR (42%, n=9) did not differ from that in EGFR (31%, n=26). The locations of metastasis in patients with advanced cancer were 3 in mediastinal lymph nodes, 12 in the ipsilateral lung, 11 in malignant pleural effusion, 8 in the brain, 4 in the bones, 3 in the adrenal glands, and two in the liver.



Conclusion: We treated EGFR-TKI as the first therapeutic agent for the recurrent and advanced lung cancer patients with EGFR gene mutation positive and obtained relatively good results.

Keywords: Epidermal growth factor receptor, Advanced lung cancer, Postoperative recurrence treatment

EP1.01-86 COMPREHENSIVE NEXT-GENERATION SEQUENCING-GUIDED TARGETED THERAPY CORRELATES WITH SURVIVAL IN NON-SMALL-CELL LUNG CANCER

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Background: Although increasingly common in clinical practice, whether genetic testing confers a survival benefit remains to be firmly established. **Method:** We performed retrospective analysis of 82 lung adenocarcinoma patients who were diagnosed at the Second Affiliated Hospital of Nanjing Medical University from 2013 to 2018. We evaluated progression-free survival (PFS) with respect to genetic testing status. **Result:** 63 (77%) patients received targeted next-generation sequencing. Of these, 43 (69%) patients received tailored targeted TKI therapies. No significant difference in mPFS was observed between patients with and without genetic testing (Fig.1). However, an increase in PFS started to manifest at later times in patients who received genetic testing. In patients treated with osimertinib, PFS was longer in those who received genetic testing and had EGFR T790M mutation status confirmed (Fig.2 and Table 1). A cis-C797S mutation was identified in a patient who progressed on osimertinib treatment. Patient 6 with EGFR L858R responded poorly to osimertinib. We found that genetic testing was conducted using a 139-gene panel, and more comprehensive testing may be necessary to uncover potential resistance mechanism(s) to osimertinib in this patient.

Figure 1.

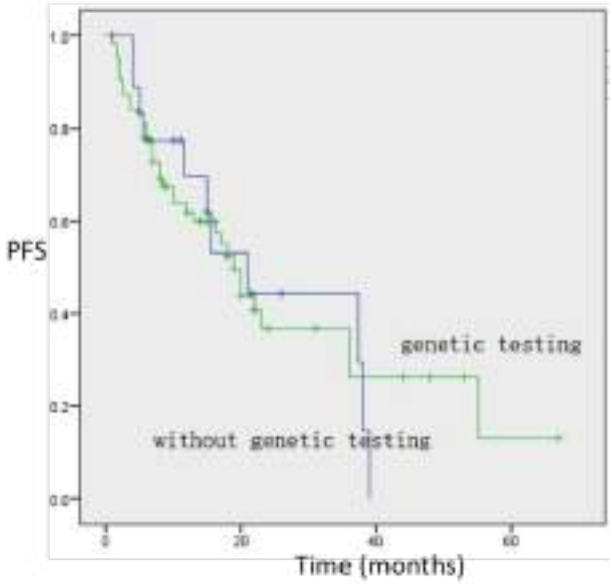

Figure 2.

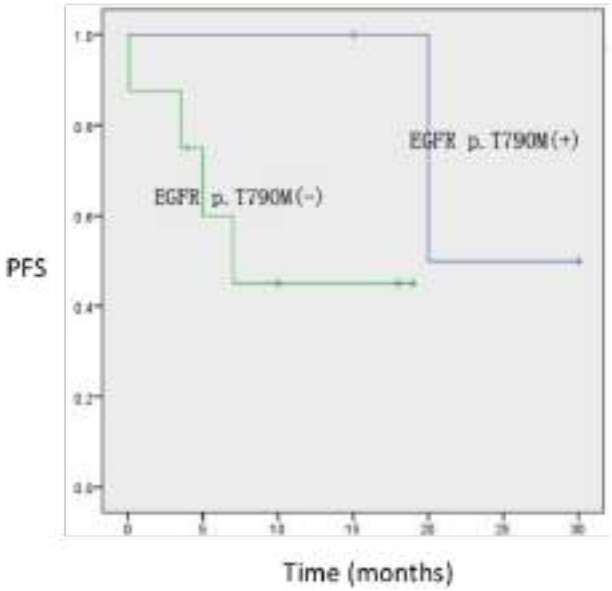

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Table 1. NSCLC patients treated with osimertinib

Patient ID	Age/ Gender	Sample Type	Previous Targeted Therapy	Mutations	PFS (months after osimertinib
1	65 / F	Blood	Gefitinib	EGFR p.745_750del EGFR p.T790M	20
2	59 / F	Blood/ Tissue	Gefitinib	EGFR p.746_751del EGFR p.T790M	30
3	54 / M	Blood	Erlotinib	EGFR p.L747_ T752del MAP2K1 p. C121S NF1 p.L732X	0.3
4	48 / M	Blood	Osim-ertinib	EGFR p.L858R EGFR p.T790M EGFR p.C797S	4
5	87 / M	Tissue	Osim-ertinib	EGFR p.745_750del	10
6	48 / M	Blood	Osim-ertinib	EGFR p.L858R	4
7	77 / M	Blood/ Tissue	No	EGFR p.L861Q	18
8	60 / F	Blood	Gefitinib	EGFR p.L858R EGFR p.T790M	15
9	77 / M	Tissue	Gefitinib	KRAS	7
10	50 / M	Blood/ Tissue	Osim-ertinib	No	18
11	79 / M	Blood/ Tissue	Osim-ertinib	EGFR p.L858R	5

Conclusion: Routine genetic tests should implemented in treating patients with advanced NSCLC, particularly in those who developed resistance to first-generation TKIs.

Keywords: targeted therapies, Next-generation sequencing, NSCLC

EP1.01-87 CUTANEOUS METASTASIS IN LUNG CANCER – A RETROSPECTIVE STUDY IN A LOCAL HEALTH UNIT IN GUARDA, PORTUGAL

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Background: Cutaneous metastasis from lung cancer is rare, occurring in 0.22-12% of cases. Their presence has generally been considered a sign of an already disseminated, poor-prognosis and non-surgical disease. Current data suggest lung cancer is the second most frequent cause of cutaneous metastasis in men, behind malignant melanoma. **Method:** We conducted a retrospective analysis of patients diagnosed with lung cancer and cutaneous metastasis, submitted to skin biopsy to confirmation, from November 2010 to March 2019, in our local health unit. Data regarding demographic characteristics, smoking history; location and histology and of the primary tumor; staging; number, location and type of skin lesion; overall survival and survival after detection of cutaneous metastasis were collected from clinical records. **Result:** Five patients were included, 4 were of male gender (80.0%), with median age of 79 years (range, 56-88). Three patients (60.0%) were former smokers, 1 current smoker and 1 non-smoker. The location of the primary tumor was right upper lobe (3 cases, 60.0%) and left lower lobe (2 cases, 40.0%); histology of adenocarcinoma in 3 patients (60.0%), 1 patient with squamous cell carcinoma and another with neuroendocrine carcinoma. All cases of lung cancer were diagnosed with an initial stage IV disease. Most of them had a unique skin lesion, mainly a nodule, located either in the upper abdominal wall or dorsal region. From the 5 cases, 4 had died, with a median overall survival 0.5 months (range, 0-1) and survival after cutaneous metastasis 15.5 days (range, 12-82). **Conclusion:** According to data, also in our study men had more cutaneous metastasis from lung cancer than women. Previous or active smoking history was present in almost all patients, the main histology type was adenocarcinoma and primary lung cancer was frequently located in right upper lobe, consistent with reported data. In all cases, lung cancer was diagnosed in an advanced stage and survival after diagnosis of cutaneous metastasis was extremely low.

Keywords: cutaneous metastasis, Advanced lung cancer

EP1.01-88 NEXT-GENERATION SEQUENCING IN HISPANIC PATIENTS WITH ADVANCED LUNG CANCER AND CORRELATION WITH RESPONSE TO IMMUNOTHERAPY

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Background: Cancer is a leading cause of death among Hispanics (HISP); the largest ethnic minority in the United States (17% of the total population). With the approvals of checkpoint immunotherapy in advanced lung cancer, many patients (pts) are starting to see long-lasting remissions and longer survival rates. However, response to a given treatment often depends on the tumor's genomic profile. Our aim was to analyze NGS results for HISP pts living in the US in an effort to better understand this population's genomic profile and prognosis. **Method:** Retrospective analysis on pts with biopsy proven advanced NSCLC who received checkpoint immunotherapy at two large institutions in the US. Patient charts were reviewed to obtain data on demographic characteristics including race, gender, age, and smoking history. Next generation sequencing (NGS) results were obtained from Guardant Health and Foundation One testing in blood and in tissue, respectively. We assessed progression-free survival (PFS) and overall survival (OS) associated with outcome. **Result:** Seventy HISP pts receiving immunotherapy underwent NGS testing from 10/2013 to 4/2018. 46% were male, 76% were smokers, 89% had adenocarcinoma, and 39% were PD-L1 positive (with 67% of those having TPS ≥ 50%). Thirty pts (43%) had one genetic aberration (GA), and 15 pts (22%) had >5 GA. The most frequent actionable GA was EGFR mutation (26%) and nonactionable mutation was KRAS (40%). Other less common GA were BRAF (10%), MET (10%), and STK11 (9%).

Survival	1 Genetic Aberration	>5 Genetic Aberrations	P value
Median PFS	**3.57m**	**3m**	**0.2767**
Median OS	**14.96m**	**3.8m**	**0.0117**

Conclusion: The presence of >5 GA (actionable and nonactionable) on NGS testing was associated with worse OS when compared to pts with one GA. There was no difference in PFS. In addition, PD-L1 incidence in HISP pts is high with a larger proportion of pts expressing ≥ 50% TPS compared to what is reported for NHW. Given the numerous nonactionable GA encountered, it is clear that continued development of targeted therapies would keep benefitting pts. Increased NGS profiling in HISP pts could potentially broaden treatment and clinical trial options to serve this purpose.

Keywords: Immunotherapy, Genomics, Hispanics

EP1.01-89 RETROPERITONEAL METASTASIS WITH MARKED FIBROSIS FROM LUNG ADENOCARCINOMA: AN AUTOPSY CASE REPORT

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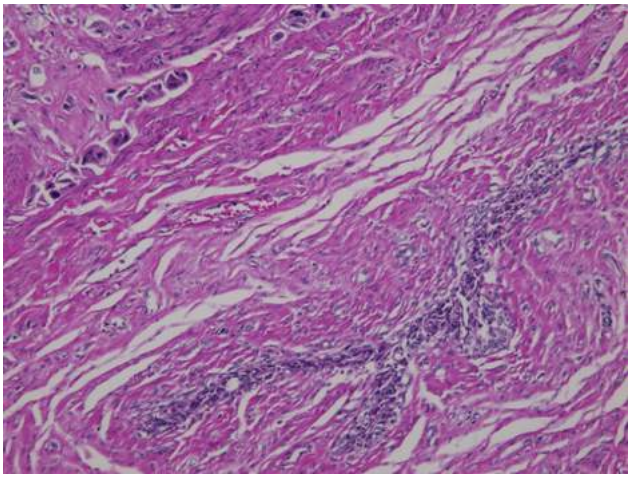
Background: Retroperitoneal metastasis of lung cancer is rare. Here we report a unique case of retroperitoneal metastasis with fibrosis from lung adenocarcinoma. Case: A 73-year-old woman was admitted to the hospital in June 2018 because of nausea and vomiting of a few days' duration. In February 2018 she had received a diagnosis of lung adenocarcinoma (clinical T3N3M1a stage IVA, epidermal growth factor receptor [EGFR] mutation positive, exon 19 deletion) in the right lower lung and was taking afatinib 20 mg once daily. On admission, chest radiography and computed tomography (CT) showed that the primary tumor was smaller than at the time of diagnosis; however, abdominal CT showed a new retroperitoneal lesion and right hydronephrosis. Contrast-enhanced CT and MRI scan revealed poorly marginated soft tissue around the duodenum and inferior vena cava. She underwent gastrojejunostomy and biopsy of the peritoneum after duodenal obstruction was revealed by examination of the upper gastrointestinal tract (Figure 1). Analysis of the biopsy specimen revealed EGFR mutation–positive adenocarcinoma with exon 19 deletion, which was consistent with retroperitoneal metastasis of the lung adenocarcinoma. She was treated with CBDCA/PEM and CBDCA/PEM/BV each one cool [DK1] but developed cerebral infarction and died 104 days after admission.

Method: Section not applicable **Result:** Autopsy showed that right ureteral obstruction and hydronephrosis were caused by markedly sclerotic retroperitoneum. Histopathologic examination revealed marked fibrosis with scattered adenocarcinoma (Figure 2).



Conclusion: Although rare, metastasis of non–small lung cancer should be considered in patients with doudenal obstruction or hydronephrosis.

Keywords: Retroperitoneal metastasis, fibrosis, lung adenocarcinoma

EP1.01-90 THE PROGNOSTIC ROLE OF MEAN PLATELET VOLUME IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Previous studies suggest the potential correlation between increased mean platelet volume (MPV) and survival in non-small cell lung cancer (NSCLC), but results are often contradictory. We herein aimed to further evaluate the prognostic value of MPV in patients with advanced-stage NSCLC in the real-world setting of a tertiary referral oncology center. **Method:** Demographic, clinicopathological and laboratory data (including complete blood count parameters) of 30 patients with stage IIIB or IV NSCLC were retrieved from the Lung Cancer registry of the Oncology Clinic of Sotiria Athens General Hospital and analyzed. All the above variables (including MPV) were correlated to each other, as well as with overall survival (OS) and progression-free survival (PFS). **Result:** Mean patients' age was 68,5 (SD=7,5) years. The majority of patients were male (76.7%), had positive smoking history (90%), squamous cell carcinoma (53.3%), and stage IV disease (76.7%). No statistically significant correlations between survival and sex, age, smoking history or tumor histology (squamous cell carcinoma versus adenocarcinoma), or between MPV and histology were noted. Worse performance status (p=0.004) and higher white blood cell count (p=0.01) were correlated with reduced OS, while increased MPV was strongly correlated both with OS and PFS (p<0.0001 in both cases). **Conclusion:** Increased MPV may correlate with improved survival of patients with NSCLC, thus potentially representing a marker of favorable prognosis. Our study findings warrant confirmation in larger prospective series

Keywords: Non-Small Cell Lung Cancer, mean platelet volume, prognostic

EP1.01-91 OUTCOMES WITH SYSTEMIC CHEMOTHERAPY WITH WEEKLY REGIMEN IN ADVANCED NSCLC PATIENTS WITH PS 2 AND ABOVE AND WITHOUT DRIVER MUTATION

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Background: Platinum-based combination chemotherapy is recommended as the standard treatment for patients with advanced NSCLC, but its benefit is limited to patientswith performance status (PS) of 0 or 1. However, it is not clear whether these benefits apply to patients with poor PS(2 and above)). These patients have inferior outcomes and have been excluded from clinical trials. We have analyzed the outcome of these patients who have been treated with weekly chemotherapy despite poor performance status. **Method:** We performed a retrospective analysis of patients of advanced NSCLC with poor PS (ECOG PS 2 or more) registered at our lung cancer clinic between January 2016 and December 2017 and treated with weekly chemotherapy. Patients with driver mutations who were treated with first line TKIs were excluded. Hospital case records were reviewed for baseline characteristics, treatment details and outcome data. **Result:** A total of 68 patients were found to be eligible for this analysis. Median age was 63.5 years (30-77 years, including 17(25%) patients 70 years or above. At presentation out of these 68 patients, 50(73.5%) were smokers, 22(32%) had cytological proven pleural/pericardial effusion, 7(10.2%) patients had brain metastasis and 35(51.5%) had extra thoracic metastasis (≥2 sites). Majority(61%) patients had ECOGPS 2 but 39 % had PS 3 or 4 also and 29(42%) had one or more associated comorbidities. The most common chemotherapy regimen used was weekly paclitaxel and carboplatin(82.8%) followed by single agent paclitaxel(17.8%).Majority (63%) patients could complete 4 or more

cycles of chemotherapy however 9 patients (13.2%) could receive only one cycle and 16(23%) patients even received maintenance chemotherapy. Chemotherapy was interrupted due to poor tolerance in 10(14.7%) patients and grade ¾ toxicity seen in 16(23%) % patients. At least one point improvement in ECOG PS from baseline was observed in 33 patients (48.5%) after 4 cycles of chemotherapy and objective response and disease control rates were 23.5 % and 50% % respectively. After a median follows up of 13 months, median progression free survival was 7.3 months. **Conclusion:** Systemic chemotherapy in modified doses and schedules in advanced NSCLC patients with PS 2 and above is feasible and may be associated with better symptom palliation with clinical benefit and improvement in survival. Further studies addressing this neglected subgroup are indicated.

Keywords: Weekly chemotherapy, advanced NSCLC, Poor performance status

EP1.01-92 EFFECTIVENESS OF SECOND-LINE TREATMENT WITH NINTEDANIB + DOCETAXEL (ND) IN PATIENTS WITH METASTATIC LUNG ADENOCARCINOMA

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Background: Nintedanib is an oral angiokinase inhibitor directed against VEGFR 3, FGFR 1-3, and PDGFR alpha and beta. It is approved by the European Medicines Agency in combination with docetaxel for the treatment of metastatic lung adenocarcinoma previously treated with platinum-doublet chemotherapy. Given the efficacy of checkpoint inhibitors in the second-line treatment of advanced lung cancer, we evaluated the outcomes of ND in this setting **Method:** Patients diagnosed with advanced lung cancer between July 2015 to October 2017 at the University Hospital Arnau de Vilanova (Lleida, Spain) and treated with ND were included. The clinical history, tumor pathology, tumor biologic characteristics, treatments prior and posterior to ND were reviewed. Statistical analysis was realized using IBM SPSS Statistics 23.0 software. Overall survival (OS) was calculated by Kaplan-Meier curve, determining a median OS with 95% confidence interval and estimated mortality rates during each year of follow-up **Result:** Thirteen of 357 patients with advanced lung cancer during the time period specified were treated with ND and included in the analysis. Median follow-up was 14.4 months (range: 7.3 – 41.2 months). Median age at diagnosis was 62.1 years (range: 46-73 years). Never-smokers comprised 15.4% of the patients, ex-smokers 46.2% and active smokers 38.5%. Bone metastases were present in 23.1% of patients, while 15.4% and 15.3% had central nervous system and hepatic metastases, respectively. The majority, 69.2%, received a platinum-doublet first-line and 46.2% received pemetrexed maintenance. The median number of ND cycles was four. Responses to ND were 53.8% partial response (PR), 23.2% stable disease (SD), and 23% progressive disease, with a disease control rate (DCR) of 77%. 53.8% of patients continued with nintedanib maintenance with the following responses: 43% PR, 14.3% SD, and 42.7% progressive disease (DCR 57.3%). There were no grade 2 or greater toxicities in the nintedanib maintenance group. Fifty-four percent of ND patients received third-line therapy: 50% atezolizumab, 16.7% carboplatin + vinorelbine, 16.7% nivolumab, and 16.7% oral vinorelbine. Eleven percent of patients received fourth-line therapy. Median OS was 14.4 months (CI 95%: 11.7 – 17.1 months). OS rates at 2 and 3 years were 69.2% (CI 95%: 44,1% - 94,3%) and 23.1% (CI 95%: 0,2 - 46%), respectively **Conclusion:** ND is an effective second-line treatment for patients with advanced lung adenocarcinoma. In this descriptive analysis, the median OS associated with ND was superior to the results of Lume-Lung 1 and Checkmate 057, although the study is limited by sample size

Keywords: adenocarcinoma, Nintedanib, NSCLC

EP1.01-93 RARE IMMUNE RELATED ADVERSE EVENTS BY IMMUNE CHECKPOINT INHIBITORS IN CLINICAL PRACTICE

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Background: Immune checkpoint inhibitors (ICIs) such as anti-PD-1 and PD-L1 antibodies including nivolumab/pembrolizumab and atezolizumab are available practically in Japan. While ICIs produce excellent antitumor activity and long-term survival, unexpected immune related adverse events (irAEs), which are different from those for cytotoxic drugs, have been reported. We experienced varieties of irAEs which have successfully been treated. **Method:** We retrospectively analyzed irAEs in 50 NSCLC patients treated with ICIs as clinical practice from January 2016 to November 2018 in TODA Central General hospital. **Result:** Nivolumab, pembrolizumab and atezolizumab was given in 27, 11 and 12 patients, respectively. The median age was 69 (43-84). Male/female: 40/10 patients, adenocarcinoma/squamous cell carcinoma/unclassified non-small cell carcinoma: 30/15/5 patients. Tissue proportional score for PD-L1 antibody was strongly positive/weakly positive/negative/unknown in 12/4/12/22 patients, respectively. The treatment response was CR/PR/SD/PD/NE in 3/14/2/22/9 patients, respectively. Various types of irAEs have been observed, exacerbation of rheumatoid arthritis: 1, hypothyroidism: 3, secondary adrenocortical insufficiency with ACTH isolated deficiency: 1, pneumonitis: 6, liver dysfunction: 1, neutropenia: 1, diarrhea: 1, rash: 3, infusion reaction: 1. Each irAEs had been basically managed according to algorism, such as treatment discontinuation, irritative treatment, steroid therapy, hormone replacement therapy etc. One patient, who developed multiple irAEs, diarrhea, liver dysfunction and neutropenia at same time, recovered from irAEs quickly by supportive care including steroid pulse therapy. **Conclusion:** A variety of unexpected irAEs have been experienced in NSCLC patients treated with ICIs, however, excellent tumor response was observed in 10 of 13 patients who developed irAEs. In patient who showed multiple irAEs, tumor size was decreased significantly by nivolumab therapy and tumor progression was not observed 33 months after the final nivolumab administration. IrAEs associated with ICIs are diverse and difficult to predict, so safety management and early detection are important.

Keywords: Non-Small Cell Lung Cancer, Immune Checkpoint Inhibitors, Immune related adverse events

EP1.01-94 THE ROLE OF NEOADJUVANT CHEMO-IMMUNOTHERAPY IN UNRESECTABLE NON-SMALL CELL LUNG CANCER

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Background: Current practices and guidelines invoke a limited role for neoadjuvant therapies in NSCLC. These strategies are not considered for use in advanced, unresectable disease. However, the development of immune checkpoint inhibitors has drastically improved the efficacy of systemic treatments for NSCLC. **Method:** We describe the case of a patient who was diagnosed with squamous cell carcinoma of the lung. **Result:** Imaging demonstrated a 7.9-cm right lower lobe lesion, a 1.8-cm satellite right middle lobe nodule, and ipsilateral mediastinal lymphadenopathy, consistent with stage IIIB disease. The tumor biopsy exhibited 5% PD-L1 positivity in tumor cells. Tissue next generation sequencing (NGS) revealed loss-of-function mutations in *RB1*, *TP53*, and *EP300*, copy number gain in *PIK3CA*, and tumor mutational burden of 4.3/Mb. Analysis of circulating tumor DNA (ctDNA) demonstrated a highest allele fraction of 4.1% (*TP53* mutant clone). As the tumor was deemed unresectable, the patient was started on carboplatin, nab-paclitaxel, and pembrolizumab. Follow-up imaging at 12 weeks after 4 cycles showed partial response, with significant reduction in tumor size and improvement in lymphadenopathy. After tumor board discussion, the decision was made to proceed with surgical resection. A right thoracotomy with bilobectomy was successfully performed. Resected tumor demonstrated major pathologic response with less than 5% viable cancer cells. Whole-genome sequencing of plasma was also carried out on blood collected over the course of treatment.

The observable cancer signal shrank to less than 5% of the baseline as early as 25 days after treatment start. Finally, repeat ctDNA analysis 6 weeks after the surgery showed no detectable somatic variants. **Conclusion:** Conversion of unresectable tumors in NSCLC may be more feasible with modern treatment regimens. The potential efficacy of neoadjuvant strategies using chemoimmunotherapy warrants further clinical investigation.

Keywords: Non-Small Cell Lung Cancer, Immune Checkpoint Inhibitors, Neoadjuvant therapy

EP1.01-95 UP-REGULATION OF C-MET BY COX-2 PROMOTES RESISTANCE OF GEFITINIB IN NSCLC PATIENTS

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Background:c-Met amplification is one of the reasons for Gefitinib resistance in NSCLC patients. **Method:** 1.Explore the mechanism of the up-regulation of c-Met by Cox-2; 2.Combination of Cox-2 inhibitor and Gefitinib can overcome Gefitinib resistance in cells or animal study; 3.Test the expression pattern or activity of Cox-2 in NSCLC patients, and evaluate the possibility of Cox-2 serving as biomarker for Gefitinib resistance and prognosis for NSCLC patients. **Result:** 1.Both c-met and Cox-2 are highly expressed in Gefitinib resistant lung cancer cell lines; 2.Cox-2 is highly expressed in malignant lung adenocarcinoma than in matched normal tissues; 3.Inhibition of Cox-2 can decrease c-Met expression, and promote apoptosis induced by Gefitinib in Gefitinib resistant cells. **Conclusion:** Up-regulation of c-Met by Cox-2 promotes resistance of Gefitinib in NSCLC patients

Keywords: NSCLC; Cox-2; c-Met

EP1.01-96 METASTATIC LYMPHOEPITHELIAL LUNG CANCER

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Background: NSCLC remains the leading cause of cancer deaths globally. Lymphoepithelial-like carcinoma (LELC) of the lung, (EBV)-driven tumor; mostly found in East Asian population; is not only one of the rarest subtypes of non-small cell lung cancer (NSCLC) but is also quaint to have a good prognosis. Advanced or metastatic Lymphoepithelial lung cancer is even rarer. LELC of the lung is traditionally considered be chemo-sensitive; although recurrences common lending to chemo-related toxicity and increased morbidity. High predilection of LELC for Programmed Death Ligand-1 (PDL-I) positivity and its long established association with EBV, led to the exploration of the role of PD- 1/PDL- 1 inhibitors in its management. **Method:** poster / case report **Result:** There have been only 4 cases reported in literature highlighting the use of PDL/PDL-1 inhibitors in LELC of lung and that too in recurrent/relapsed setting; out of which three had a favorable outcome and only one patient was treated with Pembrolizumab. We report the first case of a young Pilipino female who presented with metastatic LELC of the lung with vertebral metastases causing severe lower backache; initially treated with chemotherapy, followed by Pembrolizumab alone due to high PDL-I expression in her tumor, resulting in complete remission of symptoms and radiological evidence of complete metabolic resolution of multiple metastatic bony lesions. This case not only necessitates the need for larger prospective trials to assess the role or PD- 1/PDL-1 inhibitors in this rare kind or lung cancer but also reiterates the long-brewing dilemma regarding the duration of treatment with these agents after achievement of complete remission. **Conclusion:** Pembrolizumab used alone in high PDL-I expression, results in complete remission of symptoms and radiological evidence of complete metabolic resolution of multiple metastatic bony lesions in patients with NCSLC Lymphoepithelial-like carcinoma (LELC)

Keywords: High PDL-I expression, Pembrolizumab, Lymphoepithelial-like carcinoma (LELC)

EP1.01-97 IS SURGICAL TREATMENT SUITABLE FOR STAGE III OR IV PRIMARY LUNG CANCER?

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Background: It is generally known that advanced lung cancer is not an indication for surgical treatment, whereas it is an indication for chemotherapy and/or immunotherapy. We examined cases in which surgery was performed for clinical stage III or IV lung cancer and investigated whether this treatment was effective or not. **Method:** We retrospectively reviewed 34 patients who underwent radical resection for stage III or IV primary lung cancer at Ehime University Medical Hospital from October 2010 to February 2019. **Result:** In this series, 23, 5, and 6 patients had stage IIIA, stage IIIB, and stage IV disease, respectively. Following were the histological types: adenocarcinoma, 14; squamous cell carcinoma, 9; large-cell carcinoma, 5 (large-cell neuroendocrine carcinoma [LCNEC], 1); adenosquamous carcinoma, 1; pleomorphic carcinoma, 1; LCNEC + adenocarcinoma, 1; LCNEC + squamous cell carcinoma, 1; and LCNEC + small-cell carcinoma, 1. As preoperative treatment, 8 and 7 patients received full-dose chemoradiotherapy (salvage surgery) and induction chemoradiotherapy, respectively. We also included 2 cases involving salvage surgery after only chemotherapy and 1 case involving salvage surgery after chemotherapy and brain metastasis resection. The remaining 16 patients underwent surgery without any pre-surgical treatment. In addition, adjuvant chemotherapy was administered in 17 cases. In a mean observation period of approximately 4 years, the overall 3-year and 5-year survival rates were 57.2% and 30.6%, respectively. In patients with clinical stage IIIA disease, the 3-year and 5-year survival rates were 55.9% and 21.7%, respectively. In patients with clinical stage IIIB disease, the 3-year and 5-year survival rates were 75% and 50%, respectively. In patients with stage IV disease, the 3-year and 5-year survival rates were 50% and 33.3%, respectively. In patients without any multimodal treatments (n = 16), the 3-year and 5-year survival rates were 55.0% and 23.6%, respectively. In patients who underwent surgery after induction chemoradiotherapy (n = 7), the 3-year and 5-year survival rates were 85.8% and 42.9%, respectively. In patients who underwent salvage surgery (n = 11), the 3-year and 5-year survival rates were 41.7% and 41.7%, respectively. **Conclusion:** Long-term survival can be achieved even in stage III or IV lung cancer patients by combining multimodal treatment with surgery in appropriate cases.

Keywords: Advanced lung cancer, salvage surgery, induction chemoradiotherapy

EP1.01-98 OUTCOMES OF NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASIS TREATED BY WHOLE BRAIN RADIOTHERAPY, A SINGLE INSTITUTION EXPERIENCE

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Background: Whole brain radiotherapy (WBRT) is predominantly used in the treatment of brain metastasis but recent data suggests that it does not significantly contribute to improved overall survival in patients. This study was carried out to review our practice by assessing the survival outcome for NSCLC patients with brain metastasis treated with WBRT in relation to the QUARTZ trial data (Mulvena et al, 2016). **Method:** A retrospective study of such patients over a period of 12 months was carried by obtaining data from electronic record systems and radiotherapy records. Data demographics and analysis of overall survival were calculated and comparison was made with literature findings. **Result:** Over 12 months 39 patients with brain metastasis had received WBRT (30G in 10# or 20G in 5#). 68% (n=29) were of NSCLC origin with a gender ratio of 1:1. The average age at diagnosis of NSCLC was 67.8 and 70 years for males and females respectively. Majority of NSCLCC patients treated with WBRT had a WHO performance status (PS) of 1(41.3%, n=12) or 0 (27.5%, n=8). Mean survival following treatment with WBRT was 16.7 weeks. The median survival was 10 weeks and average ages of death in the female and male patients were 67.8 and 70 years respectively. An incidental finding of longer survival (31.8 weeks) was noted in patients treated with 30Gray and 10 fractions compared with those treated with 20Gray and 5# (9.5 weeks). 43.8% of those receiving 30Gray and 10 fractions were of PS 0 in contrast with 14.2% of those receiving 20G in 5#. **Conclusion:** The

median survival in our patients treated with WBRT was comparable to that obtained in the QUARTZ study (9.2 weeks in those who received WBRT and optimal supportive care). Although a retrospective study, it is suggestive of an above average survival outcome in our practice when compared to the multinational QUARTZ study. The incidental observation of higher survival in the group who received higher RT dose and fraction may be explained by clinical decision influencing RT categorisation due to the fact that patients with better performance status are more likely to tolerate higher doses of RT and be given same.

Keywords: WBRT, Lung cancer, brain metastasis

EP1.01-99 EFFECT OF IMMUNE CHECKPOINT INHIBITORS RE-ADMINISTRATION IN NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Immune checkpoint inhibitors, drugs targeting the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) pathways, are approved for the treatment of patients with non-small-cell lung cancer (NSCLC) with impressive clinical activity and durable responses in some patients. But the re-administration of immune checkpoint inhibitors have not be clarified. **Method:** From December 2015 to December 2018, 93 NSCLC patients received immune checkpoint inhibitor monotherapy. We retrospectively evaluated these 93 patients. **Result:** 6 patients received re-administration of immune checkpoint inhibitors. Median progression free survival of immune checkpoint inhibitors initial treatment and re-administration were 98 and 55 (p = 0.139). Overall response rate was 24.7% and 0% (p = 0.331) and disease control rate was 53.7% and 16.7% (p = 0.105). There was no significant difference between initial treatment and re-administration. The effect of re-administration of immune checkpoint inhibitor is not so high, but one patient received more than 6months. **Conclusion:** The effect of re-administration of immune checkpoint inhibitors are not high, but few patients can receive long term of therapy.

Keywords: non-small-cell lung cancer, Immune Checkpoint Inhibitors, Re-administration

EP1.01-100 EVALUATION OF THE CLINICOPATHOLOGICAL FEATURES OF PATIENTS IN WHOM RESIDUAL CARCINOMA IN BRONCHIAL STUMP AFTER SURGERY FOR LUNG CANCER

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Background: Operation for lung cancer should be carried out with no residual carcinoma at bronchial stump. Rarely, we encounter unexpected microscopic residual carcinoma at surgical bronchial stump after surgery. Additional therapy for these patients is still controversial. **Method:** From January, 2008 to December, 2018, 812 consecutive patients with non-small lung cancer underwent surgery (99 of segmentectomy, 694 of lobectomy, and 19 of pneumonectomy) in our institution. Among them, there were 7 cases (0.9%) which had bronchial stump with residual cancer cells. We investigated the clinicopathological characteristics and outcomes of these patients retrospectively. **Result:** The procedures for the 7 cases consist of 5 lobectomy, 1 segmentectomy, and 1 pneumonectomy. In 3 cases, frozen diagnosis were done and in 2 of 3 cases additional resection were done. Histologically, there were 4 case of adenocarcinomas and 2 of squamous cell carcinomas, and 1 of adenosquamous cell carcinoma. 3 cases were stage IIIB(pT4N2M0, pT3N2M0), and 3 cases were IIIA (pT2bN2M0, pT4N1M0), 1 case was stage II*B (pT1bN1M0) respectively. All cases had lymphatic invasion microscopically.* 6 cases developed recurrence or distant metastasis. 2 had local recurrence at bronchial stump and 4 had distant metastasis (1 was in brain, 1 was at lymph nodes, 1 was at vertebrae, 1 was at bilateral lungs). 5 cases were received postoperative additional therapies. 4 cases were received cytotoxic chemotherapy only, and another case was recieved cytotoxic chemotherapy and TKI. None of them were received radiotherapy for bronchial stump. 5 cases passed away because of cancer progression and 1 case was because chronic heart failier. Another case is alive with lung metastases taking TKI therapy. In all cases, preoperative CT scan didn't show bronchial wall thickning, and preoperative bronchoscopic findings showed normal bronchial mucosa. **Conclusion:** In surgical cases of non-small cell lung cancer, 1.2% had microscopic residual cancer at surgical bronchial stump. Our study revealed that such cases tended to have a relapse as distant metastasis rather than local recurrence. Preoperative evaluation whether bronchial invasion exists or not is difficult and post-operative additional treatment strategy is still uncertain. In postoperative follow-up, systemic survey for not only local region but distant organs is necessary.

Keywords: Lung cancer, Residual carcinoma, Bronchial stump

EP1.01-101 TRANSPOSITION OF THE PULMONARY VEINS FOR MOBILIZATION OF RT-MIDDLE AND LOWER LOBES FOR SAFE RECONSTRUCTION AFTER CARINAL RT-UPPER LOBECTOMY

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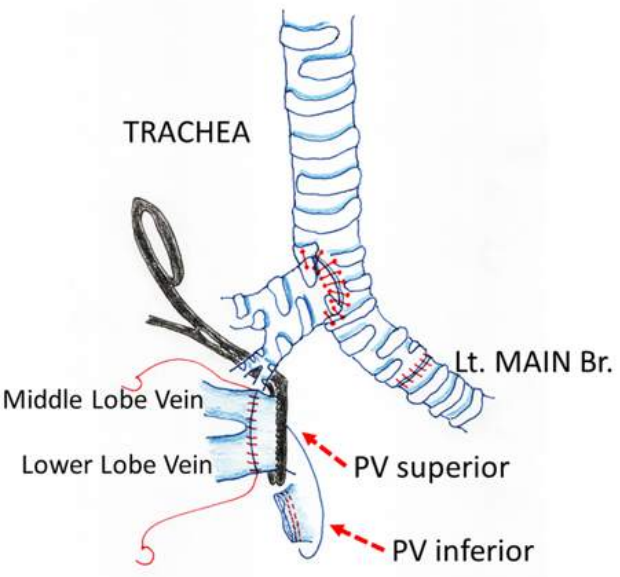
Background: A variety of techniques for reconstruction of the carina after carnal or carinal right upper lobe resection have been proposed. The most important point to accomplish this complex surgery is to achieve safe tension free airway anastomosis. Here we report a case of carinal right upper lobectomy, in whom transposition of the middle and lower pulmonary veins to the opening of the *right superior pulmonary vein* was performed to achieve safe tension free anastomosis between the trachea and right intermediate bronchus (RIB). **Method:** A 70-year-old female was admitted with severe cough. Bronchoscopy and CT scan revealed an intraluminal tumor obstructing the right main bronchus. A biopsy returned a diagnosis of adenoid cystic carcinoma. After tumor debulking by rigid-bronchoscope, extension of the tumor to the RIB and left main bronchus (LMB) was clarified and it was judged that complete resection of the lesion is possible by carinal right upper lobectomy. **Result:** A standard posterolateral thoracotomy was performed. Firstly, the trachea and LMB were transected at 2 cartilage rings above and below the carina respectively, and end-to-end anastomosis was safely performed. Then the RIB was transected immediately after the tumor invasion and the carinal right upper lobectomy was completed. Because the patient's LMB was narrow, side-to-end anastomosis of the RIB to the lateral wall of LMB was considered to be at high-risk for anastomotic stenosis. Thus the most desirable reconstruction procedure of the RIB was thought to be the side-to-end anastomosis to the lateral wall of the trachea. However, the opening of the RIB was far apart from the desirable anastomosis point of the trachea despite mobilization procedures such as right hilar release. The right middle and lower pulmonary veins were thus resected and transferred to the opening of the *superior pulmonary vein* and anastomosed by the double-barrel fashion. The opening of the RIB was then elevated and implanted to the lateral wall of the trachea.



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Conclusion: The technique of pulmonary venous transposition can be an excellent airway release maneuvers to achieve safe tension free anastomosis between trachea and RIB in case of carinal right upper lobectomy.

Keywords: Surgery, Carinal Resection, Venous Transposition

EP1.01-102 EFFICACY AND TOXICITY OF ERLOTINIB AND GEFITINIB IN MOROCCAN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER WITH EGFR MUTATION

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Background: BACKGROUND Lung cancer, the second most common cancer in Morocco, is a public health problem. It is also the leading cause of cancer death in the world because its prognosis is poor and the diagnosis is often made at a metastatic stage. The advent of tyrosine kinase inhibitors has improved survival in patients with epidermal growth factor receptor mutation (EGFR) There are few studies in Morocco, the aim of this study was to evaluate the efficacy and safety of anti-EGFR in patients with non-small cell lung cancer with EGFR mutated in Morocco. **Method:** METHODS We had collected twenty-three patients followed for metastatic non-small cell lung cancer with EGFR mutation and management in the onco-radiotherapy department of the IBN ROCHD University Hospital of Casablanca (MOROCCO) **Result:** RESULTS Of the twenty-three patients collected, the sex ratio was 7 men to 16 women, the average age was 59 years, only one case had a history of smoking, all cases had adenocarcinoma, the mutation on exon 19 was found in 87%. The median progression-free survival was 4 months and the median overall survival was 12 months, For tolerance; diarrhea and folliculitis were found in all patients with 50% grade II. **Conclusion:** CONCLUSIONS The EGFR mutation appears to be more frequent in women and non-smokers, and anti-EGFR treatment improves survival with a particular tolerance profile that should be known.

Keywords: metastatic lung cancer, EGFR mutation, advanced NSCLC

EP1.01-103 LONG-TERM RESPONSE TO SECOND-LINE AFATINIB FOR THE TREATMENT OF ADVANCED LUNG SQUAMOUS CELL CARCINOMA

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Background: Lung squamous cell carcinoma (SqCC) with large heterogeneity and complex genetic map accounts for 25–30% of non-small-cell lung cancer (NSCLC) cases. SqCC is lack of defined molecular targets and often diagnosed at a advanced stage, which contribute to poor prognosis. Afatinib is an irreversible ErbB family inhibitor that is approved for the second-line treatment of patients with advanced SqCC who progressed after platinum-based chemotherapy based on the significant clinical benefits in Lux-Lung8. **Method:** We presented a case of a 56-year-old male with a 30-year history of smoking was diagnosed as SqCC of the left lung (cT2N3M0, IIIB). After neoadjuvant chemotherapy +sugery + adjuvant chemotherapy, CT scans showed disease progressed with disease-free survival (DFS) of 12 months. Thus, continuous chemoradiotherapy was administered. Seven months later, chest CT suggested that the disease progresssed again. Subsequently, the patient was enrolled into LUX-Lung 8 study and began the second-line therapy of afatinib (40 mg/day). **Result:** The patient remaining in stable disease (SD) after 8 weeks and achieving complete response(CR) after 12 weeks treatment.The patient is still alive and the disease has not progressed more than 5 years since initiation of treatment. There's no obvious side effects during the treatment. **Conclusion:** We found that the patient had a favorable progosis with the overall survial of more than five years treated with afatinib. Long-term response to afatinib in this case provides an important reference for the treatment of patients with advanced SqCC.

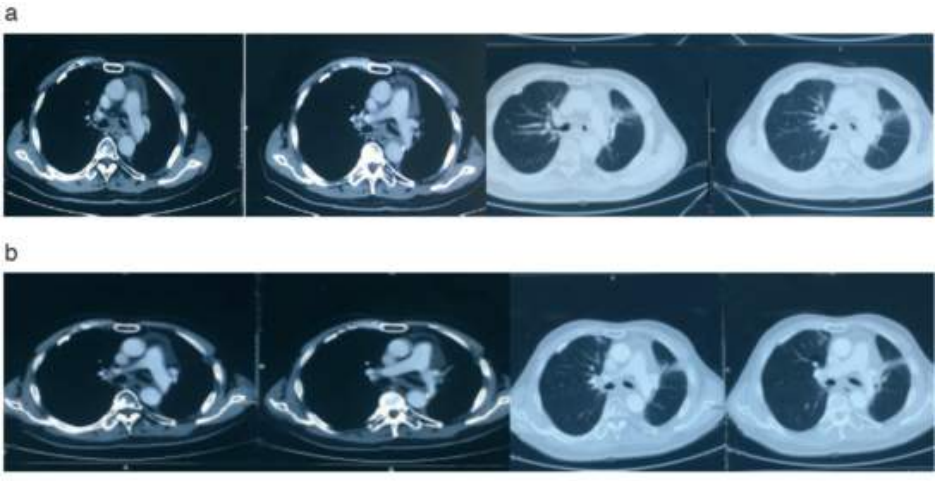

Fig. 1 (a) CT scan showing PD before enrolled into Lux-Lung8.

(b) showing CR after 12 weeks treatment of second-line afatinib.

Keywords: lung squamous cell carcinoma, long-term response, Afatinib

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EP1.01-104 DENOSUMAB EXPERIENCE IN LUNG CANCER PATIENTS WITH BONE METASTASES

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Background: Denosumab, is a monoclonal antibody against receptor activator nuclear factor kappa B ligand (RANKL). It inhibits the bone resorbtion and therefore decreases skeletal related events (SRE). It is practically used instead of zoledronic acid in the tumors with bone metastasis. This study aims to reveal general characteristics and adverse event profile of lung cancer patients with bone metastasis. **Method:** This study includes 17 patients referred to outpatient clinic who have lung cancer with bone metastasis between July 2014 and July 2018. We retrospectively analyzed the data. The patients who were on denosumab treatment at least 2 months were included. **Result:** All of the patients were men (n=17). The median age was 66,8 years old (range 34-84 years). All of the patients had non small cell lung cancer histology. Six patients (35,2 %) had squamous cell carcinoma and eleven patients were with adenocarcinoma histology. Except for two patients, all had metastatic disease. 3 had bone metastasis after the cancer diagnosis while others had bone metastasis initially. Seven patients had another metastatic sites besides bone metastasis and the most common metastatic site was lung (57,1 %). Among eleven adenocarcinoma patients, 4 had EGFR mutation (36 %): 2 with exon 19 deletion and 2 with exon 21 mutation. These 4 patients had anti-EGFR treatment. The patients had denosumab in the range of 2-33 months, with the median 6,5 months. 10 patients had radiation therapy besides denosumab treatment. Six patients (35,2 %) were switched from zoledronic acid therapy to denosumab because of renal failure. There was no hypocalcemic status because all the patients had laboratory checks for calcium, vitamin D and albümin and treated according to the deficiency before denosumab therapy. Also during denosumab treatment we did not see any osteonecrosis because all had undergone dentist examination before the initiation of the drug. 29,4 % (five patients) died during the therapy. All of the patients passed on because of the disease progression. **Conclusion:** Bone is the most common metastatic site of lung cancer. Bone metastasis cause morbidities like pain, fracture, hypercalcemia and spinal cord compression. In our study, unlike the literatüre, there were no hypocalcemia or osteonecrosis. This outcome may be connected not only the shortness of the follow-up but also the initial replacement of calcium and vitamin D. Because of being effective and with less toxicity, denosumab may be a positive option in lung cancer patients with bone metastasis.

Keywords: lung, cancer, denosumab

EP1.01-105 EXPERIENCE IN TREATING RECURRENT NON-SMALL LUNG CANCER PATIENTS AFTER SURGERY WITH IMMUNE-CHECKPOINT INHIBITOR

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Background: Recent rapid advancements in the development of chemotherapy, including immune checkpoint inhibitors (ICIs), such as program death-1 (PD-1) inhibitor or program death-ligand 1 (PD-L1) inhibitors, in the field of non-small cell lung cancer (NSCLC) have remarkably prolonged patients' survival. Several clinical trials currently underway are assessing the efficacy of ICIs in adjuvant chemotherapy (AC) following complete resection of Stage I-IIIA NSCLC. One of the issues with AC for completely resected NSCLC is the limited proportion of patients who benefit from such treatment, as some patients will experience recurrence despite AC while others will not experience recurrence even without AC. Given the emergence of adverse events (AEs), including immune-related AEs at a constant rate, the appropriate timing of treatment with ICI remains unclear whether AC or at the time of recurrence. **Method:** In this single-institutional retrospective study, to clarify the treatment effect of ICIs in terms of the survival or response, we reviewed 21 patients treated with ICIs for recurrent NSCLC who had undergone complete surgical resection between March 2016 and October 2018. **Result:** The median age was 61 years old (range: 47-75 years old). There were 16 men and 5 women. Thirteen patients had adenocarcinoma, 5 had squamous cell carcinoma, and 3 had others. The PD-L1 expression by 22C3 antibody was <1% in 7 patients, 1%-50% in 3 patients, >50% in 5 patients and not done in 6 patients, and the treatment lines of ICIs was first- to second-line in 8 patients and third-line or later in 13 patients. The response was partial response (PR) in 3 patients, stable disease (SD)in 10 patients, progressive disease (PD) in 6 patients and not evaluable in 2 patients. The median overall survival time from the initial administration of ICIs was 22.8 (2.0-80.1) months, while that from surgical resection was 63.7 (9.5-109.7) months. **Conclusion:** The efficacy of administering ICIs after recurrence should be compared with that of AC with ICIs.

Keywords: non-small cel lung cancer, immune-checkpoint inhibitor, recurrence after surgery

EP1.01-106 A SPECIAL CASE OF SYNCHRONOUS MULTIPLE PRIMARY LUNG CANCER WITH MEDIASTINAL LYMPH NODE METASTASES OF UNKNOWN PRIMARY ORIGIN

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Background: Coexisting lung cancers that are independent of each other and have either different or the same histology type are designated synchronous multiple primary lung cancer (sMPLC). The incidence of sMPLC is 0.2%-8% and has been increasing due to the recent development of early detection technology. Cancer of unknown primary site (CUP) accounts for 3%-5% of cancers, it rarely occurs in mediastinal lymph nodes and accounts for only 1.0–1.5% of all CUP cases. **Method:** We presented a 61-year-old man with a history of smoking and old tuberculosis. The image data showed a large mass (2.4 cm*2.3 cm*2.0 cm) in the left lower lobe, and the 5th group of mediastinum lymph nodes was enlarged, suggesting peripheral lung cancer with lymph node metastasis. Multiple GGNs had been found in both lungs and the tuberculosis in the upper lobes of both lungs was identified. No other distant metastases were detected from other image data. Left lower lobe resection and lymph node dissection were performed on the patient. **Result:** Intraoperative pathology revealed squamous cell carcinoma with no driver mutations in the left lower lobe. Adenocarcinoma harbouring the EGFR gene exon 18 mutation (G719A/G719C) was diagnosed in the mediastinum lymph node dissection. Multiple gene sequencing showed that there's no relationship was between two primary sites. The hypothesis of the primary origin of the metastatic mediastinal lymph nodes is scar cancer from tuberculosis or multiple GGNs. Chemotherapy consisting of four cycles of gemcitabine plus cisplatin were prescribed for this patient after the operation. The current status of the patient was evaluated as stable disease (SD) with a PFS of more than 12 months. https://cpaper.ctimeetingtech.com/wclc2019/submission/mediafiles/view?id=1019&type=mediafile **Conclusion:** We found a sMPLC patient with different pathological types between the lung and lymph node lesions. Lung scar cancer or GGNs is highly suspected to be the origin of the metastatic mediastinal lymph node.

Keywords: synchronous muitiple primary lung cancer, cancer of unknown primary site, Lymph node metastasis

EP1.02 ADVOCACY

EP1.02-01 PROSPECTS OF CANCER PATIENTS AND PATIENT ASSOCIATION FROM THE VIEWPOINT OF LIVE SURVEY AT PARTICIPATORY SYMPOSIUM

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Background: At the Japan Cancer Patient Meeting, which is held once a year in November 2018, a live Internet survey was conducted for the symposium "Let's talk together, patient strength". Based on the results, we discussed the status of support for cancer patients and the problems that cancer patients have. And as a patient groups, we put together requests to the government and the medical association. **Method:** We conducted an online questionnaire using the survey-monkey system immediately before the symposium, targeting participants in the cancer patient association (including online viewers). While presenting the results of the questionnaire at the symposium, we exchanged opinions with the panelists and the

participants, and summarized the contents of the request. **Result:** The total number of responses was 257 people in total, including net and documents, including 85% of cancer patients and families. At the time of cancer diagnosis, 59.5% had someone to consult, and 16.6% of those who consulted cancer survivors showed the spread of peer support activities. On the other hand, 12.6% were not available for consultation. The information that helped to get over the cancer was in order of website, patient's association, and medical staff. 95.1% of the participants felt that they could receive support and livelihood from the words of the cancer experienced person. Conversely, 90% wanted to make use of their own cancer experiences. The requests for medical institutions were in the order of palliative care, collaboration with the patient association, and home care. **Conclusion:** While the patient association activities play a role in making the most of "patient strength" through questionnaires and discussions, the place of activity, funding, and aging of the patient association officers were regarded as important issues in the future.

Keywords: Internet survey, Cancer Advocacy

EP1.02-02 THE PATH OF A SURVIVOR

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Background: Being diagnosed with lung cancer was both the worst and best day in my life. Dying was not on my agenda but then again I lived my life the way so many do. Without thought going through the motions of living. I truly started to live after my diagnosis. Funny when you think you have a finite amount of time you live differently. From deep down; at least in some of us comes a strength and determination be change and enact change in the world around us. I found that strength and the deep feeling that I could be the pebble to start the avalanche of change and acknowledgement that seems to be so lacking for lung cancer and those affected by it. Another patient who has a bigger battle then I would ever have put it aptly. We are the invisible cancer, masked behind stigma that is difficult to shake off, myths, misinformation; finally the lack of knowledge people have relating to lung cancer. This means most patients have two fronts to fight; the disease and the stigma. One saps the life out of a person, the other takes their self-respect leaving them having to defend themselves on being diagnosed with lung cancer. I on the other hand had a rather short fight with lung cancer which leaves me the ability and the wherewithal to speak up and bring the world of lung cancer out from behind the mask into the open through dialogue, events, sharing and hopefully supporting others who hqve to endure a much harder, longer battle. Each one of us personally and with organizations need to keep our eye on the end of the road. We are all working for the same outcomes. Each has their own way of doing, presenting the knowledge, sharing. What we should have is the support of each other. A united front; each working in their own manner to achieve results. Creating a safer environment for those diagnosed to speak and be seen without the censor of stigma. Those diagnosed with lung cancer and their caregiver families belong in the world, embraced and supported throughout their ordeal. Not feeling like they need to be hidden away. Every person deserves to be the best and live the best **Method:** As an advocate and patient I continue to speak whenever opportunities present themselves. I have spearheaded and will continue to expand events bringing lung cancer to the forefront. The more it is in the public realm the easier it will be over time. **Result:** Bringing lung cancer into the light; even if one person has a better understanding then we are achieving something. **Conclusion:** not applicable

Keywords: advocate, unmasking, patients

EP1.03 BIOLOGY

EP1.03-01 MOLECULAR SPECTRUM OF PATIENTS WITH JAK1 MUTATIONS IN EAST ASIAN NON-SMALL CELL LUNG CANCER

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[1]*Affiliated Hospital of Xiamen University, Xiamen/China,* [2]*Fujian Cancer Hospital, Fuzhou/China,* [3]*Zhejiang Cancer Hospital, Hangzhou/China,* [4]*Zhejiang Rongjun Hospital, Jiaxing/China,* [5]*Jinling Hospital, Nanjing/China*

Background: JAK1 is a critical effector of pro-inflammatory cytokine signaling and plays important roles in immune function, while abnormal JAK1 activity has been linked to immunological and neoplastic diseases. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring *JAK1* mutations. **Method:** A total of 933 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *JAK1* mutations and other genes were detected by next generation sequencing. **Result:** *JAK1* gene mutation rate was 1.50% (14/933) in non-small cell lung cancer, including D660G (2 patients), Q499E (1 patient), L954P (1 patient), C16* (1 patient), R239W (1 patient), S295* (1 patient), I359T (1 patient), E791K (1 patient), Q207L (1 patient), R69H (1 patient), H434Y (1 patient), K218N (1 patient) and E662Q (1 patient), and median overall survival (OS) for these patients was 13.0 months. Among them, all patients were *JAK1* gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=10) co-occurring *EGFR* mutations had a median OS of 14.5 months and 13.0 months respectively (P=0.70); patients with (n=13) or without (n=1) co-occurring *TP53* mutations had a median OS of 15.0 months and 13.0 months respectively (P=0.64); patients with (n=5) or without (n=8) co-occurring *KRAS* mutations had a median OS of 11.0 months and 15.0 months respectively (P=0.79); patients with (n=3) or without (n=11) co-occurring *NF1* mutations had a median OS of 11.0 months and 20.0 months respectively (P=0.11). **Conclusion:** Althoght *EGFR*, *TP53*, *KRAS*, *NF1* gene accompanied may have less correlation with *JAK1* mutation in NSCLC patients, predict which patients may harbor *JAK1* mutations, could have implications in triaging toward *JAK1* variant identification for potential future targeted therapy. These data have implications for the identification of therapeutic target candidates.

Keywords: non-small-cell lung cancer, JAK1 mutation, prognosis

EP1.03-02 FREQUENCY OF MICROSATELLITE INSTABILITY IN PATIENTS WITH PRIMARY NON SMALL LUNG CANCER IN A SINGLE INSTITUTION FROM COLOMBIA

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Background: Lung carcinogenesis is a focus of research for prognosis and development of possible therapeutic objectives. The microsatellite instability (MSI) has been described as a potential mechanism of cancer development mainly in colorectal cancer as a marker of prognosis and treatment response. In lung cancer is not known the precise frequency of MSI and its possible implications for precision therapeutics. Past trials reported a low incidence of this biological signature, but this finding could improve some immune characterization of lung cancer focused in immunotherapeutics. Is very important to know the incidence of MSI in lung cancer in a sample of latin patients to know its indicence y relation with some clinical features. **Method:** The present study is a case series were we describe microsatellite instability (MSI) in patients with primary non small cell lung cancer. First, the patients with non-small cell lung carcinomas of the Hospital Militar Central diagnosed between january 2010 and january 2016 were included, then the clinical charts of each patient were reviewed to identify clinical and socio-demographic variables. The immunohistochemical staining were realized in the paraffin blocks using the Ventana Benchmark Ultra and GX equipment allowing the identification of the mismatch repair proteins (MMRP) MLH1, PMS2, MSH2 y MSH6; defining microsatellite instability with the negativity for any of these markers. We reviewed other molecular biology signatures:EGFR mutation and KRAS in some cases were this finding could be avaliable. In Colombia there´s no health system coverage for this mutations. **Result:** 33 patients with non-small cell lung carcinoma

were included in the study. Of this patients we can identify 69.7% with lung adenocarcinoma and 30.3% with squamous cell lung carcinoma. 54.5% of the total of patients were diagnosed in stage IV (TNM 7th edition). We identified a history of tobacco exposition in 45.5% of this patients. In the immunohistochemical staining, we identify that 9.1% of all the patients had microsatellite instability (MSI high); with negativity for the expression for MHL1 gene in 2 patients and for MSH6 gene in 3 patients, all of this patients were diagnosed with lung adenocarcinoma and all of this patients were EGFR wild type, in 1 of this patients we found a registry of KRAS mutated tumor. For the MHL1-negative patients, one of them had tobacco exposition history (heavy smoker) and for the MSH6-negative patients 2 of 3 had a tobacco exposition history. Unfortunately we didn´t found any of this patients treated with immunooncology agents. **Conclusion:** In a small latin population at a single institution the present study found a frequency of 9.1% in 33 patients with non-small cell lung cancer with microsatellite instability (MSI-High). All of this patients were adenocarcinoma subtype, non related with EGFR mutations and with a correlation with tobacco exposure. Unfortunately this is a small case series and we could not establish a response to immunooncology agents because in Colombia we have this medications available since 2018. The frequency of this finding is higher than previous reports and must be confirmed in a multiinstitutional registry from latin population in development.

Keywords: Non small cell lung cancer, Microsatellite Instability, Lung Cancer Biology

EP1.03-03 ASSOCIATION BETWEEN MOLECULAR SPECTRUM OF EZH2 VARIANTS AND PROGNOSIS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER IN CHINESE PATIENTS

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Background: Enhancer of zeste homolog 2 (*EZH2*) shows upregulated expression in tumors and is an important driver of tumor development and progression. However, the mechanism underlying the mediation of tumor aggressiveness in non-small-cell lung cancer (NSCLC) by *EZH2* remains unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *EZH2* mutations. **Method:** A total of 1122 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *EZH2* mutations and other genes were detected by next generation sequencing. **Result:** *EZH2* gene mutation rate was 0.62% (7/1122) in non-small cell lung cancer, including K515R (1 patient), I55M (1 patient), D142H (1 patient), K222N (1 patient), Q66R (1 patient), P486S (1 patient), and S652C (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, all patients were *EZH2* gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=5) co-occurring *EGFR* mutations had a median OS of 16.0 months and 20.0 months respectively (P=0.88); patients with (n=6) or without (n=1) co-occurring *TP53* mutations had a median OS of not up to now and 20.0 months respectively (P=0.79); patients with (n=2) or without (n=5) co-occurring *BRAF* mutations had a median OS of 14.0 months and 20.0 months respectively (P=0.45); patients with (n=2) or without (n=5) co-occurring *SMARCA4* mutations had a median OS of 20.0 months and not up to now respectively (P=0.88). **Conclusion:** *EZH2* mutation may predict a worse prognosis of NSCLC. Methyltransferase inhibitor may be beneficial for NSCLC patients with specific *EZH2* mutations. *EGFR*, *TP53*, *BRAF*, *SMARCA4* gene accompanied may have less correlation with *EZH2* mutation in NSCLC patients. The findings of this study could facilitate both clinical trial design and therapeutic strategies.

Keywords: non-small-cell lung cancer, EZH2 mutation, prognosis

EP1.03-04 ANALYSIS OF POST-SURGICAL SYSTEMIC INFLAMMATORY INDEXES AFTER NON-SMALL CELL LUNG CANCER SURGICAL INTERVENTION

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Background: High NSCLC´s mortality rates pushes the research of new prognostic indexes further tan TNM staging and could help in better treatment´s selection. Neutrophil-Lymphocyte Ratio (NLR) preoperatively determined has demonstrated its relation with the immunologic status of the patient prior to the intervention and its capacity of "beating" tumor growing and its prognostic influence. OBJECTIVE: Evaluate the prognosis influence of NLR, Lymphocyte-Monocyte Ratio (LMR) and Platelet-Lymphocyte Ratio (PLR) in patients who underwent surgery for NSCLC with R0 resection and abscence of neoadjuvant treatment in peripheric blood determinations after surgery. **Method:** A retrospective review of all consecutive patients operated on stage I to IIIA NSCLC from may 2014 – october 2018, completely resected and with no neoadjuvant treatment. Patients with previous oncologic history, haematologic neoplasms, perioperatory blood transfussion, perioperative infections or corticosteroids treatment were excluded. Peripheral blood determinations were taken during the first 6-months follow-up period. NLR, LMR and PLR were calculated. A descriptive analysis of demographic, tumor and surgical details is done. Overall survival (OS) was calculated since the date of surgery to date of death or last follow-up date. Disease-free survival (DFS) was calculated since the date of surgery to the date of recurrence. The discrimination capacity of the ratios was assessed with the calculation of the area under the ROC curve [AUC (CI 95%)]. The relationship among relevant clinico-pathological variables, DFS and OS was calculated. Analysis of recurrence risk factors with univariate and multivariate binary logistic regression (LR) OR(95%CI) was performed. **Result:** 86 patients were included in the analysis. Median follow-up time was 45.7 months. Median OS and DFS were 27 and 24 months respectively. The AUC values of NLR [0.59(0,44-0,74)] and PLR [0,61(0,45-0,76] were not statistically significant, but value of LMR was significant with [0,70(0,57-0,83)]. The LR model found as factors associated with a higher probability of recurrence adjusted by sex and age: the value of LMR with OR=0,38 (0,20-0,73) and a higher stage than the OR=11,3 (1,89-67.5). **Conclusion:** Conversely to other publications, in our study the results showed the only relationship between LMR, tumor stage and risk of recurrence.

Keywords: platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio

EP1.03-05 A META-ANALYSIS OF ASSOCIATION BETWEEN SERUM IRON LEVELS AND LUNG CANCER RISK

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Background: Many studies conducted on the relationship between serum iron levels and lung cancer risk had produced inconsistent results. We therefore conducted a meta-analysis to determine whether serum iron levels were lower in lung cancer patients compared to those in controls. **Method:** A literature survey was conducted by searching the PubMed, WanFang, CNKI, and SinoMed databases for articles published as of Mar 1, 2018. Standard mean differences (SMD) with the corresponding 95% confidence intervals (CI) were executed by Stata 12.0 software. **Result:** A total of 13 publications involving 1118 lung cancer patients and 832 controls were included in our study. The combined results showed that serum iron levels in lung cancer cases had no significantly lower when compared to those in controls [summary SMD = -0.125, 95%CI= -0.439, 0.189, Z = 0.78, p for Z test= 0.435], with high heterogeneity (I2= 89.9%, P< 0.001) found. In the stratified analysis by geographic locations, consistent results were found for serum iron levels between lung cancer patients and controls both in Asian populations [summary SMD = -0.113, 95%CI= -0.471, 0.245] and European populations [summary SMD = -0.215, 95%CI= -0.835, 0.404]. **Conclusion:** Publication bias was not found when evaluated by Begg's funnel plot and Egger's regression asymmetry test.In summary, the current study showed that serum iron levels had no significant association on lung cancer risk.

Keywords: Iron levels, Lung cancer, Serum

EP1.03-06 POLD1 MUTATIONS DEFINE A UNIQUE MOLECULAR CLASS OF NON-SMALL CELL LUNG CANCER IN CHINESE PATIENTS

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Background: Somatic *POLE* mutations have been found in a subset of non-small cell lung cancer (NSCLC) while *POLD1* mutations are reportedly rare in NSCLC. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *POLD1* mutations. **Method:** A total of 833 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *POLD1* mutations and other genes were detected by next generation sequencing. **Result:** *POLD1* gene mutation rate was 1.20% (10/833) in non-small cell lung cancer, including L357Rfs*36 (1 patient), R225H (1 patient), D76H (1 patient), I659M (1 patient), T582R (1 patient), A930T (1 patient), A749S (1 patient), G178V (1 patient), V455L (1 patient) and D102N (1 patient), and median overall survival (OS) for these patients was 13.0 months. Among them, all patients were *POLD1* gene with co-occurring mutations. Briefly, patients with (n=4) or without (n=6) co-occurring *EGFR* mutations had a median OS of not up to now and 11.0 months respectively (P=0.11); patients with (n=8) or without (n=2) co-occurring *TP53* mutations had a median OS of 13.0 months and 12.6 months respectively (P=0.80); patients with (n=2) or without (n=8) co-occurring *NRAS* mutations had a median OS of 15.0 months and 13.0 months respectively (P=0.61); patients with (n=3) or without (n=7) co-occurring *PTPRD* mutations had a median OS of not up to now and 13.0 months respectively (P=0.79). **Conclusion:** *POLD1* mutations represents an uncommon phenotype in NSCLC and may thus reprensent a candidate biomarker for response to immunotherapy in patients with NSCLC.

Keywords: prognosis, non-small-cell lung cancer, POLD1 mutation

EP1.03-07 PREVALENCE AND CLINICOPATHOLOGICAL CHARACTERISTICS OF EIF1AX MUTATIONS IN CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: The *EIF1AX* gene was recently described as a new thyroid cancer-related gene. Its mutations were mainly reported in poorly differentiated (PDTC) and anaplastic thyroid cancers (ATC), but also in well-differentiated thyroid cancer (WDTC) and in benign thyroid lesions, although less frequently. The prevalence of these mutations in non-small-cell lung cancer (NSCLC) is unknown. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *EIF1AX* mutations. **Method:** A total of 923 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *EIF1AX* mutations and other genes were detected by next generation sequencing. **Result:** *EIF1AX* gene mutation rate was 1.30% (12/923) in non-small cell lung cancer, including D125N (1 patient), G6D (1 patient), R14G (1 patient), G15D (1 patient), W70C (1 patient), K3N (1 patient), G9D (1 patient), R13P (1 patient), R14S (1 patient), R57G (1 patient), G135E (1 patient), and P2L (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, all patients were *EIF1AX* gene with co-occurring mutations. Among them, 11 patients with co-occurring mutations had a median OS of 20.0 months, and OS of one patient without complex mutations was 19.8 months. No statistically significant difference was found between the two groups (P=0.84). Briefly, patients with (n=2) or without (n=10) co-occurring *TP53* mutations had a median OS of 14.0 months and 20.0 months respectively (P=0.87); patients with (n=2) or without (n=10) co-occurring *STK11* mutations had a median OS of 4.0 months and 20.0 months respectively (P=0.02); patients with (n=3) or without (n=9) co-occurring *NRAS* mutations had a median OS of 4.0 months and 20.0 months respectively (P=0.17); patients with (n=3) or without (n=9) co-occurring *KRAS* mutations had a median OS of not up to now and 20.0 months respectively (P=0.88). **Conclusion:** There is no significant difference of molecular features in *EIF1AX* gene mutations in NSCLC. Patients with complex mutations benefited more from therapy than those with single mutations. Next generation sequencing provides a simplified strategy and reasonably high detection rate for *EIF1AX* mutation, which suggested application of the strategies into clinical molecular diagnostics.

Keywords: non-small-cell lung cancer, EIF1AX mutation, prognosis

EP1.03-08 MIR-744 FACILITATES NON-SMALL CELL LUNG CANCER PROGRESSION BY TRANSCRIPTIONAL REGULATION OF C-FOS

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Background: Metastasis is the leading cause of lung cancer associated death. Here, we focused on the function and downstream molecular mechanism of miR-744 and its potential clinical application in non-small cell lung cancer (NSCLC) progression. **Method:** The clinical cohort and data from TCGA were analyzed for the correlation of miR-744 and clinical outcomes. Multiple NSCLC cell lines and a NSCLC xenograft model were applied for the functional studies *in vitro* and in vivo respectively. Reporter assays were used for transcriptional regulatory mechanism study. **Result:** It was confirmed that the overexpression of miR-744 was significantly correlated with lymph node metastasis and poor prognosis in NSCLC. It was an independent prognostic molecular marker for NSCLC. Both *in vitro* and in vivo studies revealed that miR-744 overexpression aggravated the invasion and metastasis of NSCLC cells. MiR-744 positively regulated c-FOS by directly binding to the promoter of c-FOS. We also identified -358 to -332 bp and -221 to -192 bp upstream of c-FOS gene as the direct and efficient miR-744 binding site in c-FOS promoter region. MicroRNA-744 could regulate MAPK signaling and enhanced the resistance of lung cancer cells to radiotherapy and paclitaxel. **Conclusion:** Our findings uncover the function of miR-744 in NSCLC and reveal a novel mechanism of miR-744 in mediating growth and metastasis of NSCLC cells. Our data suggests that miR-744 may serve as a possible therapeutic target for NSCLC. Support: 81572279, 2016J004, LC2016PY016, 2018CR033.

Keywords: miR-744, transcriptional regulation, c-FOS

EP1.03-09 EPIDEMIOLOGICAL STUDY OF TSC1 MUTATIONS AMONG NON-SMALL CELL LUNG CANCER PATIENTS IN CHINA

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Background: The tuberous sclerosis complex 1 (TSC1) is an endogenous regulator of the mechanistic target of rapamycin (mTOR). While mTOR has been shown to play an important role in neoplasm. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *TSC1* mutations. **Method:** A total of 1106 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *TSC1* mutations and other genes were detected by next generation sequencing. **Result:** *TSC1* gene mutation rate was 1.90% (21/1106) in non-small cell lung cancer, including Q654E (2 patients), R429K (2 patients), A1072D (1 patient), R850S (1 patient), E625K (1 patient), R715Q (1 patient), A84T (1 patient), S1038G (1 patient), M1090I (1 patient), D903H (1 patient), I143N (1 patient), Q3H (1 patient), L134F (1 patient), T1065M (1 patient), V407M (1 patient), S673F (1 patient), D675Y (1 patient), Q149H (1 patient) and T1144P plus L916M (1 patient), and median overall survival (OS) for these patients was 14.0 months. Among them, all patients were *TSC1* gene with co-occurring mutations. Briefly, patients with (n=12) or without (n=9) co-occurring *TP53* mutations had a median OS of 14.0 months and 15.0 months respectively (P=0.58); patients with (n=9) or without (n=12) co-occurring *KRAS* mutations had a median OS of not up to now and 14.0 months respectively (P=0.56); patients with (n=2) or without (n=19) co-occurring *BRAF* mutations had a median OS of 18.5 months and 12.0 months respectively (P=0.71); patients with (n=4) or without (n=17) co-occurring *CDKN2A* mutations had a median OS of 8.0 months and 18.0 months respectively (P=0.47). **Conclusion:** Accompanied gene has not well been connected with *TSC1* gene mutations. Our finding expands the mutant spectrum of *TSC1* gene and adds new understanding of the phenotype.

Keywords: non-small-cell lung cancer, TSC1 mutation, prognosis

EP1.03-10 EXPRESSION OF ANTI-AGING GENE, KLOTHO IS A SURROGATE MARKER OF PEMETREXED FOR LUNG CANCER TREATMENT

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Background: Adjuvant chemotherapy using cisplatin is recommended for patients with lung cancer p-stage IB-IIIA, who were received surgical resection completely. In order to improve the prognosis of the patients with lung cancers, we need to find a new predictive factor for anti-cancer agents and establish a new regimen for the adjuvant chemotherapy. We have previously reported that anti-aging gene Klotho expression was a prognostic factor for small cell lung cancer and LCNEC so far. Therefore, in this study, we investigate the association between the expression of Klotho and the sensitivity against anti-cancer agents, and we examined the anti-tumor tumor effect of Klotho expression. **Method:** We established a cell line, A549/Klotho, which stably overexpress Klotho, and then examined the association between the expression of Klotho and Epithelial-Mesenchymal Transition related proteins such as N-cadherin, E-cadherin, Snail, Vimentin, etc. Next, we performed the sensitivity test for various anticancer agents including pemetrexed, CDDP, paclitaxel, gefitinib, etc, using A549 cells and A549/Klotho cells. Moreover, we evaluated the role of Klotho expression against anti-tumor effect. **Result:** By western blot analysis, the expression of N-cadherin was completely inhibited in A549/Klotho cells, but in A549 cells. This result suggested that Klotho expression may regulate the expression of N-cadherin and Klotho can play an important role in cancer metastasis/invasion by regulating EMT. Moreover, we clarified that miR145 was related to the inhibition of N-cadherin in analysis of A549/Klotho cells but not miR218, miR67. A549/Klotho cells were more sensitive seven times against pemetrexed compared to A549 cells (IC50; 0.1 micro M) by MTT assay. There is no difference of sensitivity between A549/Klotho cells and A549 cells against molecular target drugs such as gefitinib, other kinds of TKI. **Conclusion:** From these results, we conclude that overexpression of Klotho may regulate the sensitivity against pemetrexed through the inhibition of expression of mir145 and N-cadherin. In the future, we may establish a new strategy of chemotherapy for patients with advanced lung cancer based on the expression of anti-aging gene Klotho.

Keywords: Klotho, anti-aging gene, pemetrexed

EP1.03-11 MECHANISMS OF GEFITINIB PLUS PEMETREXED ON HUMAN NON-SMALL CELL LUNG CANCER

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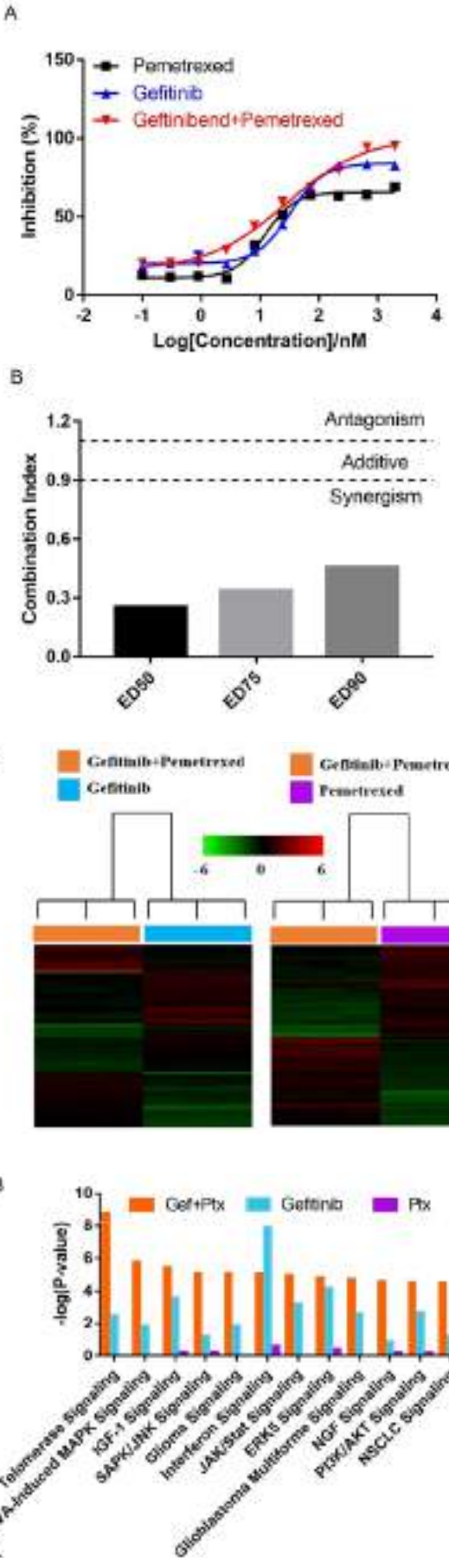
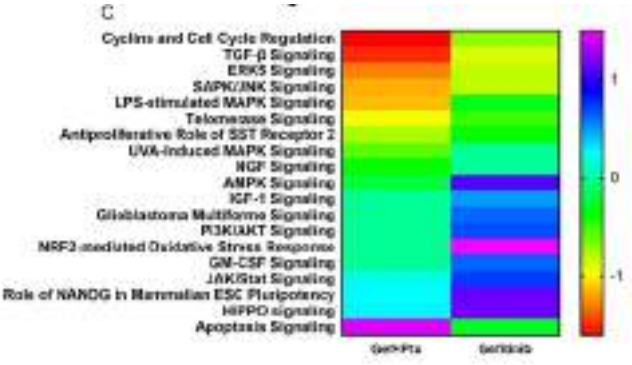
Background: Resistance to EGFR tyrosine kinase inhibitors (EGFR-TKI) is often acquired in non-small cell lung cancer (NSCLC) patients during treatment. We previously demonstrated that combined treatment with EGFR-TKI gefitinib plus chemotherapy improved progression-free survival (PFS) in NSCLC patients carrying sensitive EGFR mutations. **Method:** Pharmacological interaction between gefitinib and pemetrexed was evaluated in NSCLC cell line PC-9 using MTT assay. The influence of combined treatment with gefitinib plus pemetrexed on gene expression profiles and signaling pathways has been investigated using microarray and Ingenuity Pathway Analysis (IPA). **Result:** Synergistic inhibitory effect between gefitinib and pemetrexed was observed in NSCLC cell line PC-9. Figure 1A suggested representative proliferation inhibitory effects of gefitinib, pemetrexed and combined treatment for 48 hours. Figure 1B showed CI values of concurrent gefitinib-pemetrexed treatment in PC-9 NSCLC cell line. CI values at ED50, ED75 and ED90 were shown. Furthermore, widespread gene expression changes and critical signaling pathways were induced significantly by combined treatment in PC-9 cells. Figure 2A was heatmap of gene expression prolifes in human NSCLC PC-9 cell line treated with gefitinib (blue), pemetrexed (purple) or gefitinib-pemetrexed combination (orange) with the criteria P<0.05 and |fold change |>1.5. Genes and samples were listed in rows and columns, respectively. A colour standard for data normalization was shown at the bottom with green representing downregulated genes while red representing upregulated genes. In Figure 2B, pathway enrichment of differential expressed genes was analysed using Ingenuity Pathway Analysis (IPA). Signaling pathways shown here were based on a *P<0.0001*. Figure 2C showed heatmap of critical pathways affected by combined treatment as compared to gefitinib single treatment. Heatmap colour represented the Z-score of signalling pathways. Z-score>0 meant the signalling pathway was stimulated by related treatment while Z-score<0 meant the signalling pathway was inhibited by related treatment.





Conclusion: Gene expression profiles revealed potential signaling pathways contributing to the synergism.

Keywords: synergism, gene expression profile, Non-Small Cell Lung Cancer

EP1.03-12 IL-10 PROMOTES TUMOR AGGRESSIVENESS IN NON-SMALL CELL LUNG CANCER VIA DOWN-REGULATED THE EXPRESSION LEVEL OF MIR-125B

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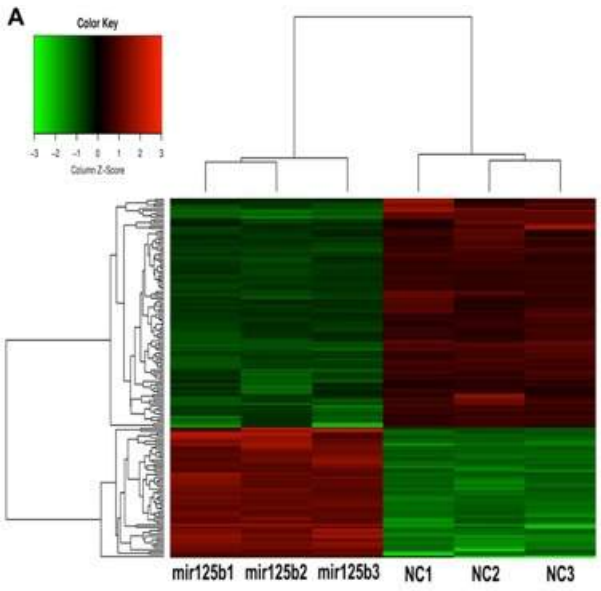
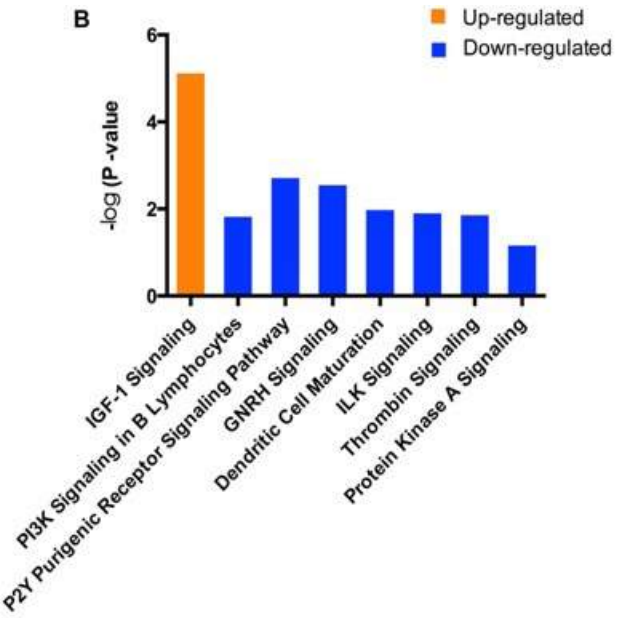
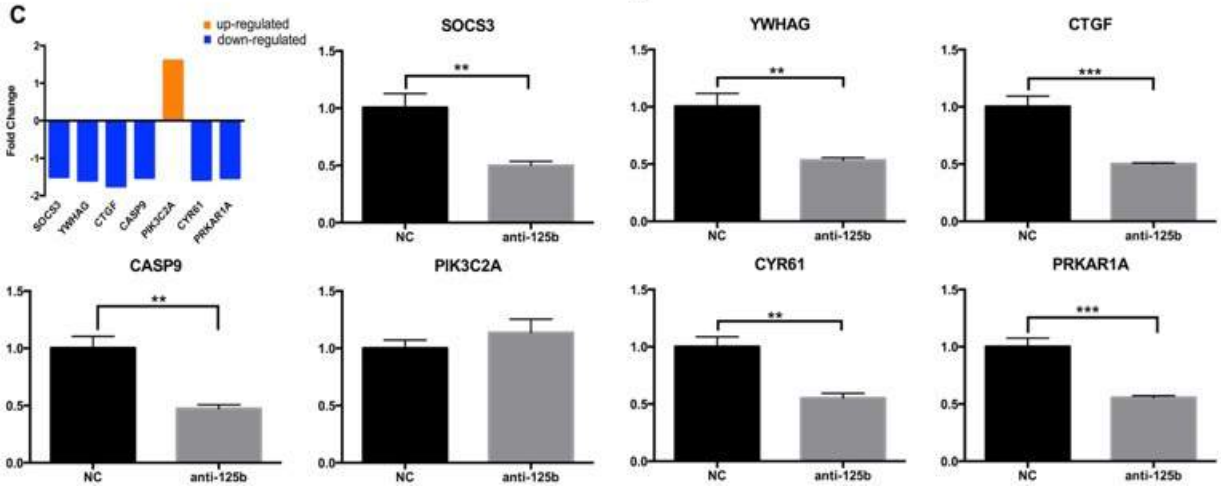
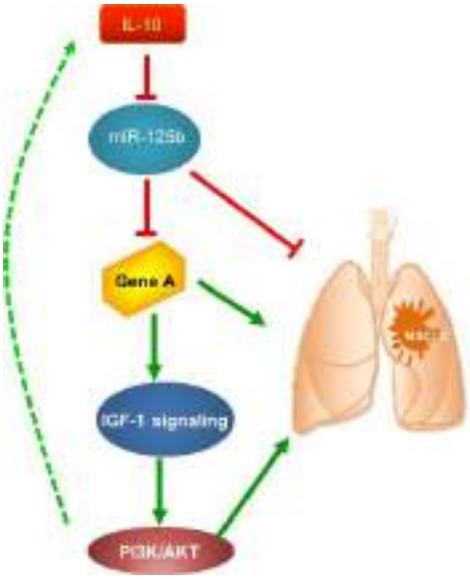
Background: IL-10 is an anti-inflammatory factor with bi-directional regulation of tumor immunity. While, the role and mechanism of IL-10 in lung cancer is not clear. The aim of the present study was to identify the potential mechanisms of IL-10 in lung carcinogenesis. **Method:** RT-PCR was used to detect the expression of miRNAs and mRNAs. CKK8 and flow cytometry assays was performed for the function experiments. Microarray analysis and IPA analysis were used to predict the potential signal pathway. **Result:** IL-10 was found significantly associated with the risk of non-small cell lung cancer (NSCLC). Meanwhile, the expression level of miR-125b in NSCLC cell line was dramatically decreased when stimulated by IL-10. The results of cell function experiments showed that miR-125b inhibited the tumor promoting effects of IL-10 in NSCLC. Then, microarray and IPA analysis found that IGF-1 signaling pathway was significantly activated after down-regulated the expression of miR-125b









Conclusion: IL-10 promotes tumor aggressiveness via down-regulated the expression level of miR-125b in lung cancer.

Keywords: miR-125b, Lung cancer, IL-10

EP1.03-13 MOLECULAR CHARACTERISTICS OF EAST ASIAN PATIENTS WITH VHL-MUTATED NON-SMALL-CELL LUNG CANCER: A RETROSPECTIVE STUDY

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Background: The von Hippel-Lindau (*VHL*) gene is inactivated frequently in sporadic clear-cell renal cell carcinomas (ccRCCs) by genetic alteration. However, the pathological or prognostic significance of *VHL* gene alteration has not been well defined in the other cancers, especially non-small cell lung cancer (NSCLC). The aim of this study is to investigate mutations and prognosis of NSCLC harboring *VHL* mutations. **Method:** A total of 972 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *VHL* mutations and other genes were detected by next generation sequencing. **Result:** *VHL* gene mutation rate was 0.72% (7/972) in non-small cell lung cancer, including W117fs*15 (1 patient), G44A (1 patient), G44V (1 patient), P81S (1 patient), R120T (1 patient), E51K (1 patient) and T100A (1 patient), and median overall survival (OS) for these patients was 22.0 months. Among them, all patients were *VHL* gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=5) co-occurring *EGFR* mutations had a median OS of 22.0months and 12.0 months respectively (P=0.16); patients with (n=3) or without (n=4) co-occurring *TP53* mutations had a median OS of not up to now and 12.0 months respectively (P=0.23); patients with (n=3) or without (n=4) co-occurring *KRAS* mutations had a median OS of 3.0 months and 22.0 months respectively (P=0.07); patients with (n=2) or without (n=5) co-occurring *SETD2* mutations had a median OS of 3.0 months and 22.0 months respectively (P=0.01). **Conclusion:** The present study expanded the database on *VHL* gene mutations in NSCLC and enriched the spectrum of known somatic mutations of the *VHL* gene. Chemotherapy may be considered as a possible treatment for carriers of the mutation. *SETD2* mutated accompanied mutations might play a poor prognosis in *VHL* gene mutation NSCLC.

Keywords: non-small-cell lung cancer, VHL mutation, prognosis

EP1.03-14 CLINICOPATHOLOGIC CHARACTERISTICS AND OUTCOMES OF CHINESE PATIENTS WITH NON-SMALL-CELL LUNG CANCER AND INPP4B MUTATIONS

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Background: Inositol polyphosphate 4-phosphatase B (*INPP4B*) has been identified as a tumour suppressor in different human cancers. However, the role of *INPP4B* in the angiogenesis of human non-small cell lung cancer (NSCLC) remains unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *INPP4B* mutations. **Method:** A total of 750 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *INPP4B* mutations and other genes were detected by next generation sequencing. **Result:** *INPP4B* gene mutation rate was 2.80% (21/750) in non-small cell lung cancer, including p.R623K (2 patients), p.N378S (1 patient), p.G187W (1 patient), p.V117I (1 patient), c.1721-1G>T (1 patient), p.R818* (1 patient), p.T829R (1 patient), p.Q753H (1 patient), p.L542M (1 patient), p.I68M (1 patient), p.Q814E (1 patient), p.K448N (1 patient), p.C617F (1 patient), p.Q600H (1 patient), p.G479* (1 patient), p.L155Q (1 patient), p.P572A (1 patient), p.L16V (1 patient), p.F652Y (1 patient), and p.T671S plus p.N228K (1 patient), and median overall survival (OS) for these patients was 15.0 months. Among them, all patients were *INPP4B* gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=19) co-occurring *EGFR* mutations had a median OS of 20.0 months and 5.5 months respectively (P=0.01); patients with (n=17) or without (n=4) co-occurring *TP53* mutations had a median OS of 15.0 months and 14.4 months respectively (P=0.68); patients with (n=7) or without (n=14) co-occurring *PTPRD* mutations had a median OS of not up to now and 15.0 months respectively (P=0.48); patients with (n=8) or without (n=13) co-occurring *KRAS* mutations had a median OS of 17.0 months and 15.0 months respectively (P=0.68). **Conclusion:** *INPP4B* mutations were observed in 2.80 % of cases of NSCLC. *INPP4B*-mutated NSCLC can exhibit other driver gene alterations. No clinical characteristics were significantly associated with *INPP4B* mutation.

Keywords: non-small-cell lung cancer, INPP4B mutation, prognosis

EP1.03-15 COMPARISON OF PLASMA EXPRESSION OF DROSHA AND DICER MRNAS IN EARLY AND ADVANCED STAGES OF NSCLC PATIENTS

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Background: Drosha and Dicer are the enzymes necessary during the miRNA biogenesis. They have the same effect on all microRNAs. Many studies have focused on profiling the expression of selected miRNAs or whole miRNom's analysis in serum or plasma, as potential tool for early detection of diseases. We would like to check, whether the expression of *Drosha* and *Dicer* mRNA is detectable in plasma of NSCLC patients, and whether it can differentiate early and advanced stages of this disease. **Method:** We enrolled 59 (43.1%) NSCLC patients in early (I-IIIA) stages and 78 (56.9%) in locally advanced or advanced (IIIB-IV) stages. We isolated total mRNA and reverse transcription PCR (RT-PCR) was performed. RT-PCR was made using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Real-time PCR (qPCR) was performed for assessment of *Drosha* and *Dicer* mRNA expression on Eco Illumina Real-Time PCR system device (Illumina Inc.). We used TaqMan probe Hs00203008_m1 (Applied Biosystems) for *Drosha* and Hs00229023_ m1 (Applied Biosystems) for *Dicer* mRNA expression measurement. *GAPDH* was used a housekeeping gene. Statistical analysis were performed with use of Statistica 13.1 software (Tibco). **Result:** *Drosha* mRNA expression was detectable in plasma of 57 (41.6%) patients. 17 (28.8%) patients with *Drosha* mRNA expression were in early stages and 40 (51.3%) patients were in stages IIIB or IV (χ^2=6.98, p=0.008). Expression of *Dicer* mRNA was detectable in plasma of 71 (57.8%) patients. 15 (25.4%) of patients from this group were in early stages and 56 (71.8%) – in IIIB or IV stages (χ^2=28.93, p<0.0001). Significant higher expression of *Drosha* mRNA was observed in group of patients with lymph node involvement

compared with group of patients without lymph node metastases (p=0.001). Moreover, significantly higher expression of *Dicer* mRNA was observed in group of patients with distant metastases compared with group without metastases (p=0.0002). Furthermore, we found statistically nonsignificant (p=0.07) lower expression of *Drosha* mRNA in stages IIIB-IV compared with early stages. We did not find any differences between *Drosha* or *Dicer* mRNAs expression in patients stratified by age, tumor size or histopathological diagnosis (p<0.1). **Conclusion:** Plasma expression of *Drosha* and *Dicer* mRNAs is detected more often in advanced stages of NSCLC. Probably, different mRNAs from more damaged tumor cells in more advanced disease stages are present in higher expression in blood stream. However, this proves that free mRNAs of *Drosha* and *Dicer* are mainly produced by cancer cells in NSCLC patients. indirectly, it can be concluded that cancer cells have disturbed production of microRNAs. There are necessity to use more sensitive tools (i.e. Next Generation Sequencing method) to asses expression of *Dicer* and *Drosha* mRNAs in early stages of NSCLC.

Keywords: NSCLC patients, Drosha, Dicer

EP1.03-16 LYSIMACHIA CAPILLIPES CAPILLIPOSIDE C RESTORES RADIATION SENSITIVITY IN RADIATION RESISTANT LUNG CANCER CELLS BY ENHANCING ERRFI1 EXPRESSION

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Background: Radiation therapy is used as the primary treatment for lung cancer. Unfortunately, radiation resistance and local failure remain to be the major clinic problems for lung cancer patients. It is therefore crucial to find new therapeutic targets and/or drugs to enhance the effects of radiation without increasing the adverse effects. Lysimachia capillipes capilliposide C (LC-C) extracts from LC Hemsl. show anti-cancer effects both *in vitro* and in vivo. The purpose of this study is to investigate a potential therapeutic impact of LC-C as a radiation sensitizer in lung cancer cells. **Method:** Non small cell lung cancer (NSCLC) cell line A549 was initially irradiated with a total dose of 60 Gy (3 Gy/Fx, 20 Fx, 2-3 Fx/week) to generate radiation-resistant cancer cell line A549-IR. RNA-seq analysis was used to examine the whole-transcriptome alteration in A549-IR cells treated with or without LC-C, and the differentially expressed genes with most significance were verified by RT-qPCR. Colony formation assays were performed to determine the effect of the target gene ErbB receptor feedback inhibitor 1 (ERRFI1) on radiosensitivity of A549-IR cells. In addition, effects of ERRFI1 on cell cycle distribution, DNA damage repair activity were assessed by flow cytometry and γ-H2AX immunofluorescence staining respectively. Western blot was performed to identify the activation of related signaling pathways. Tumor xenograft experiments were conducted to observe the effect of LC-C and ERRFI1 on radiosensitivity of A549-IR cells in vivo. **Result:** ERRFI1 was significantly up-regulated in A549-IR cells when cells were treated with LC-C (IC20=3.5 μM). With irradiation treatment, clonogenic formation decreased in the ERRFI1 overexpressed cells when comparing to the parental cells, with reduced survival fraction-2 value from 0.54±0.07 to 0.24±0.06 (p<0.01). The sensitizing enhancement ratio for LC-C was 1.667. Furthermore, ERRFI1 overexpression may enhance radiosensitivity of A549-IR cells *in vitro* by inducing G2/M phase arrest and inhibiting DNA damage repair. Overexpression of the ERRF11 decreased the activation of EGFR and STAT3 signaling pathways in A549-IR cells. Knocking down ERRFI1 expression in A549-IR cells attenuated the radiosensitization effect of LC-C. Moreover, in a A549-IR cells-derived xenograft model, combination treatment with LC-C (25 $mg \cdot kg^{-1} \cdot d^{-1}$, qod, ig) and irradiation (6Gy) dramatically enhanced tumor growth suppression comparing with LC-C or radiation alone. **Conclusion:** LC-C can restore the cells' sensitivity to irradiation through regulation of ERRFI1 expression in lung cancer cells. Combination treatment of LC-C and irradiation may serve as a promising therapeutic strategy to overcome the radiation resistance and ERRFI1 may be a poteintal therapeutic target to improve radiosensitivity in NSCLCs.

Keywords: Radiosensitivity, lysimachia Capillipes capilliposide C, ErbB receptor feedback inhibitor 1

EP1.03-17 OUTCOMES OF MOLECULAR CHARACTERISTICS IN CHINESE BAP1-MUTANT NON-SMALL CELL LUNG CANCER PATIENTS

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Background: BRCA1-Associated-Protein 1 (*BAP1*) is a dynamic tumor suppressor which, when mutated, has been associated with an increased risk of uveal melanoma, cutaneous melanoma, mesothelioma, and several other cancers. There is some clinical evidence for the use of *BAP1* mutations as prognostic and predictive biomarker. The aim of this study is to investigate mutations and prognosis of non-small-cell lung cancer (NSCLC) harboring *BAP1* mutations. **Method:** A total of 851 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *BAP1* mutations and other genes were detected by next generation sequencing. **Result:** *BAP1* gene mutation rate was 1.88% (16/851) in non-small cell lung cancer, including H94Y (1 patient), T177P (1 patient), E198Gfs*45 (1 patient), R238K (1 patient), D34Y (1 patient), Y173C (1 patient), E450K (1 patient), G41C (1 patient), S325F (1 patient), P293L (1 patient), Q28* (1 patient), E498K (1 patient), E631Q (1 patient), H144D (1 patient), Q280* (1 patient), (1 patient) and R518L (1 patient), and median overall survival (OS) for these patients was 24.0 months. Among them, all patients were *BAP1* gene with co-occurring mutations. Briefly, patients with (n=4) or without (n=12) co-occurring *EGFR* mutations had a median OS of 14.5 months and not up to now respectively (P=0.35); patients with (n=9) or without (n=7) co-occurring *TP53* mutations had a median OS of not up to now and 24.0 months respectively (P=0.79); patients with (n=3) or without (n=13) co-occurring *CDKN2A* mutations had a median OS of 24.0 months and not up to now respectively (P=0.57); patients with (n=4) or without (n=12) co-occurring *KEAP1* mutations had a median OS of 5.0 months and 24.0 months respectively (P=0.07). **Conclusion:** *BAP1* genetic alter occurs in a subset of NSCLC, and improved understanding of the implications of *BAP1* aberrations is critical for the identification of therapeutic target candidates.

Keywords: non-small-cell lung cancer, BAP1 mutation, prognosis

EP1.03-18 ANALYSIS OF IDH1 MUTATION SPECTRUM FROM NON-SMALL-CELL LUNG CANCER IN EAST ASIAN PATIENTS

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Background: Isocitrate dehydrogenase 1 (IDH1) is a metabolic enzyme that converts isocitrate to alpha-ketoglutarate. *IDH1* mutations are associated with the accumulation of the oncometabolite D-2-hydroxyglutarate, which acts as an epigenetic modifier, and the development of multiple malignancies. Previous studies uncovered mutations in IDH1 in several malignancies, with the most frequent mutation being IDH1 R132H. It has been demonstrated that IDH1 expression is induced in non-small-cell lung cancer (NSCLC). The aim of this study is to investigate mutations and prognosis of NSCLC harboring *IDH1* mutations. **Method:** A total of 893 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *IDH1* mutations and other genes were detected by next generation sequencing. **Result:** *IDH1* gene mutation rate was 1.23% (11/893) in non-small cell lung cancer, including Q138S (1 patient), D79V (1 patient), T373N (1 patient), C114* (1 patient), W336L (1 patient), I99M (1 patient), G104R (1 patient), R132C (1 patient), A193S (1 patient), Y34C (1 patient) and H67R (1 patient), and median overall survival (OS) for these patients was 11.0 months. Among them, all patients were *IDH1* gene with co-occurring mutations. Briefly, patients with (n=9) or without (n=2) co-occurring *TP53* mutations had a median OS of not up to now months and 8.5 months respectively (P=0.32); patients with (n=2) or without (n=9) co-occurring *KMT2D* mutations had a median OS of 11.5 months and 11.0 months respectively (P=0.80); patients with (n=5) or without (n=6) co-occurring *KRAS* mutations had a median OS of not up to now months and 8.0 months respectively (P=0.22); patients with (n=2) or without (n=9) co-occurring *CREBBP* mutations

had a median OS of 15.5 months and 8.0 months respectively (P=0.67). **Conclusion:** Our results demonstrated that decreased *IDH1* gene mutation correlated with poor overall survival in NSCLC patients. *IDH1* gene mutation may define a subset of patients with lung cancer appropriate for investigational therapeutic strategies.

Keywords: non-small-cell lung cancer, IDH1 mutation, prognosis

EP1.03-19 THE FREQUENCY AND PROGNOSIS OF MDM2 MUTATIONS IN EAST ASIAN NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: In neoplasm, the mouse double minute 2 (*MDM2*) is an oncoprotein that contributes to the promotion of cell growth, survival, invasion, and therapeutic resistance. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring *MDM2* mutations. **Method:** A total of 1152 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *MDM2* mutations and other genes were detected by next generation sequencing. **Result:** *MDM2* gene mutation rate was 0.52% (6/1152) in non-small cell lung cancer, including D179N (1 patient), S84L (1 patient), T195M (1 patient), V234L (1 patient), A471S (1 patient) and E184Q (1 patient), and median overall survival (OS) for these patients was 24.0 months. Among them, all patients were *MDM2* gene with co-occurring mutations. Briefly, patients with (n=2) or without (n=4) co-occurring *EGFR* mutations had a median OS of 18.5 months and 24.0 months respectively (P=0.89); patients with (n=4) or without (n=2) co-occurring *TP53* mutations had a median OS of 24.0 months and 7.0 months respectively (P=0.05); patients with (n=2) or without (n=4) co-occurring *BRCA1* mutations had a median OS of 24.0 months and 13.0 months respectively (P=0.20); patients with (n=2) or without (n=4) co-occurring *KEAP1* mutations had a median OS of 15.5 months and 24.0 months respectively (P=0.59). **Conclusion:** *MDM2* mutations represent a distinct subset of NSCLC. Next generation sequencing showed that *MDM2* mutations commonly co-existed with other driver genes. Our results show that *MDM2* mutations delineate an aggressive subtype of lung cancer for which a targeted treatment through *MDM2* inhibition might offer new opportunities.

Keywords: non-small-cell lung cancer, MDM2 mutation, prognosis

EP1.03-20 DIAGNOSTIC AND PROGNOSTIC UTILITY OF DIFFERENTIALLY EXPRESSED CIRCULATING MICRORNAS IN INDIAN NSCLC PATIENTS

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Background: The presence of circulating tumour DNA, mRNA and non-coding RNAs, such as microRNA (miRNA), in the serum and plasma of cancer patients has sparked great interest because conventional diagnostic tests tend to be imperfect and more invasive, posing logistic difficulties for serial tumour sampling. Hence, identification of differentially expressed circulating miRNAs in the serum of non-small cell lung cancer (NSCLC) patients may have potential as cancer biomarkers for diagnosis, prognosis and predicting therapeutic response. **Method:** For the identification of differentially expressed miRNAs in the serum of NSCLC patients, we performed small RNA sequencing with illumina HiSeq 2000 platform (n=10; 4 NSCLC patients and 6 controls). The expression profile of miRNAs in each subject was analyzed using miRNAkey software and fold change was performed to identify differentially expressed miRNAs in NSCLC as compared to controls. We validated the expression of few differentially expressed miRNAs in the serum of 75 NSCLC patients and 40 controls using miScript qRT-PCR assay. The expression of miRNAs was correlated with overall survival (OS), progression-free survival (PFS), response to therapy and various clinico-pathological parameters. **Result:** The mean age of NSCLC patients and controls was 56.2 years and 55.3 years, respectively (p = 0.3242). Majority of the NSCLC patient and controls were male. 67% of NSCLC patients and 53% of controls were smokers (p = 0.099). Global miRNA profiling revealed 16 differentially expressed miRNAs (cut-off: fold change > 2.0, or p < 0.05, or both) in the serum of NSCLC patients as compared to controls. Our qRT-PCR data revealed significant down-regulation of miR-15a-5p, miR-320a, miR-25-3p, miR-192-5p, let-7d-5p, let-7e-5p, miR-148a-3p and miR-92a-3p in the serum of NSCLC patients as compared to controls. None of the miRNAs were correlated with survival outcome and therapeutic response. The expression of miR-320a, miR-25-3p and miR-148a-3p significantly correlated with stage, while miR-375 expression significantly correlated with lymph node involvement and pleural effusion. **Conclusion:** The expression of majority of miRNAs was down-regulated in the serum of NSCLC patients as compared to controls. Some of the miRNAs, such as miR-375 and miR-320a, are less studied for their involvement in the pathogenesis of NSCLC. Hence, future mechanistic studies are warranted to elucidate their role in disease biology and as candidate biomarkers for diagnosis and prognosis of NSCLC.

Keywords: MicroRNA, non-small cell lung cancer, diagnosis

EP1.03-21 CIRCULATING TUMOR CELLS ISOLATION IS NOT A USEFUL PROGNOSTIC TOOL FOR NON-SMALL CELL LUNG CANCER PATIENTS CANDIDATES TO SURGICAL TREATMENT

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Background: It is well known that prognostic stratification according to TNM classification of non-small cell lung cancer (NSCLC) patients is somehow imprecise as there exist notable differences among patients endorsed in the same staging. Because of this it is mandatory to find complementary tools to reach a more accurate classification in order to the best selection of treatments for every patient. The presence of circulating tumor cells (CTC) in periferic blood samples has showed worse prognosis in other primary tumors. The aim of this study is analyzing the impact of CTC on disease free survival (DFS) and overall survival (OS). **Method:** Periferic blood samples from 28 patients diagnosed with NSCLC in early stages candidates for surgical treatment were obtained. Study period was from June 2011 to October 2013. Blood samples were obtained at least at three different moments: before surgery (S1), one year after the operation (S2) and the last one 2 years after the operation (S3). Blood samples were analyzed by CellSearch method. Probability of survival was calculated following the Kaplan-Meier method; differences in survival were examined by the Long-Rank test. **Result:** Median OS was 34 months and DFS was 11 months. There was no statistically significant differences among patients with or without CTC in S1, S2 and/or S3. When CTC were present, no relationship was observed between the variations in the number of CTCs among the different blood samples and the OS and DFS. **Conclusion:** In our study, the presence of CTCs in any of the blood samples obtained during the follow-up showed no relationship with OS and DFS. The same results were observed in relation to variations of CTCs' count.

Keywords: circulating tumour cells, Early stage, surgery

EP1.03-22 PROGNOSTIC VALUE OF SERUM INFLAMMATION BIOMARKERS IN EARLY STAGE LUNG ADENOCARCINOMA

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Background: Non-small cell lung cancer is the main cause of cancer-related death worldwide, with a low 5-year survival rate even in early-stage. And adenocarcinoma accounts for the majority of all Non-small cell lung cancer cases. Biomarkers to identify prognosis of early stage lung cancer are needed. Increasing evidences indicate a relationship between inflammation and lung carcinogenesis. One of our previous studies found inflammation biomarkers, BLC and MDC, are significantly related with the risk of early stage lung cancer. The present study was performed to evaluated the value of inflammation biomarker in predicting the prognosis of early stage lung adenocarcinoma. **Method:** Ten inflammation biomarkers were tested by Luminex bead-based

assay in 157 patients with resected early-stage lung adenocarcinoma (IA-IIB) from whom serum samples were collected pre-surgery. **Result:** A total of 152 early stage lung adenocarcinoma patients were analyzed in this study. The mean age (SD) of was 59.9 (9.4) years. 58.6% of them were females, and never smokers accounted for 84.0%. By TNM stage, 109 (71.7%) patients were at stage I and 43 (28.3%) at stage II. The median follow-up time was 60.6 months. Patients with higher MIG levels were at a 70% reduced risk of recurrence compared with patients with lower MIG levels (HR=0.3, 95% CI: 0.1–0.7, *p*=0.0035). As for BLC, patients with higher levels had the risk of recurrence decreased by 50% (HR=0.5, 95% CI: 0.3–0.9, p=0.031) compared with patients with lower levels. After the Bonferroni correction, only MIG was significantly associated with the recurrence risk of early stage lung adenocarcinoma. For overall survival (OS), patients with higher MIG levels were still have a reduced dead risk compared with the lower group (p=0.0065). **Conclusion:** Our results demonstrate for the first time that pretreatment MIG level was identified as a protective factor for the prognosis of early stage lung adenocarcinoma.

Keywords: Early Stage Lung Cancer, Inflammation Biomarkers, prognosis

EP1.03-23 UPDATE OF THE ANALYSIS OF THE STATUS OF LYMPHOCYTE INFILTRATION IN PATIENTS WITH NSCLC

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Background: Current evidence highlights the potential role of tumor-infiltrating lymphocytes (TILS) as a prognostic factor in many types of tumors; in non-small cell lung cancer (NSCLC), this relationship is not well determined. TILs are being studied with different methods such as immunohistochemistry and optical microscopy. The primary endpoint is to identify TILS in patients with NSCLC, classified as present or absent, and its relation to progression free survival (PFS). **Method:** Retrospective and analytical case study of Instituto Oncológico de Córdoba. 187 patients with stage IIIB and IV NSCLC were analyzed. TILS are descriptively classified as present or absent. Survival curves were calculated using the Kaplan-Meier method. **Result:** 63% of patients had adenocarcinoma and 37% squamous cell carcinoma. 72% were men. 82% were smokers. 65% of patients with squamous histology and % 58 with adenocarcinoma, showed TILS. Patients with adenocarcinoma with TILS present had higher PFS 13.3 months, compared to patients with absent, 8.8 months. These differences were statistically significant (PFS: p=0.004). The patients with squamous cell carcinoma with TILS had 10.8 months PFS. Those who had infiltrated absent had a PFS of 5.6 months. These differences were also statistically significant (PFS: 0.001). **Conclusion:** Our study shows that patients whose pathological samples presented inflammatory infiltrate had higher PFS. The presence of TILS could be used as an important prognostic factor in this patient population.

EP1.03-24 CLINICOPATHOLOGIC CHARACTERISTICS AND SURVIVAL OUTCOME IN CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER AND HGF MUTATIONS

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Background: Hepatocyte growth factor (*HGF*) is the ligand for the tyrosine kinase receptor *MET* (Mesenchymal Epithelial Transition Factor also known as Hepatocyte Growth Factor Receptor, *HGF*R). HGF and its receptor, MET, play critical roles in cell proliferation, angiogenesis and invasion in a wide variety of cancers, especially non-small cell lung caner (NSCLC). The aim of this study is to investigate mutations and prognosis of NSCLC harboring *HGF* mutations. **Method:** A total of 526 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *HGF* mutations and other genes were detected by next generation sequencing. **Result:** *HGF* gene mutation rate was 4.56% (24/526) in non-small cell lung cancer, including E437K (1 patient), L677I (1 patient), S386L (1 patient), R242Q (1 patient), H717N (1 patient), G520R (1 patient), R234H (1 patient), A713G (1 patient), P703S (1 patient), D264N (1 patient), N127K (1 patient), G506E (1 patient), C84* (1 patient), R647Q (1 patient), G133V (1 patient), D257N (1 patient), S386L (1 patient), S166R (1 patient), P27H (1 patient), C612* (1 patient), W528L (1 patient), G133V (1 patient), G694Wfs*31 (1 patient), and T143S plus G146A (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, all patients were *HGF* gene with co-occurring mutations. Briefly, patients with (n=4) or without (n=20) co-occurring *EGFR* mutations had a median OS of not up to now and 20.0 months respectively (P=0.18); patients with (n=19) or without (n=5) co-occurring *TP53* mutations had a median OS of 20.0 months and 21.0 months respectively (P=0.96); patients with (n=4) or without (n=21) co-occurring *BRAF* mutations had a median OS of not up to now and 20.0 months respectively (P=0.46); patients with (n=5) or without (n=19) co-occurring *ERBB4* mutations had a median OS of 20.0 months and 19.6 months respectively (P=0.83). **Conclusion:** *EGFR*, *TP53, BRAF* and *ERBB4* gene accompanied may have less correlation with *HGF* mutation in NSCLC patients. Results of ongoing studies will provide a platform for further research to offer individualized therapy with the purpose of improving outcomes.

Keywords: non-small-cell lung cancer, HGF mutation, prognosis

EP1.03-25 IMPACT OF PREOPERATIVE COMPLETE BLOOD CELL COUNT-DERIVED INFLAMMATION BIOMARKERS IN EARLY-STAGED NON-SMALL CELL LUNG CANCER PATIENTS

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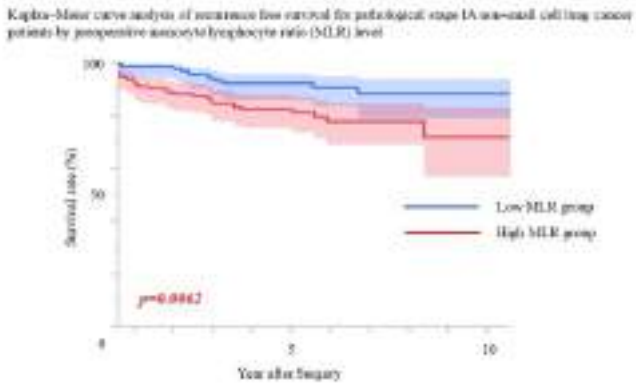
Background: Although stage IA non–small-cell lung cancer (NSCLC) has an optimistic survival rate, up to 10% of these patients relapse after surgery and die. Inflammation plays a critical role in the development and progression of various cancers by promoting cancer cell proliferation and survival, angiogenesis and tumor metastases. Inflammatory cells in the tumor microenvironment significantly affect tumor development, and markers of systemic inflammation may indicate tumor status. In recent years, complete blood cell count (CBC)-derived inflammation biomarkers such as systemic immune-inflammation index (SII), neutrophils lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and monocyte lymphocyte ratio (MLR), are used as prognostic factors in various malignancies. These markers are based on two or three parameters selected among neutrophils, lymphocytes, platelets and monocytes. SII has been investigated as a prognostic factor in several malignancies. NLR, PLR and MLR have been used as markers as systemic inflammation and are associated with poor outcomes in sloid tumors. Concerning non-small cell lung cancer, these parameters have been also reported as poor indicators, but few have specifically studied stage IA disease. We retrospectively analyzed clinicopathological features of patients with stage IA NSCLC to identify recurrence predictors and to investigate effects of preoperative CBC-derived inflammation biomarkers. **Method:** We selected 311 consecutive patients with stage IA NSCLC treated from April 2006 to December 2012 for this study, and tested their preoperative SII, NLR, PLR and MLR in uni- and multivariate Cox proportional analyses of recurrence free survival (RFS). **Result:** Preoperative high MLR level was significantly associated with sex, smoking status, postoperative recurrence (P<0.0001, =0.0307 and =0.0146) and preoperative high SII level was only correlated with postoperative recurrence (*P*= 0.0458), although both NLR and PLR were not found any related factors. Intratumoral vascular invasion (*P*= 0.0412), intratumoral lymphatic invasion (*P*= 0.0097) and preoperative MLR level (*P*= 0.0269) were identified as independent predictors of shorter RFS. Relative risk for preoperative high MLR level patients was 2.259 compared with patients with low MLR level (95% CI: 1.094–5.000). 5-year RFS rate in preoperative high MLR group was significantly lower than that in low MLR group (82.21% vs. 92.05%, p=0.0062).



Conclusion: Preoperative MLR level is a simple and novel predictor of recurrence in patients with stage IA NSCLC.

Keywords: Pathological stage IA non-small cell lung cancer, Preoperative complete blood cell count-derived inflammation biomarkers, Predictive factor of postoperative recurrence

EP1.03-26 ANALYSIS OF GENE EXPRESSION PROFILING OF LUNG ADENOCARCINOMA BRAIN METASTASIS

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Background: The molecular biology of lung adenocarcinoma (ADC) brain metastasis is poorly understood. We aimed to explore genes that are implicated in the process of brain metastasis of primary lung adenocarcinoma. **Method:** Twelve primary lung ADC with brain metastasis (ADCBM), six non-metastatic lung ADC (NMADC) and six lung ADC with metastasis except in the brain (ADCEB) were selected. Samples from all primary lung ADC were obtained after surgical resections performed at Incheon St. Mary's hospital. All tumors were analyzed with the NanoString nCounter system for gene expression using the nCounter PanCancer Progression panel composed of 740 genes. Expression data were analyzed using the NanoString nSolver software ver 4.0 and nCouter Advanced Analysis ver 2.0.115. **Result:** Eleven out of the 740 genes were differentially expressed between the ADCBM and ADC without brain metastasis including NMADC and ADCEB. The genes that were downregulated in the ADCBM included RGCC, ACHE, TPSB2, and FHL1. Expression levels of EPHB3, AGRN, ISLR, TNFRSF12A, TPM2, PTRF and BGN were upregulated in the ADCBM compared to ADC without brain metastasis including NMADC and ADCEB. The ADCBM was compared with NMADC and ADCEB, respectively. Four genes were differentially expressed between the ADCBM and NMADC. 23 genes were differentially expressed between the ADCBM and ADCEB. The differentially expressed genes (DEGs) in NMADC vs. ADCEB were not identified the same DEGs in ADCBM vs. NMADC and ADCEB. As a result, the EPHB3, AGRN and TNFRSF12A that were upregulated and the RGCC that was downregulated in ADCBM was common identified. **Conclusion:** Although our findings are not conclusive, we have identified differentially expressed genes that might mediate the brain metastasis process. A prospective validation is needed to confirm candidate genes associated with ADCBM.

Keywords: adenocarcinoma, brain metastasis, gene expression

EP1.03-27 THE ANTI-MIGRATION AND ANTI-INVATION MECHANISMS OF CAPILLIPOSIDE C FROM LYSIMACHIA CAPILLIPES ON LUNG CANCER

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Background: Approximately 50% of lung cancer patients had distant metastases when initial diagnosed. Lysimachia capillipes is one of traditional medicine in China. It is proved to be safety in clinical use. Several studies have showed the antitumor effects of Capilliposide from Lysimachia capillipes (LC) *in vitro*. Our preliminary data showed LC could inhibit the migration and invasion of lung cancer. This study aims to explore the detailed mechanisms of LC as well as its extracts on lung cancer. **Method:** Four non-small cell lines were selected. The invasive response of lung cancer cells was determined by Wound Healing assay. Proteins and the phosphorylation of proteins were evaluated by iTRAQ-based proteomics. The phosphorylation chip was used to evaluate the phosphorylation effect. PC-9 xenografts were used to evaluate the antitumor of LC-C in vivo. Immunohistochemistry (IHC) was used to evaluate the antitumor mechanisms in vivo. **Result:** The migration capa city of lung cancer cells was significantly reduced after treatment of LC-C. Proteomics showed there were 364 differentially expressed proteins and 456 differentially expressed phosphorylated proteins in both LC-C treated PC-9 and H1975 cells. Differentially expressed proteins were enriched in EGF receptor signaling pathway, Wnt signaling pathway, Cadherin signaling pathway, Notch signaling pathway, TGF-beta signaling pathway, and p38 MAPK pathway by bioinformatic analysis. Phosphorylation chip showed LC reduced the phosphorylation of AKT, WNK1 and PRAS40, but not EGFR. Western blot showed the phosphorylation of mTOR, AKT and PRAS40 were significantly inhibited after LC-C treatment; besides, the inhibitory effects of AKT and mTOR were dose-dependent. While the total proteins of AKT and mTOR were not changed. Western blot showed the phosphorylation of Smad2 and Smad3 were significantly inhibited after LC-C treatment. Western blot showed E-Cadherin was up-regulated and N-Cadherin was down-regulated after LC-C treatment; while other EMT related proteins including ZO-1, Snail and Vimentin were not changed. Nor did cell adhesion related protein Claudin-1. PC-9 xenograft model showed the tumor growth inhibitory rates were 114.4% in 7 days after LC-C administration. IHC showed the phosphorylation of AKT was down-regulation after LC-C administration, Ki-67 was also down-regulation, while cleaved caspase-3 was not changed. **Conclusion:** The study showed LC-C inhibit the growth and the capacity of invasion and migration of lung cancer cells. The detailed mechanisms might crosstalk with several critical pathway such as AKT pathway, TGF-β pathway and EMT.

Keywords: Capilliposide C from Lysimachia capillipes, migration, invastion

EP1.03-28 FREQUENCY AND MOLECULAR CHARACTERISTICS OF BRCA1 MUTATIONS IN NON-SMALL CELL LUNG CANCER FROM EAST ASIAN PATIENTS

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Background: Previously identified as a breast and ovarian cancer susceptibility gene, *BRCA1* has gained major scientific interest as a potential prognostic and/or predictive marker for various tumors, including non-small-cell lung cancer (NSCLC), the leading cause of cancer related mortality worldwide. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *BRCA1* mutations. **Method:** A total of 730 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *BRCA1* mutations and other genes were detected by next generation sequencing. **Result:** *BRCA1* gene mutation rate was 2.60% (19/730) in non-small cell lung cancer, including Y856H (3 patients), M1689T (2 patients), N909I (2 patients), G275D (2 patients), N473S (2 patients), S1217C (1 patient), M1628T (1 patient), E649* (1 patient), R1443* (1 patient), V191I (1 patient), I783V (1 patient), M669T (1 patient), and R71K (1 patient), and median overall survival (OS) for these patients was 14.0 months. Among them, all patients were *BRCA1* gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=16) co-occurring *EGFR* mutations had a median OS of 20.0 months and 13.0 months respectively (P=0.56); patients with (n=4) or without (n=15) co-occurring *TP53* mutations had a median OS of 20.0 months and 19.5 months respectively (P=0.82); patients with (n=4) or without (n=15) co-occurring *PIK3CA* mutations had a median OS of not up to now and 13.5 months respectively (P=0.36); patients with (n=5) or without (n=14) co-occurring *CDKN2A* mutations had a median OS of not up to now months and 13.5 months respectively (P=0.28). **Conclusion:** Our data reveal *BRCA1* mutations represent a distinct subset of NSCLC. NGS might be useful for evaluation of *BRCA1* unclassified variants. Our results show that *BRCA1* mutations delineate an aggressive subtype of lung cancer for which a targeted treatment through PARP inhibition might offer new opportunities.

Keywords: non-small-cell lung cancer, BRCA1 mutation, prognosis

EP1.03-29 THE EVALUATION OF NON-CANONICAL WNT/β-CATENIN LIGANDS EXPRESSION STATUS IN NON-SMALL CELL LUNG CANCER

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Background: The family of secreted glycoproteins forming the WNT/β-catenin signaling pathway is shown to play a significant role in many types of carcinomas including NSCLC. Therefore, the aim of the study was to evaluate the WNT pathway status in NSCLC. **Method:** The study was performed on 80 pairs of cancerous and non-cancerous tissue samples and 5 NSCLC cell lines (A549, H1299, H1395, Calu-3, H520 and non-cancerous control line HBEpC). Selected WNT genes expression analysis was assessed with qPCR with TaqMan Gene Expression Assays. The relative expression of chosen genes was estimated with ΔΔCt method. Statistical analyses were performed with the use of: Shapiro-Wilk test, T-test Wilcoxon matched pairs singed-rank test and Mann-Whitney U test. **Result:** In the cell lines deregulation of most selected genes was detected. Fold-change analysis of obtained results has shown a down-regulation of WNT4, -5A, -7A and -11 expression in comparison to control. However, in H520 and A549 cell lines up-regulation of WNT-5A and WNT -11 was found. Analysis of patient's tissue shows statistically significant ($p < 0.05$) inhibition of non-canonical WNT pathway ligands WNT-4, WNT-5A, WNT-7A and WNT-11 in cancerous tissue in comparison to non-cancerous tissue. In adenocarcinoma statistically significant dysregulation of WNT5A ($p = 0.0094$), -7A ($p < 0.0001$), and -11 ($p < 0.0001$) was identify. In squamous cell carcinoma statistically significant dysregulation of WNT4 (p, 0.0001), -7A ($p < 0.0001$) and -11 ($p < 0.0001$) was found. Moreover, in large cell carcinoma statistically significant dysregulation of WNT-4 ($p = 0.0068$), -5A ($p = 0.0210$), -7A ($p = 0.0156$) and -11 ($p = 0.0117$) was discovered. Furthermore, a statistically significant difference of WNT-7A expression between stage IA and IIA tumors ($p = 0.0203$) has been found. **Conclusion:** Dysregulation of non-canonical WNT/β-catenin signaling pathway ligands expression profile in NSCLC tissue samples suggests that it play an important role in NSCLC. Further studies, are necessary to proof the mechanisms of WNT/β-catenin pathway in NSCLC.

Keywords: Non-Small Cell Lung Cancer, WNT signalling pathway

EP1.03-30 FAM83A AND FAM83B AS PROGNOSTIC BIOMARKERS AND POTENTIAL NEW THERAPEUTIC TARGETS IN NSCLC

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Background: Although targeted therapy improved survival rates in the last decade, non-small cell lung cancer (NSCLC) is still the most common cause of cancer related death. As most precision medicines lead to resistance, the challenge of identifying new targets for further effective therapies still remains. The FAMily with sequence similarity 83 (FAM83) members have recently been described as novel oncogenes in numerous human cancer specimens and shown to be involved in EGFR signaling. However, their function in cancer cells is largely unknown and especially their role in lung cancer remains unclear. **Method:** Here, we investigated the expression and function of FAM83A and B in NSCLC. First, gene expression of the two FAM83 members was analyzed in a set of 362 NSCLC patients using qPCR. We further investigated relations in expression and their prognostic value using correlation and multivariate COX regression analyses. Functional assays in NSCLC cell lines were performed to analyze their involvement in proliferation, anchorage-independent growth, migration and the epidermal growth factor receptor (EGFR) pathway. **Result:** We observed a highly increased gene expression level of *FAM83A* (ø = 68-fold) and *FAM83B* (ø = 20-fold) which resulted in poor survival prognosis ($p < 0.0001$ and $p = 0.002$). Correlation analysis showed poor relation between *FAM83A* and *B* in the two sub-histologies adenocarcinoma (ADC) and squamous cell carcinoma (SQCC) but confirmed correlation between *FAM83A* and *B* and *EGFR* expression levels in patients and cell lines. Their expression was further influenced by EGFR pathway signaling and mutation status. Both genes affected cell proliferation and *FAM83A* depletion resulted in reduced migration and AIG. **Conclusion:** The results support the hypothesis that *FAM83A* and *B* have different specific functions in the histological subtypes of NSCLC and might be new therapeutic targets.

Keywords: EGFR-TKI, NSCLC, FAM83

EP1.03-31 CELL MIGRATION AND EPITHELIAL MESENCHYMAL TRANSITION IN LUNG CANCER - DIFFERENT ROADS AND COMMON THEMES

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Background: Cell migration is an indispensable function for many cells in multicellular organisms. When deregulated, however, especially in conjunction with the ability to degrade extracellular matrix and invade surrounding tissues, it is a hallmark of malignancy and forms the basis for cancer metastasis. This is often linked to epithelial mesenchymal transition (EMT) which is widely recognized in cancer cell biology to be intricately connected to metastasis, drug resistance and stemness. Multiple extracellular stimuli that induce EMT and cell migration in diverse cellular contexts have been described, nevertheless, a lot still needs to be learned about pathway-specific mechanisms. We have chosen the Ras-mutated A549 lung adenocarcinoma cell line for investigating how the two growth factors EGF and TGFb, which each play fundamental roles in tumor development but activate clearly distinct signaling cascades both stimulate EMT and migration individually and when acting in cooperation. **Method:** A549 cells were treated with EGF, TGFb or a combination of both in serum-free conditions. Also, inhibitors of downstream pathways were used at sub-lethal concentrations. Changes in cell morphology were determined using ImageJ from microscopy images. Cell migration was assessed by live cell videomicroscopy followed by singe cell tracking. The invasive capacity was determined by a 3D sprouting assay. Expression changes were identified by qPCR and immunoblots. **Result:** Treatment with TGFb and EGF resulted in cell scattering and distinct changes in cell morphology, which were different for each growth factor. While cells treated with TGFb showed classic EMT-like, elongated morphology, cells exposed to EGF rounded up. Combining both factors resulted in a mixed population. EGF-induced changes could be prevented by Akt but not MAPK inhibitors. Importantly, each growth factor induced a significant increase in cell migration compared to untreated cells and the combination of both factors stimulated migration even further. Interestingly, the increase in migration occurred earlier with EGF than with TGFb, and this was in concordance with increased pERK levels. However, only TGFb was able to induce significantly increased sprouting. **Conclusion:** Our data describes two independent signaling pathways which both are able to induce cell scattering and cell migration, albeit along different roads. Especially in cancer cells, a better understanding of signaling pathway-dependency of EMT and migration and potential cross talks could lead to more effective antimetastatic therapies.

EP1.03-32 PREVALENCE OF EGFR AND ALK MUTATIONS IN NON SMALL CELL LUNG CANCER IN VIET NAM NATIONAL CANCER HOSPITAL

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Background: A significant percentage of non small cell lung cancer (NSCLC) have driver mutations. Epidermal growth factor receptor (EGFR) mutations and anaplastic large-cell lymphoma kinase (ALK) rearrangements are now routine biomarkers that have been incorporated into the practice of managing NSCLC. To date, there has been no assessment of the prevalence of these mutations in NSCLC in Viet Nam National Cancer Hospital. The prospective study of formalin fixed paraffin embedded (FFPE) tissues from patients diagnosed with NSCLC was performed to assess the prevalence of EGFR and ALK mutations in NSCLC in Viet Nam National Cancer Hospital. **Method:** Patients with NSCLC in Viet Nam National Cancer Hospital were prospectively enrolled. FFPE tissue samples were tested for EGFR mutation by PCR and for EML4-ALK translocation

by fluorescence in situ hybridization (FISH) **Result:** A total of 103 patients were enrolled, 78 (76.7%) males and 25 females (23.3%), with a mean age of 57.7 years. Adenocarcinoma and Squamous cell carcinoma rate were 89.3% and 10.7%, respectively. EGFR testing of 103 patients (100%) demonstrated the wild type in 76 (73.8%) and mutated forms in 27 (26.2%). Some 74.0% of EGFR positive patients were non-smokers and 44.4% were females. Regarding the EML4-ALK translocation, testing in 103 cases (100%) gave positive results in only 11 (10.7%). Among 11 patients with EML4-ALK translocation, 6 patients (54.5 %) were females and 6 patients (54.5 %) were smokers. Moreover, only two squamous cell carcinoma patients had positive EGFR mutation and only one patient had concurrent EGFR mutation and ALK rearrangement **Conclusion:** In this sudy investigating the prevalence of EGFR and ALK mutations in non small cell lung cancer in Vietnam National Cancer Hospital, 26.2% had EGFR mutation and 10.7% had ALK translocation mutations, as compared to 35% and 6.1%, respectively, in Asian

Keywords: NSCLC, EGFR mutation and EML4-ALK translocation, Viet Nam

EP1.03-33 CD26/DPP4 AS A NOVEL PROGNOSTIC MARKER FOR LUNG ADENOCARCINOMA

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Background: CD26/dipeptidyl peptidase 4 (DPP4) is a transmembrane exopeptidase expressed on various malignancies in conjunction with activity of epithelial-mesenchymal transition (EMT). We found previously that the activity of CD26/DPP4 in human lung adenocarcinoma is four times higher than in normal lung tissue and the inhibition of CD26/DPP4 decreased the growth of lung tumors in experimental models. These data prompted us to analyze the expression of CD26/DPP4 and EMT markers in samples from non-small cell lung cancer patients to unravel a function of CD26/DPP4 as a prognostic marker and potential therapeutic target for lung cancer. **Method:** We employed multi-organ tissue micro array (TMA) of non-small cell lung cancer patient samples from two institutions, University Hospital Zurich and Dongsan Medical Center. To identify CD26/DPP4 and EMT markers (Ecadherin, Vimentin, beta-Catenin, Elastin, Periostin, and Versican), immunohistochemistry (IHC) on TMA was performed. Three pathologists scored the intensity IHC from zero to six in a blinded manner. The cohort consisted of 1126 patients (adenocarcinoma: 593; squamous carcinoma: 443; others (large cell carcinoma, adeno-squamous carcinoma): 90). The overall survival rate of patients was considered as a measure of prognosis. To identify a correlation between CD26/DPP4 and EMT related protein expression in lung cancer the Pearson correlation coefficient test was applied. **Result:** CD26/DPP4 IHC scores revealed that adenocarcinoma expresses significantly higher amount of the protein compared to normal lung or squamous carcinoma or others ($p=0.035$, $p<0.0001$, $p<0.0001$ respectively). In adenocarcinoma, patients with high CD26/DPP4 score (4-6) showed the worst overall survival compared to patients scoring low (1-3) or zero. The correlation analysis of CD26/DPP4 with EMT markers in adenocarcinoma showed that the epithelial marker Ecadherin was negatively correlated ($p=0.001$), while mesenchymal proteins Vimentin, beta-Catenin, Elastin were positively correlated with CD26/DPP4 ($p=0.03$, 0.01, and 0.001 respectively). Periostin and Versican showed no correlation with CD26/DPP4 expression. **Conclusion:** The expression of CD26/DPP4 was significantly higher in adenocarcinoma among non-small cell lung cancers and associated with worse survival of patients. Furthermore, the expression of CD26/DPP4 was significantly correlated with the EMT status. We therefore deem CD26/DPP4 to be a novel prognostic marker for lung adenocarcinoma. In consideration with CD26/DPP4 expression of these cancer samples, inhibition of CD26/DPP4 can potentially improve lung cancer patients' survival.

Keywords: lung adenocarcinoma, CD26/DPP4, Epithelial-mesenchymal transition

EP1.03-34 SINGLE CENTER EPIDEMIOLOGICAL PREVALENCE STUDY OF MOLECULAR MUTATION IN BANGLADESHI PATIENTS WITH ADVANCED STAGE NON-SMALL CELL LUNG CANCER

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Background: In a private tertiary hospital of Bangladesh about 2953 patients have been diagnosed as primary cancer patient of which 17% (510) patients were primary lung cancer patients, 77% of which were in advanced (stage III and IV). The study was performed to investigate the molecular mutations and prevalence of EGRF, T-790M, ROS-1, and ALK mutations in Bangladeshi patients with advanced stage non-small cell lung cancer (NSCLC), as per available local molecular lab facilities. **Method:** This study was retrospective and single center, conducted in 35 patients representing the 77% advanced stage lung cancer patients aged 20 years or above with NSCLC in the outpatient department The Bangladesh Specialized Hospital Ltd. (BSHL) within the timeframe of March 2016 – March 2019 recommended for molecular mutation study. Data were collected from the electronic prescription from hospital imformation system. EGFR, T-790M, ROS-1, and ALK frequency were calculated. The tests were done by tissue sample or Liquid biopsy when tissue sample was unavailable. The tests were carried out by Real Time PCR. The frequency of molecular mutation diagnosis was compared between the number of patients advised for molecular mutation study and number of patients who performed the investigation. **Result:** Of 35 patients 63% (22) were male and 37% (13) were female, median age 61 (range 45-86) and 65% (23) test carried out with Liquid Biopsy. 25.7% (9) patients were found to be EGFR positive, and 74.3% (26) were EGFR negative; also, out of 16 patients recommended for T790M study only 6.3% (1) was positive. ROS positive was found in 40% (14), and 48.6% (17) were negative. ALK screening showed to be positive in 37.1% (13) and negative in 45.7% (16). Among the 392 patients, only 9% performed the study, due to low availability of moleculer diagnosis which was started in Bangladesh since the early July 2017. **Conclusion:** The frequency of molecular testing may not reflect the international studies due to methods applied for the testing and also with the gender frequency as high predominance of male patients. With this limited data we have seen that the prevalence of ROS-1 (40%) mutation was higher than ALK (37.1%) and EGFR (25.7 %). Due to financial constrain and limited access to tests only 9% patients performed the study, though, molecular tests are recommended most oftenly. Due to time being a limiting factor for the sample size further studies can be performed on a larger scale.

Keywords: epidemiology, Molecular mutation, Non-small cell lung cancer (NSCLC)

EP1.03-35 PREVALENCE, CLINICOPATHOLOGIC CHARACTERISTICS, AND MOLECULAR ASSOCIATIONS OF IGF1R MUTATIONS IN EAST ASIAN PATIENTS WITH NSCLC

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Background: IGF1R is a ubiquitous receptor tyrosine kinase that plays critical roles in cell proliferation, growth and survival. Clinical studies have demonstrated upregulation of IGF1R mediated signaling in a number of malignancies including colon, breast, and lung cancers. The aim of this study is to investigate mutations and prognosis of non-small cell lung cancer (NSCLC) harboring *IGF1R* mutations. **Method:** A total of 812 patients with non-small-cell lung cancer were recruited between July 2012 and December 2016. The status of *IGF1R* mutations and other genes were detected by next generation sequencing. **Result:** *IGF1R* gene mutation rate was 1.60% (13/812) in non-small cell lung cancer, including N977I (2 patients), S751T (1 patient), E1043D (1 patient), G171W (1 patient), E563K (1 patient), R275C (1 patient), F921[2>1] (1 patient), E712K (1 patient), R222W (1 patient), D1024A (1 patient), A760T (1 patient), and K533N (1 patient), and median overall survival (OS) for these patients was 9.0 months. Among them, all patients were *IGF1R* gene with co-occurring mutations. Briefly, patients with (n=3) or without (n=10)

co-occurring *EGFR* mutations had a median OS of 6.0 months and 11.0 months respectively (P=0.10); patients with (n=12) or without (n=1) co-occurring *TP53* mutations had a median OS of 18.0 months and 8.0 months respectively (P=0.68); patients with (n=4) or without (n=9) co-occurring *KRAS* mutations had a median OS of 14.5 months and 7.0 months respectively (P=0.76); patients with (n=5) or without (n=8) co-occurring *NF1* mutations had a median OS of not up to now and 6.5 months respectively (P=0.24). **Conclusion:** *EGFR*, *TP53*, *KRAS*, *NF1* gene accompanied may have less correlation with *IGF1R* mutation in NSCLC patients. We report different mutations than those previously reported, which emphasizes the importance of personalized medicine that could be empowered by the use of bioinformatics tools in the diagnostic process and therapeutic approaches.

Keywords: non-small-cell lung cancer, IGF1R mutation, prognosis

EP1.04 IMMUNO-ONCOLOGY

EP1.04-01 ASSOCIATION OF PD-L1 EXPRESSION WITH LUNG ADENOCARCINOMA CONTAINING SOLID OR MICROPAPILLARY COMPONENTS

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Background: The assessment of programmed cell death ligand 1 (PD-L1) expression by immunohistochemistry (IHC) is important to treat patients in lung adenocarcinoma (LUAD). However, little is known about the relationship between PD-L1 expression and high-grade components, such as solid components (SCs) and/or micropapillary components (MPCs), which show worse prognosis. Here, the aim of this study is to evaluate the association of the PD-L1 expression with LUAD containing high-grade components. **Method:** The expression of PD-L1 protein in 39 surgically resected LUAD was evaluated by IHC analysis using the clone 22C3. PD-L1 tumor proportion score (TPS) were divided to three groups: TPS at least ≥50% was high expression, ≥1% was intermediate expression, and <1% was negative expression. We compared retrospectively the three groups and the percentage of high-grade components. **Result:** PD-L1 high expression was seen in eight patients (20.5%), intermediate expression in 22 patients (56.4%), and negative expression in 9 patients (23.1%). Thirty five cases with at least ≥1% SCs and/or MPCs were identified. The mean of the percentage of high-grade components was 60% in high expression group, 22% in intermediate expression group, and 10% in negative expression group. The statistical significance was shown comparing the PD-L1 high expression with the intermediate expression group (p<0.013), and comparing the high expression and the negative expression group (p<0.002). **Conclusion:** LUAD with many high-grade components showed the PD-L1 high expression. Therefore, PD-L1 IHC should be performed on sections including a high percentage of SCs and/or MPCs in evaluating its expression in surgical resected specimen.

Keywords: PD-L1, solid, micropapillary

EP1.04-02 PREDICTORS OF LUNG TOXICITY IN FIRST LINE PEMBROLIZUMB FOR ADVANCED NSCLC: AN INTERIM ANALYSIS OF PRELUTOX STUDY

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Background: Pembrolizumab, an anti-PD–1 antibody, is an immune-checkpoint inhibitor (ICI) approved for advanced disease in frontline setting if PDL1 is ≥ 50%, in second line if PDL1 is >1%. ICIs are associated with immune-related adverse events (irAE), including pneumonitis or interstitial lung disease (ICI–ILD): the mechanisms that lead to irAE are not entirely known. Clinical trials found an incidence of ICI–ILD of 3 to 5% but in recent studies it is greater, with fatal cases described. Reports about real incidence, risk factors, features of pneumonitis are still few. We designed a prospective observational study in this setting of patients in order to predict pulmonary toxicity by clinical -radiological and respiratory functional variables. **Method:** PRELUTOX is a prospective observational study. Our purpose is to enroll at least 50 patients in 2 years. Inclusion criteria: locally advanced or metastatic NSCLC whit PD-L1 expression ≥ 50%, with no EGFR or ALK-ROS1 mutations. Exclusion criteria: previous chemotherapy or thoracic radiotherapy; active infections or systemic autoimmune disease; interstitial lung diseases; prior pneumonitis requiring systemic steroids; immunosuppressive or corticosteroid treatment; renal or hepatic failure. Aims of our study: incidence of ICI – ILD; features of all patients including pulmonary function and comorbidities, especially the respiratory ones; features of patients who develop pneumonitis with greater attention to the HRCT pattern. Patients perform therapy and radiological exams according to routine clinical practice; pulmonary function tests (PFTs) at the beginning of Pembrolizumab and every three months **Result:** This is an interim analysis. 33 patients have been recruited from May 2018 to March 2019. Patients characteristics are summarized in table 1.

Patients' characteristics (n=33)	
Gender	
male	19 (57.6%)
female	14 (42.4%)
Age (median, range)	68.2 (38.7-82.3)
Smoking	
current	6 (18.2%)
former	24 (72.7%)
never	3 (9.1%)
Histological type	
adenocarcinoma	27 (81.8%)
squamous	3 (9.1%)
other	3 (9.1%)
PD-L1 positivity	
≥70%	25 (75.7%)
<70%	8 (24.3%)
ECOG performance status	
0	8 (24.3%)
1	24 (72.7%)
2	1 (3.0%)
Tumour stage	
IIIb	2 (6.1%)
IV	31 (93.9%)

ILD occurred in one patient with thoracic massive involvement (incidence 3%) with an HRCT pattern of organizing pneumonia. He presented progressive worsening of the obstructive ventilatory defect and drastic reduction of diffusing capacity, associated with severe hypoxemia **Conclusion:** In literature incidence of ICI-ILD seems to be higher for NSCLC compared with other cancers: this may be related to the underlying lung status (exposure to tobacco, COPD and the thoracic tumor burden). PFTs have been described in several studies for their capacity to predict lung toxicity. In our preliminary data, during Pembrolizumab therapy, if toxicity does not occur, airways obstruction parameters and lung volumes seem to remain constant and related to the respiratory comorbidity (COPD). The same appears for diffusing capacity. Finally we suppose that the thoracic tumor burden could be related to the risk of lung toxicity but the study is still ongoing.

Keywords: Predictors, Lung-toxicity, Pembrolizumb

EP1.04-03 IMMUNE CELL FILTRATION AS A BIOMARKER FOR THE DIAGNOSIS AND PROGNOSIS OF LUNG ADENOCARCINOMA

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Background: Since tumor-infiltrating immune cells provides meaningfully information of prognosis in lung adenocarcinoma, we aimed to construct a novel prognostic immune model on the basis of a systematic assessment of the immune landscape calculated from cancer transcriptomes of lung adenocarcinoma patients. **Method:** We used an advanced algorithm, which named "Cell type Identification By Estimating Relative Subsets Of RNA Transcripts (CIBERSORT)", to estimate the 22 immune cell types from public datasets. The selection operator model and least absolute shrinkage and random forest method were then applied to develop immune scores for tumor diagnosis and prognosis. **Result:** 355 lung adenocarcinoma patients and 204 normal controls were obtained to develop a diagnostic model and the diagnostic immune risk score (dIRS) suggested high sensitivity and specificity in both the training sets (AUC= 0.93, P<0.01) and validation sets (AUC=0.89). A prognostic immune score (pIRS) was also established and served as an independent prognostic factor for overall-free survival, which showed better prognostic value than TNM stage. Additionally, by integrating the pIRS with clinical information in a complete nomogram, the result suggested higher accuracy of recurrence risk prediction with well-calibrated curves. **Conclusion:** In summary, we studied the potential application of immune cells in cancer diagnosis, prognosis and treatment. The proposed diagnostic and prognostic model (dIRS and pIRS) might provide integrative and meaningful signatures for precision medicine and personal management of lung adenocarcinoma patients.

Keywords: Immune risk score, lung adenocarcinoma, CIBERSORT

EP1.04-04 PEMBROLIZUMAB-INDUCED FATAL ENCEPHALOPATHY

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Background: Pembrolizumab is a monoclonal antibody against programmed cell death 1 (PD-1) receptor approved for PD-L1 positive metastatic non-small cell lung cancer (NSCLC). Neurologic adverse events associated with anti-PD-1 antibodies are rare but might be fatal. **Method:** We report a case of fatal encephalopathy in a patient with metastatic NSCLC treated with pembrolizumab. **Result:** A 65-year-old former smoker woman with advanced lung adenocarcinoma with a *KRAS*mutation and an intermediate expression of PD-L1 (20-30%) previously treated with combination of carboplatin and pemetrexed started pembrolizumab (200 mg, every three weeks) after disease progression. After the second infusion of pembrolizumab, she presented with seizures and decreased level of consciousness. Concerning neurological examination, the patient was vigil, carried out only simple commands with absence of speech. Additionally, her muscular tonus was increased. Blood tests were unremarkable. Electroencephalogram was consistent with diffuse encephalopathy and also showed frequent epileptiform activity. Cerebral computed tomography and magnetic resonance revealed central nervous system (CNS) multifocal demyelination. Cerebrospinal fluid was acellular with glucose and protein within normal range. Also, microbiologic examination and polymerase chain reaction (PCR) assay for cytomegalovirus, herpes simplex 1 and 2 and John Cunningham (JC) virus were negative. Anti-onconeural antibodies were absent. Systemic corticosteroid therapy (dexamethasone 4 mg, every six hours) was initiated, with no improvement. Best supportive care was decided by a multidisciplinary team and patient died one month after admission. **Conclusion:** After excluding other causes for encephalopathy as paraneoplastic syndrome, CNS infection and metastasis, temporal association with pembrolizumab administration made us suspect of an adverse event of this drug. A case of pembrolizumab-induced encephalopathy was reported in advanced NSCLC, after two doses administration and the patient recovered after high dose corticosteroids. However, another case of nivolumab-induced encephalopathy in advanced renal cell carcinoma was fatal, even with drug discontinuation and high dose corticosteroid therapy. Although anti-PD-1 rarely cause encephalopathy, our case highlights not only its occurrence but also shows that it may be rapidly progressive and irreversible. As this entity probably represents an autoimmune process due to PD-1 block, its course is impossible to predict.

Keywords: Immunotherapy, Adverse events, encephalopathy

EP1.04-05 OUTCOMES OF IMMUNOTHERAPY IN ELDERLY PATIENTS. RETROSPECTIVE STUDY OF CLINICAL CHARACTERISTICS IN A SINGLE-CENTER AND A 4-YEAR EXPERIENCE

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Background: Median age of patients with lung cancer is 71 years old. We have study outcomes of NSCLC patients with more than 75 years that have receive immunotherapy since 2014 **Method:** We have performed a retrospective observational study, reviewing all patients with lung cancer treated in Medical Oncology in our institution (tertiary center in Spain) in a 4-year period (2015 to 2019), and followed until April 2019. The inclusion criteria are: 1) Age of 75 years or older at the time of diagnosis of the lung cancer, and 2) Receiving any anti PD-1 or anti PD-L1 therapy in advance disease. We included 16 patients. **Result:** Most patients were male, 79.2%, and average age is 77 years (75-84). They represent a 14.7% of all patients with advanced NSCLC that received any anti PD-1 or anti PD-L1 therapy in our institution (19 patients from a total of 128 patients, in a 4-year period). Squamous cell carcinomas represent a 57% of total, and adenocarcinoma a 39%. None of this patient harbour an oncogenic driver mutation. 51% of patients were diagnosed in stages II-III, and 49% in stage IV; but only 15% patients had a curative-intent therapy at the diagnosis. We study also the pattern of treatment in patients under active cancer therapy. Median survival time is 11.6 months (p-value: 0.001). Longer survival was seen in ECOG 0-1 patients (15.8 months) than in ECOG 2 patients (7 months) Most patients received immunotherapy in second line (16 patients, 2 in first line and 1 in third line). The drugs used were nivolumab (9 patients, 56.2%), followed by atezolizumab (7 patients, 37.5%) and pembrolizumab (3 patients, 6.2%). Median number of cycles received was 4 cycles (1-21). In terms of PD-1 status in biopsy, 5 patients were unknown, 8 patients were PD-1 negative and 6 patients were PD-1 positive (2 of them more than 50%). Most common adverse events related to immunotherapy were hypothyroidism (4 cases, 1 grade 1 and 3 grade 2), pneumonitis (3 cases, 2 grade 1 and 1 grade 2) and diarrhea (2 cases, grade 1). There were also dermatitis, adrenal insufficiency and xerostomia (1 case each). **Conclusion:** Although our cohort is small, we can suggest that immunotherapy is slightly underused in this cohort of patients, because patients of 75 years and older are a 21% of all our patients, and only a 14% of patients received an anti PD-1/PD-L1 drug. Survival rates seems very similar that communicated in younger patients, and they are clearly lower in ECOG 2 patients.

EP1.04-06 ANALYSIS OF THE RELATIONSHIP BETWEEN RATIO N / L AND SURVIVAL IN PATIENTS TREATED WITH IMMUNOTHERAPY IN LUNG CANCER

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Background: The neutrophil-lymphocyte (N / L) ratio is a marker of general immune response in different stress situations, having shown a relationship between the quotient and the evolution of patients treated with immunotherapy (IT), emphasizing the importance of inflammation in these patients. **Method:** In order to evaluate this relationship in a context of usual clinical practice, a retrospective review of patients with pulmonary neoplasia who received IT treatment in the first line or successive, between November 2015 and December 2018, excluding those who received treatment within of ±±clinical trial. Data were collected from the clinical history of each patient, with special attention to baseline neutrophil and lymphocyte numbers, objective response to therapy by criteria iRECIST 1.1 after 3 months of treatment and overall survival (OS) defined from the beginning of treatment until death

by progression of the disease. **Result:** 92 patients (29 women and 63 men) were analyzed with a mean age of 64 ±8 years. 15 (16,3%) patients received immunotherapy as first line treatment, 65.2% (60 patients) received it as 2nd line and 18,4% (17 patients) as 3rd or succesive lines. The average number of cycles received was 14 (1-52). Two stretches of baseline N / L ratios ≤5 (low) and > 5 (high) were defined. Low ratio N / L (≤5) was identified in 62p (67.4%) of the patients treated with IT and high ratio N/L (> 5) in 30p (32,6%). Of the 62 patients with a low ratio: 41 patients (66.1%) had some type of response or stabilization of their disease, 13 patients (21%) had progression and 8 patients (12.8%) received less than three months of treatment, 6 patients for PS deterioration and the other 2 patients continue with the treatment and are pending reevaluation. Among the 30 patients patients with high N / L quotient: 7 patients (23.3%) presented response or stabilization of the disease, 23 patients (76,7%) presented progression or treatment was interrupted due to deterioration of the ECOG. The average survival in the group with a low N / L ratio (≤5) was 213 weeks compared to the group with a high N / L ratio (> 5) 144 weeks (p <0.05). **Conclusion:** The N / L ratio has been identified in some studies as an adverse prognostic factor in patients treated with IT. Our data from the usual clinical practice support this theory. If these findings are confirmed in future studies, it could be used as a response biomarker for better patient selection.

Keywords: RNL

EP1.04-07 INFLUENCE OF RADIOTHERAPY IN SECOND-LINE TREATMENT WITH IMMUNOTHERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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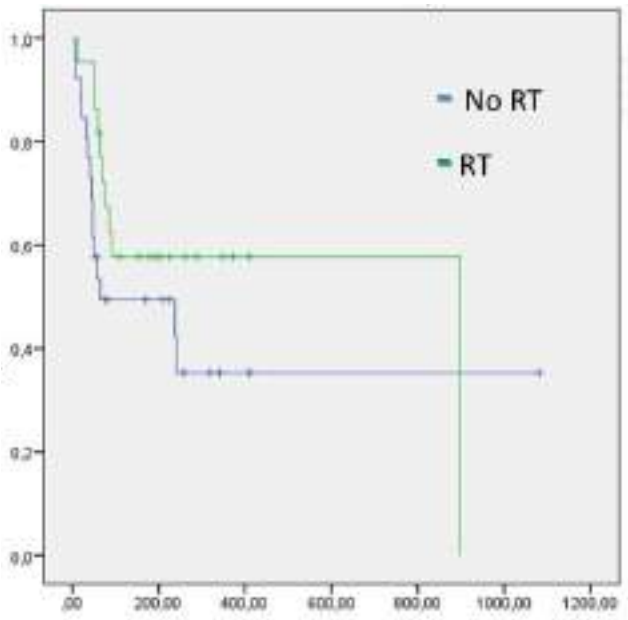
Background: The aim of the present study is to analyze the influence of previous radiotherapy (RT) in the efficacy and toxicity in patients (pts) with non small cell lung cáncer (NSCLC) treated with inmunotherapy in second line. **Method: Method:** This is a retrospective study conduted between January 2017 and December 2018 at Hospital Universitario Cruces (Bizkaia) on pts treated with inmunotherapy (nivolumab or pembrolizumab) in second line. The primary end point was to analyze if the RT influence in the progression free survival (PFS) of inmunotherapy or in the toxicity. Secondary end points were overall survival (OS) and if any variable influences the difference between both cohorts in the PFS. **Result:** Forty eight pts were evaluated, and 22 (45.83%) had received RT previously. The baseline characteristics were as follows: median age 62 years (range 40-82); 62.5% males; 91.66% had an ECOG performance status (PS) 0-1; 37.5% had stage IV at diagnosis; only 3 of the 22 pts had received less tan 60 grays (Gys). There were no differences in the PFS, 14.49 months (m) in the cohort without RT and 18.19 m in those who have received it (p = 0.196) (image). The incidence of any grade of toxicity was similar, 26.92% and 22.72% in pts without and with RT respectively (p =0.112). 3 pts in the first group stopped inmonotherapy because of toxicity versus 2 pts in the cohort of RT. The OS was significantly longer in the cohort of RT, 36.49 vs. 20.54m, p = 0.034. It was calculated whether the time interval from the end of RT and the initiation of immunotherapy influences on the PFS; neither the cutoff point of 6 months (p = 0.788) nor the cutoff of 4 (p = 0.454) influenced the PFS. As in the second group more patients were diagnosed in EIII, the possible influence of the stage on the PFS was valued, and no significant differences were seen. Neither the previous QT scheme, sex, state of PD-L1 nor the baseline respiratory pathology influenced the PFS or the incidence of toxicity.



Conclusion: Conclusions: Our study suggests that having received prior RT does not influence the efficacy or toxicity of immunotherapy in the second line of treatment in NSCLC. A larger cohort and more follow-up time is needed to be able to draw conclusions.

Keywords: Inmunotherapy, radiotherapy, NSCLC

EP1.04-08 IS PSEUDOPROGRESSION REALLY UNCOMMON AFTER IMMUNOTHERAPY IN LUNG CANCER?

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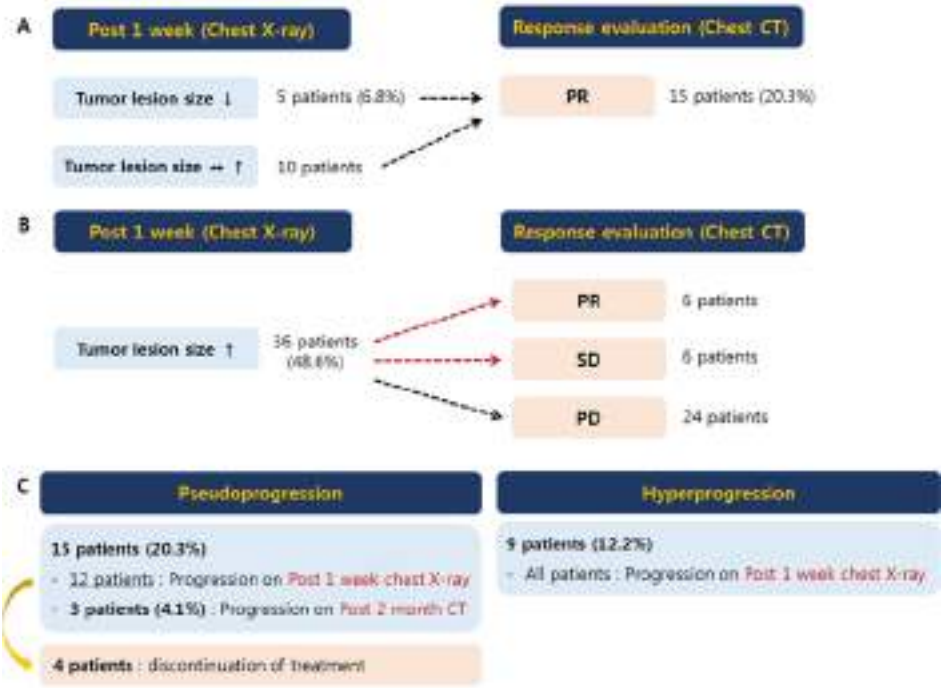
Background: Immune checkpoint inhibitors (ICIs) are more effective and less toxic than cytotoxic chemotherapy, which has led to change in the paradigm of lung cancer treatment. However, unlike classical chemotherapy, pseudoprogression has been reported in which the size of a lesion is temporarily increased or a new lesion occurs due to the effect of treatment, not the actual progress of disease. Pseudoprogression was histologically confirmed by necrosis or inflammatory cell infiltration, which is thought to be due to immune-related responses. To date, the incidence of pseudoprogression has been reported to be 4-6% in lung cancer patients. The aim of this study was to evaluate the incidence and prognosis of pseudoprogression in lung cancer patients treated with ICIs. **Method:** We retrospectively analyzed 74 patients who received ICIs at Chungnam National University Hospital from January 2017 to October 2018. Chest x-ray was examined 1 week after the first treatment to identify changes in initial lesions after immunotherapy. The response was evaluated in accordance with RECIST 1.1 and evaluated in chest x-ray as well as computed tomography (CT). Pseudoprogression was defined as the case in which the response was confirmed after continued treatment when the disease progression was showed on chest x-ray or CT. **Result:** Five patients (6.8%) had partial response (PR) on the chest x-ray at 1 week after treatment, and PR of the first response evaluation CT was observed in 15 patients (20.3%). All 5 patients who had PR in the first week x-ray showed response in CT. On the other hand, 36 patients (48.6%) had increased tumor lesions at the first week after treatment. Of these, 24 patients were progression disease (PD), 6 patients were PR, and 6 patients were stable disease (SD) on CT at 2 months after treatment. Pseudoprogression was observed in 15 of 74 patients, with a frequency of 20.3%, which was higher than previously reported. Twelve patients (80%) had progression of lesion on chest x-ray at 1 week after treatment, and showed decreased lesion size on response evaluation CT. Of the 12 patients with early pseudoprogression, 4 patients were unable to proceed with further treatment due to progression-related symptoms and systemic deterioration.



Conclusion: Unlike previous studies, pseudoprogression after immunotherapy is more frequent in lung cancer patients, especially during the early stage of treatment. Pseudoprogression at the beginning of treatment is relatively common to cause symptoms, so it is important to monitor early in the treatment.

Keywords: Chest x-ray, Immunotherapy, Pseudoprogression

EP1.04-09 A CROSS-SECTIONAL STUDY OF CLINICAL TRIALS ON RADIOTHERAPY COMBINED WITH IMMUNOTHERAPY FOR LUNG CANCER

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Background: For patients with lung cancer, remarkable advances have been made in Immune-Oncology (IO) therapy, especially immune checkpoint inhibitors (ICI). However, multi-modality treatment is needed to improve the efficacy or enlarge the beneficial populations of IO treatment. This study is to comprehensively summarize and analyze the clinical trials focusing on radiotherapy (RT) combined with IO therapy, explore the trend of research, as well as provide a view of the latest landscape of combination strategies. **Method:** Trials registered on the electronic database(https://clinicaltrials.gov)between Jan.2009 and Jan.2019 were searched using "Radiotherapy AND Immunotherapy | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Interventional Studies | Lung Cancer". SPSS 20.0 was used to analyze the data. **Result:** Totally 69 clinical trials of RT and IO combination therapy for lung cancer were recorded, including 54 active and 15 completed. Geographically, most of the trials were carried out in the USA (n=47, 68.1%), followed by the European countries (n=18, 26.1%). From timeline, the past 2 years has seen a soaring number of 40 clinical trials accounting for 58.0% of the total. The combination therapy trials were more often in non-small cell lung cancer (NSCLC) (n=52, 75.4%) than small cell lung cancer (SCLC) (n=10, 14.5%), with the remaining 7 trials unspecified. As for combination strategies, trials of tumor vaccine combined with RT were the most frequent before 2016. But at present, ICI has exceeded tumor vaccine in the combination with RT and makes up the absolute most (n=62, 89.9%). On the whole, most of the combination therapy trials are in phase I/II (n=64, 92.8%). Although most trials are set for advanced or metastatic cancers (n=43, 62.3%), there are a few exploring the safety and effectiveness of combination therapy for early stage cancers or as adjuvant therapy (n=9, 13.0%). One trial was set as neo-adjuvant therapy. As for RT details, 22 trials were SBRT combined with IO therapy. Two trials were exploring the optimal sequence of RT and IO therapy. And one trial is to compare high versus low dose RT in the combination with ICI in NSCLC. **Conclusion:** From the trials of RT and IO combination therapy for lung cancer, those of ICI combined with RT are increasing rapidly, although most are in phase I/II. Further studies are needed to explore the more detailed rational combination strategies, such as the sequencing, fractionation and dose of RT, and the optimal IO agent.

Keywords: Lung cancer, radiotherapy, Immunotherapy

EP1.04-10 NIVOLUMAB IN NON-SMALL CELL LUNG CANCER (NSCLC): A REAL-LIFE STUDY

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Background: Immunotherapy is an option in locally advanced or metastatic lung cancer (LC), depending on the PD-L1 value. Nivolumab, an anti-PD1 immunological checkpoint inhibitor, can be used in LC in subsequent lines, regardless of the PD-L1 value. The aim of this study was to analyze patients with LC treated with nivolumab in the Multidisciplinary Thoracic Tumor Unit (MTTU) of our hospital. **Method:** Retrospective analysis of patients treated in the MTTU of our hospital who with nivolumab in subsequent lines between Dec-2015 and Dec-2018. **Result:** 49 patients were enrolled in this study with a mean age at the start of immunotherapy of 62.1 ± 9.1 years. 38 patients (77.6%) were male. Regarding the histological type, 30 (61.2%) were adenocarcinomas, 16 (32.7%) squamous cell carcinomas and 3 (6.1%) corresponded to other histological types. Regarding the expression of PD-L1, 30 patients (61.2%) had no expression, 13 (26.5%) had PD-L1 ≥1%, and in 6 patients (12.2%) this parameter was unknown. 27 patients (55.1%) were treated with 1 prior therapeutic line, 12 patients (24.5%) with 2 and 10 patients (20.3%) with > 2 previous therapeutic lines. With immunotherapy, 7 (14.3%) had partial response, 22 (44.9%) stable disease and 12 (24.5%) progressive disease. 28 patients (57.1%) have died so far. The median PFS was 5 months (95% CI 1.4-8.6) and the median overall survival (OS) was 10 months (95% CI 7.6-12.4). There were no significant differences between patients with or without PD-L1 expression. **Conclusion:** The OS of our patients

treated with nivolumab was slightly lower than some literature which perhaps is related to the fact that this is a real-life study, patients had a high number of previous therapeutic lines and there were different histologic types of LC.

Keywords: nivolumab, Lung cancer

EP1.04-11 FREQUENCY OF MICROSATELLITE INSTABILITY (MSI) IN BRAZILIAN TKI NON-TREATABLE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Lung cancer is the most common cause of cancer deaths worldwide. Personalized medicine based on driver mutations has improved tailored treatment for patients with non-small cell lung cancer (NSCLC). However, only a subset of patients is benefited with tyrosine kinase inhibitors. Non-treatable advanced NSCLC patients may be eligible for treatment with immunotherapies. Recently, microsatellite instability (MSI) phenotype was reported as a predictive biomarker of response to immunotherapy, making it a crucial biomarker for clinical management for NSCLC patients. This study aimed to determine MSI frequencies in Brazilian NSCLC patients who are not eligible for TKi therapy. **Method:** 522 patients diagnosed with NSCLC patients at Barretos Cancer Hospital (Brazil) were evaluated. All samples were molecularly analyzed for *EGFR* (exons 18, 19, 20 and 21), *KRAS* (codons 12/13) and *BRAF* (exon 11 and 15) mutations by PCR followed by Sanger direct sequencing. The molecular MSI evaluation was performed using a hexa-plex marker panel by PCR followed by fragment analysis. **Result:** The mean age of the patients was 61y (22-87) and 54% were male. *EGFR*, KRAS, and BRAF wild-type status were identified in 62.6% (327/522) of cases. In 297 *EGFR/KRAS/BRAF* wild-type cases, MSI analysis was performed and we observed the presence of MSI-H in only three (1%) cases. Overall, two out of these three patients were female and one was male, the age at the diagnosis ranged from 55 to 76 years old, they were current or former smokers and all three cases were diagnosed at stage IV. Of note, one of the patients with MSI-high status received treatment with immune checkpoint inhibitor, and he is the only one out of the three patients that remains alive with 51-months survival. **Conclusion:** The frequency of MSI-high status is low in Brazilian NSCLC patients, in accordance with other population literature. Nevertheless, these MSI-positive patients are eligible for immunotherapy approaches.

Keywords: NSCLC, MSI, Immunotherapy

EP1.04-12 RESPONSE TO COMBINATION OF METFORMIN AND NIVOLUMAB IN A NSCLC PATIENT WHOSE DISEASE PREVIOUSLY PROGRESSED ON NIVOLUMAB

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Northwestern University Feinberg School of Medicine, Chicago/United States of America

Background: Beyond metformin's success as a widely used anti-diabetic, there is mounting evidence for its anti-cancer properties. Metformin disrupts many molecular pathways, in particular causing mTOR inhibition. Additionally, it causes metabolic alterations that might impact cancer cell survival. Recent experiments have also suggested that metformin has immune modulatory properties. Metformin impairs immunologic exhaustion of CD8+ lymphocytes, potentiating immune response to tumors. Thus, when curbing acquired resistance to immune checkpoint inhibition, adding metformin could prove to be a valid strategy. Here, we present a case of a NSCLC patient for whom the addition of metformin coincided with reversal of disease progression on a single-agent nivolumab. **Method:** This is a case report obtained by medical records revision. **Result:** Case report: A 75-year-old male, ex-smoker, initially presented with symptomatic left pleural effusion and multiple lung nodules 7 years ago. Pathology confirmed poorly differentiated adenocarcinoma, wild-type for molecular targets. Disease was Stage IV based on the presence of a malignant pleural infusion. The patient underwent VATS and left pleurodesis and was started on systemic therapy. After four cycles of pemetrexed-platinum doublet, he was put on maintenance chemotherapy with clinical response but, eventually, maintenance treatment was discontinued due to worsening fatigue. The patient developed significant disease progression resulting in a left peripheral mass adjacent to the cardiac silhouette. He then underwent localized SBRT followed by disease stability for approximately 6 months. 48 months ago, the patient developed progressive disease and was briefly put on vinorelbine. Due to toxicity and worsening kidney function, the treatment was stopped after one cycle. One month later, the patient started the immune checkpoint inhibitor, nivolumab. In the first imaging assessment there was evidence of response to immunotherapy and that was followed by disease control for 10 months. After that, asymptomatic lung and pleural progression ensued. Initial decision was made to continue nivolumab. Repeat scans revealed continued interval increases in the lung nodules. Metformin XR 2000mg PO daily was added to the treatment regimen. Since then, the patient has been tolerating the combination treatment well and new response was observed in the following scans with interval diminishing of the lung nodules followed by on-going stability for 17 months. **Conclusion:** There has been some evidence that metformin can enhance anti-PD-1/PD-L1 activity. We here presented a case of metastatic lung adenocarcinoma with long-term disease stability coinciding with the addition of metformin to nivolumab regimen. A new phase-2 clinical trial (NU16L04) open in our institution has been accruing NSCLC patients, including those previously refractory to anti-PD-1/PD-L1 to receive nivolumab and metformin combination.

Keywords: Immunotherapy, nivolumab, metformin

EP1.04-13 IMMUNOTHERAPY VERSUS CHEMOTHERAPY FOR PREVIOUSLY TREATED METASTATIC NSCLC. RESULTS FROM DAILY CLINICAL PRACTICE

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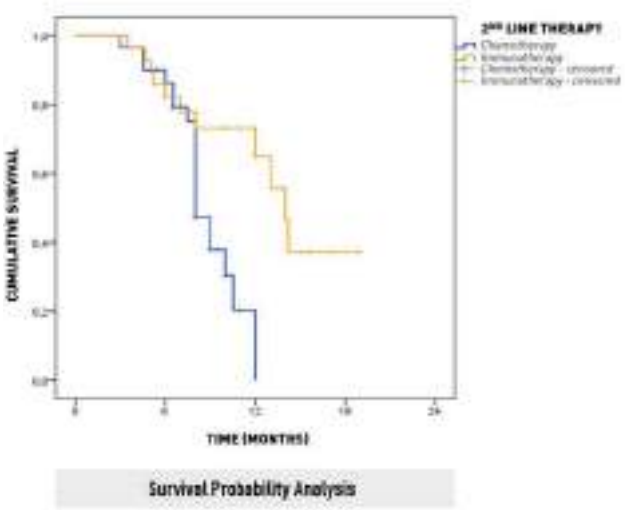
Background: Immunotherapy has shown promising results in the treatment of mNSCLC.The aim of this retrospective analysis was to compare the efficacy and toxicity of chemotherapy and immunotherapy in the 2nd line treatment of mNSCLC. **Method:** Fifty-nine patients with advanced NSCLC consecutively admitted in our Medical Oncology Department were enrolled in the study. A total of 83% were men, and 17% women. Patients had median ECOG 1 (0-3), median age 68 (47-86) years, squamous(32%) and non-squamous histology(68%). All of them were previously treated with 1st line chemotherapy regimens. Following disease progression, they received either chemotherapy or immunotherapy as 2nd line therapy .We compared both the efficacy and toxicity of the two therapeutic options. In the immunotherapy arm, patients received either Nivolumab, or Pembrolizumab. **Result:** The number of patients whose disease progressed after receiving chemotherapy in the 2nd line, was similar to those who received immunotherapy. However, time to progression, was significantly shorter in the chemotherapy arm (p=0,015). There was significant difference in disease progression probability between the two arms in both 3 and 6 months (p<0,05). Patients with at least one adverse event had 2,27 times higher probability of disease progression. Median overall survival was 8 months for the chemotherapy arm in second line, compared to 14 months in the immunotherapy arm.



Survival Probability Analysis

EPOSTERS

There was no difference in survival between the two arms in the 6 month evaluation (p>0,05). However, in the 12 and 18 month evaluation, survival rates were significantly higher for patients in the immunotherapy arm (p=0,006 και p=0,001 respectively). **Conclusion:** Patients who received immunotherapy in 2nd line, had siginificantly higher overall survival rates, compared to those that received chemotherapy (p=0,006). There was no correlation between PD-L1 expression levels and clinical benefit. Immunotherapy had a better safety profile compared to chemotherapy. Data from our daily clinical practice are in line with current literature.

Keywords: Immunotherapy, NSCLC, 2nd Line

EP1.04-14 EFFECTS OF FOXP3-POSITIVE REGULATORY T CELL ON LYMPHOID FOLLICLE FORMATION OF PATIENT WITH LUNG SQUAMOUS CELL CARCINOMA

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Background: We have reported that lymphoid follicle formation by tumor infiltrating lymphocytes (TILs) is a negative predictor of patients with lung squamous cell carcinoma (SCC) following surgery. However, the role of FoxP3-positive regulatory T cells on lymphoid follicle formation and survival is still unclear **Method:** Specimens obtained from patients during resection of lung SCC were examined for lymphoid follicle formation and immunohistochemistry of TILs. **Result:** Appearance of CD3/25/FoxP3-triple positive regulatory T cell was correlated with lymphoid follicle formation (p=0.001). Univariate analysis showed that pathological stage (p=0.037), lymphoid follicle formation (p=0.007), pleural invasion (p=0.025), vascular invasion (p=0.013), and appearance of CD3/25/FoxP3-triple positive regulatory T cell (p=0.097) were correlated with overall survival. Multivariate analysis revealed that lymphoid follicle formation (p=0.042) and pleural invasion (p=0.040) were independent prognostic factors related to overall survival, whereas CD3/25/FoxP3-triple positive regulatory T cells were not. **Conclusion:** Appearance of CD3/25/FoxP3-triple positive regulatory T cell was correlated with lymphoid follicle formation. Lymphoid follicle formation, rather than appearance of CD3/25/FoxP3-triple positive regulatory T cell, is a predictor of patient survival following surgery for lung SCC.

Keywords: tumor infiltrating lymphocyte, lung squamous cell carcinoma, lymphoid follicle formation

EP1.04-15 NSCLC RESPONSE DETERMINANTS TO CHEMOIMMUNOTHERAPY: DEEP PROFILING OF TUMORS FOLLOWING NEOADJUVANT CEMIPLIMAB AND CHEMOTHERAPY

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Background: Clinical trials have demonstrated synergistic effects of combination chemoimmunotherapy in patients with locally advanced and metastatic non-small cell lung cancer (NSCLC), however, our understanding is limited as to why and for whom PD-1 blockade with or without chemotherapy is effective, as is our understanding of the mechanism of synergy between these therapies. While most patients with resectable NSCLC receive neoadjuvant or adjuvant chemotherapy, this intervention only changes the natural course of disease for ~5% of patients. Early studies have demonstrated major pathologic responses to neoadjuvant immunotherapy ± chemotherapy. **Method:** To investigate the immunodynamic effect of PD-1 blockade and chemotherapy, and identify potentially more effective immune modifying targets or combinations, we will use novel immunophenotyping platforms to characterize the effect of this combination on the tumor. This trial will enroll 52 patients with Stage Ib-IIIa NSCLC into three cohorts receiving 2 cycles of 1) platinum-doublet chemotherapy, 2) the PD-1 antibody cemiplimab, or 3) combination chemoimmunotherapy. Following surgery, patients will receive additional adjuvant chemoimmunotherapy; in total all patients will receive 4 cycles of standard platinum-doublet chemotherapy and 8 cycles of cemiplimab. All patients will undergo pre-treatment biopsies of their tumor, and blood will be collected at 6 time-points before and after surgery. The primary endpoint for this clinical trial is major pathologic response, defined as ≤10% viable tumor within resection. Secondary endpoints include: delay of surgery, disease-free survival, overall response rate, overall survival, measurement of adverse events, and change in CD8 T-cell infiltration. Exploratory endpoints include in-depth analysis of the pre-treatment tumor biopsies and post-treatment surgical specimens, and paired blood. We will characterize proteomic and transcriptomic changes in the stromal and immune compartment of tumors at the histologic level using a multiplexed ion-beam imaging (MIBI)—a novel multiplex immunohistochemistry platform capable of analyzing >50 markers on a single section of tissue—and at the single-cell level using Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITEseq), a novel platform combining the proteomic data-potential of mass cytometry (CyTOF) and the transcriptomic data-potential of single cell RNA sequencing including TCR sequencing. Feasibility of this multi-pronged approach has been demonstrated on untreated NSCLC (unpublished data, submitted as abstract to WCLC by our group). To probe for biomarkers correlating with response or resistance to therapy, we will perform unbiased analysis of peripheral blood lymphoid and myeloid populations by CyTOF, and measure nearly 100 soluble factors in serum using Olink. **Result:** This trial opened to accrual April 2019. **Conclusion:** Section not applicable.

Keywords: neoadjuvant, chemoimmunotherapy, immunophenotype

EP1.04-16 PREDICTIVE MARKERS FOR EFFICACY IN MALIGNANCIES TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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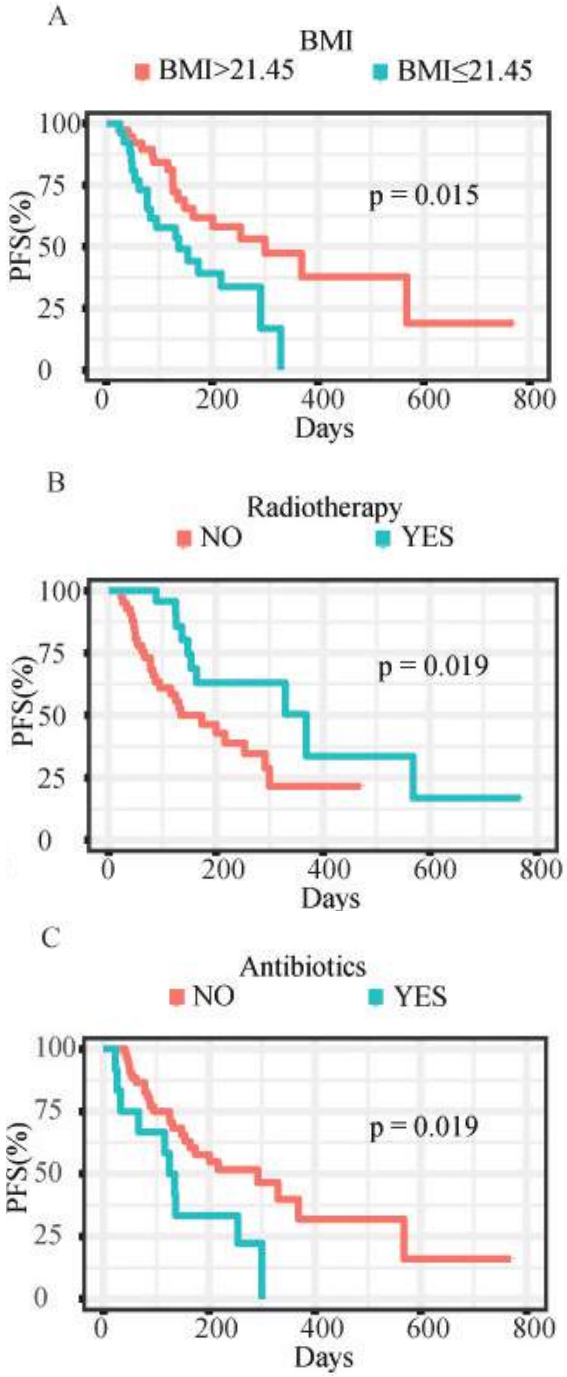
Background: Predictive markers for tumor response and efficacy of immune checkpoint inhibitors (ICIs) are still controversial. Measurements of the widespread biomarkers, such as PD-L1 expression or tumor mutational burden, are invasive and costly. Therefore, we investigated several accessible factors to predict prognosis. **Method:** Clinicopathologic features and previous treatment records were collected from 64 patients with diverse malignancies between 2016 and 2018 in oncology department of Xinqiao hospital. Endpoints were progression free survival (PFS) and best overall response (bOR). The best cut-off points of continuous variables were determined by R. Kaplan-Meier was applied to analyze survival. The correlations between bOR and biomarkers were analyzed by Chi-square test. **Result:** After a median follow-up of 5.5 months, a significant improvement in PFS was observed in 38 patients with higher body mass index (BMI, cut-off=21.45kg/m^2) compared to the other 26 patients (10.0 months vs 4.6 months, p=0.015), also the former experienced a tendency of higher bOR rate (28.9% vs 11.5%, p=0.178). Moreover, patients who had radiotherapy records experienced better PFS (12.3 months vs 4.5 months, p=0.019) and higher bOR rate (26.1% vs 19.5%, p=0.542) than the others. Further, receiving antibiotics during immunotherapy was a negative factor in the prognosis of ICIs, which led to worse PFS (4.2 months vs 9.7 months, p=0.019) and lower bOR rate (8.3% vs 25.0%, p=0.383) than its counterparts.

Progression-free survival analysis



Conclusion: Higher BMI and radiotherapy records are associated with better clinical outcomes of immunotherapy, while receiving antibiotics is negatively correlated with efficacy of ICIs.

Keywords: Biomarker, ICIs, Efficacy

EP1.04-17 THE ASSOCIATION OF CLINICOPATHOLOGIC FEATURES AND PERIPHERAL BLOOD PARAMETERS WITH HIGH PD-L1 EXPRESSION IN NON-SMALL CELL LUNG CANCER

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Background: Programmed death ligand 1 (PD-L1) is a marker that widely used for prediction of response to immune check-point inhibitors (ICIs). Especially, PD-L1 tumor proportion score (TPS) of 50% or greater strongly predict the response of ICI in non-small cell lung cancer (NSCLC). However, dynamic alteration of PD-L1 expression are the major problems for reflection of the actual status of the PD-L1 expression level. Because of that, we aimed to investigate the factors that may be associated with PD-L1 TPS expression level for reflection of the actual status of PD-L1 TPS expression. **Method:** The patients who diagnosed with NSCLC and known PD-L1 expression level at the diagnosis were enrolled to study. The data was collected as retrospectively. PD-L1 expression was assessed by using PD-L1 IHC 22C3 pharmDx assay. The patients were stratified according to PD-L1TPS expression level as ≥ 50% and < 50%. For detection of PD-L1 related factors, clinicopathologic features and peripheral blood parameters which were obtained at the diagnosis and before the initiation of any treatment was used. Neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) were calculated and also systemic immune-inflammation index was calculated by using formula as follow: (Neutrophil x Platelets)/ Lymphocyte. **Result:** Totally, 152 patients were enrolled to study. A hundred four of 152 patients (68.4%) were PD-L1 TPS expression level < 50% and 48 of 152 patients (31.6%) were also PD-L1 TPS expression level ≥ 50%.The clinicopathologic features were similar between TPS ≥ 50% and < 50% groups, except the amount of cigarette consumption. In univariate analyses; NLR, PLR, and SII were found significantly lower in patients with TPS ≥ 50% (p: 0.003 for NLR, p: 0.019 for PLR, p: 0.008 for SII).In correlation analyses NLR and PLR were found negatively correlated with PD-L1 TPS expression (r: -0.170, p:0.037 for NLR; r: -0.184, p: 0.024 for PLR).

The association of PD-L1 TPS expression and peripheral blood parameters

Parameter	PD-L1 TPS < 50% (Median)	PD-L1 TPS ≥ 50% (Median)	p
Hemoglobin (g/dl)	12.95	12.90	0.54
RDW	14.7	14.8	0.37
LDH (mg/dl)	220	218	0.66
CRP (mg/dl)	7.8	8.28	0.88
Albumin (mg/dl)	3.9	3.92	0.62
NLR	3.96	3.19	0.003
PLR	177.8	145.7	0.019
SII	1253.1	999.6	0.008

Conclusion: According to the results of our study, NLR, PLR, and SII can be used to the prediction of the high PD-L1 expression level. In addition, NLR and PLR, easily accessible - assessable and also cheap markers, can be used for reflection of current PD-L1 expression status in the during the treatment with ICIs that targeted to PD-1/PD-L1.

Keywords: PD-L1, NLR, PLR, SII, immune check-point inhibitors

EP1.04-18 REAL-WORLD TREATMENT WITH CHECKPOINT INHIBITORS: THE SWEDISH EXPERIENCE

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Background: The introduction of checkpoint inhibitors has fundamentally changed the treatment of advanced NSCLC patients. **Method:** In order to evaluate if the encouraging results from clinical trials translates into the clinical routine and to confirm the value of biomarker testing we evaluated NSCLC patients that were treated with a checkpoint inhibitor in the Uppsala-Gävle health care region between Januari 2016 and October 2018. Latest patient follow up was done in March 2019. Patient information, including therapy, response rates and survival were obtained from patient records **Result:** In total, 86 patients, were identified (44 female, median age 71 years; performance status 0=18, 1=45; 2-3=23). 28 patients were treated in the first line setting and 58 patients after previous chemotherapy. Checkpoint inhibitors that were given included pembrolizumab (31), nivolumab (36), atezolizumab (7). Two patients received a combination (durvalumab och tremelimumab). 67 of 86 patients were evaluable for response and of these 23 patients showed progressive disease, 17 stable disease, 22 partial response and 5 complete response. However, most patients that were not

evaluable for response either had only 1-2 cycles because of severe side effects or died early independent from treatment. Thus, for all patient treated with at least one course of checkpoint inhibitors response rate were lower (SD:20%; PR:26% and CR:6%). PD-L1 analysis was done for 69/86 patients (80%). The response (PR or CR) was numerically higher in the group with PD-L1 positivity ≥1% or ≥50% than with negative PD-L1 expression (54% vs 47% vs 13%), although not statistically significant (p=0.11). Median overall survival for patients with PD-L1 <1% was 2.3 years, for patients PD-L1 ≥1% 2.7 years and PD-L1≥50% 3.9 years (log rank-test, p=0.95). **Conclusion:** In conclusion, the response rates to checkpoint inhibitors in the first and second line were comparable to those observed in clinical trials. We confirmed that patients with low PD-L1 expression are unlikely to respond to checkpoint inhibition.

Keywords: NSCLC, checkpoint inhibitors, PD-L1 expression

EP1.04-19 FIRST EXPERIENCE WITH ATEZOLIZUMAB IN SLOVAKIA

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Background: New immunotherapeutics, PD-1 and PD-L1 checkpoint signalling inhibitors, have improved the prospects of patients with advanced non-small cell lung cancer (NSCLC). The purpose of this study was to assess the first results achieved with the PD-L1 inhibitor atezolizumab in the treatment of advanced NSCLC in Slovakia. **Method:** The data of patients who entered the pre-approval access programme with atezolizumab between June 2017 and September 2017 were reviewed in the retrospective multicentre study. Data regarding patients were obtained from the databases of participating institutions and patient files. Statistical analyses were performed using MedCalc® software. PFS and OS were estimated using the Kaplan–Meier method, based on the data available by the end of March 2019. **Result:** Altogether 22 patients were included. Characteristics of patients: median age, years (range): 63 (41 - 85), female/male: 3/19, ECOG PS: 0, 1, 2, 3 in 6, 11, 3, 2 patients, respectively. Histology: 8 squamous, 14 non-squamous. Patients with locally advanced disease: 1, with metastatic disease: 21. Treatment lines before atezolizumab: median: 2 (range: 1 - 3). Median PFS: 5 months (95%CI: 4 - 10). Median OS: 11 months (95%CI: 8 – 20). Complete/partial response: 1/4 patients. Median PFS in patients with complete or partial response was not achieved but will be over 19 months (range: 13 – 21+). Two patients only had to discontinue atezolizumab due to toxicities (pneumonitis and hepatitis). **Conclusion:** Results from our retrospective study are similar to those seen in the phase III trial OAK, excepting PFS. However, the different CT scanning schedules for the response evaluations and follow up in the different participating institutions could influence numerically better PFS seen in our patients.

EP1.04-20 PHASE I TRIAL OF IN SITU VACCINATION WITH AUTOLOGOUS CCL21-MODIFIED DENDRITIC CELLS (CCL21-DC) COMBINED WITH PEMBROLIZUMAB FOR ADVANCED NSCLC

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Background: Effective immunotherapy options are lacking for patients with advanced non-small cell lung cancer (NSCLC) who progress on a programmed cell death-(ligand)1 [PD-(L)1] inhibitor and for those that are epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement positive after progression on tyrosine kinase inhibitor (TKI) therapy. One potential approach to improve immune checkpoint efficacy in these patient populations is to promote cytolytic T cell infiltration into tumors. This can be accomplished via *in situ* vaccination with functional antigen presenting cells (APCs) which can take advantage of the full repertoire of tumor antigens and convert the tumor into a lymph node-like environment promoting both local and systemic T cell activation. The chemokine CCL21 promotes co-localization of naive T cells and dendritic cells (DCs) to facilitate T cell activation. Our preclinical studies and phase I trial of intratumoral (IT) administration of DC genetically modified to overexpress CCL21 (CCL21-DC) revealed augmentation of tumor antigen presentation *in situ*, resulting in effective T cell responses and systemic antitumor immunity. However, increased PD-L1 expression was observed in some patient tumors, suggesting that tumor-mediated impairment of T cell function may be forestalling a more robust antitumor response. Similarly, improved PD-(L)1 inhibitor efficacy may be possible with enhanced T cell infiltration and augmented APC function following IT CCL21-DC. Therefore, we are conducting a phase I trial, combining IT CCL21-DC with pembrolizumab in patients with advanced NSCLC that are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. **Method:** This is a phase I, single institution, non-randomized, dose-escalating, multi-cohort trial followed by dose expansion. A maximum of 24 patients (9-12 escalation + 12 expansion) with stage IV NSCLC will be evaluated who have tumors accessible for IT injection and are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. Three IT injections of autologous CCL21-DC (days 0, 21, 42) will be concurrently administered with pembrolizumab, followed by q3wk pembrolizumab up to 1 year. Primary objective of dose escalation is safety and determination of maximum tolerated dose (MTD) of IT CCL21-DC ($5x10^6$, $1x10^7$, $3x10^7$) when combined with pembrolizumab. Primary objective of dose expansion is objective response rate (ORR) of CCL21-DC at MTD combined with pembrolizumab. Secondary objectives include adverse event profiling and determination of drug target activity by immune monitoring studies. This trial, NCT03546361, is currently open for enrollment. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Pembrolizumab, CCL21, Dendritic Cells

EP1.04-21 CHRONIC INFLAMMATION AS POTENTIAL PREDICTIVE FACTOR OF NIVOLUMAB THERAPY IN NON-SMALL CELL LUNG CANCER

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Background: To investigate potential associations between clinical and standard peripheral blood biomarkers and clinical outcome in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. **Method:** A total of 120 patients with advanced NSCLC treated at seven comprehensive cancer care centers were analyzed in this national retrospective study. Survival statistics were evaluated using Kaplan–Meier method and Cox analysis. **Result:** Among clinical parameters, histology was significantly associated with progression-free survival. Univariate Cox-proportional hazards model indicated prognostic and predictive role of a panel of laboratory parameters reflecting chronic inflammatory pattern (elevated neutrophil count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein and decrease in hemoglobin and albumin). Higher serum calcium concentration was also associated with nivolumab treatment effect. **Conclusion:** Tumor histology was the only clinical parameter predicting the outcome of nivolumab treatment. Among the laboratory parameters, our analysis identified a laboratory panel reflecting chronic inflammation as potential predictive marker of nivolumab treatment.

Keywords: NSCLC, nivolumab, predictive factor

EP1.04-22 EFFICACY AND SAFETY OF IMMUNE CHECKPOINT INHIBITORS IN A DANISH REAL LIFE NON-SMALL CELL LUNG CANCER POPULATION

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Background: To investigate effect and toxicity of immune checkpoint inhibition (ICI) in a Danish unselected real life non-small cell lung cancer (NSCLC) population. By including patients underrepresented in clinical trials, such as those with brain metastasis (BM), higher age, more comorbidity, autoimmunity and poorer performance status (ECOG), comparison to pivotal data on clinical trial populations is possible. **Method:** Retrospective real life data were gathered from 118 consecutive NSCLC patients with incurable/recurrent disease stage IIIA-C and metastatic stage IV (revised according to the IASLC 8th Edition Lung Cancer TNM Staging) treated with ICI at the Department of Oncology at the University Hospital of Odense, Denmark from September 2015-April 2018. Immune related Adverse Events (irAE) grade 3-5 were registered prospectively during the same period. Patient, tumor and treatment characteristics were obtained from electronic patient records including charlsons comorbidity index score (CCIS). Overall survival (OS), progression free survival (PFS) and best response were assessed using Kaplan Meier estimates and the log-rank test. Cox regression was used for univariate analysis of factors affecting survival. Reasons for termination of ICI including level of irAEs grade 3-5 toxicity leading to termination of ICI was reported as well. **Result:** Median age for patients was 66 [IQR 59-71] and 62 [range: 55-64] for those with BM. Females 63%; adenocarcinoma/squamous/others 69%/23%/8%; ECOG ≥ 2 10%; bone/brain/liver metastases 36%/18%/15%; PD-L1 (TPS) <1%/ ≥1%≤ 49%/≥50%/NR: 3%/14%/68%/15%; baseline autoimmunity 10%, Charlsons Comorbidity Index Score (CCIS) ≥ 2 39%, treatment line: 1st/2nd/ ≥3rd 39%/30%/31%. Median OS of all patients and patients with BM comprised 16.1 months [95% CI 10.7-21.5] and 8.2 months [95% CI 1.0-15.5], respectively. Twenty-four percent of patients terminated ICI due to irAE grade 3-5 alone (grade 5, n=1). There was no association of age or BM with irAE grade 3-5. **Conclusion:** OS and PFS were comparable to clinical trial reports. Long-lasting remission is possible in patients with BM. Real life populations have higher rates of irAE grade 3-4 than reported in clinical trials, but it does not seem to impact median OS.

Keywords: Non small cell lung cancer, real-life patients, Checkpoint inhibitors

EP1.04-23 ONGOING PHASE II TRIAL OF ANTI-PD1 THERAPY IN COMBINATION WITH CIMAVAX-EGF IN PATIENTS WITH ADVANCED NSCLC OR SQUAMOUS CELL HEAD AND NECK CANCER

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Background: CIMAvax-EGF (CE) is a novel EGF-depleting immunotherapy consisting of human recombinant EGF conjugated to recombinant P64k derived from *Neisseria meningitidis*, that elicits an anti-EGF antibody response, resulting in reduction of circulating EGF levels. A randomized phase III study of CIMAvax-EGF administered after first-line platinum-based chemotherapy as switch maintenance therapy, in patients with advanced NSCLC, demonstrated improved overall survival versus best supportive care alone, particularly in patients with high baseline serum EGF levels. A recently completed phase I trial combining CE with nivolumab (N), an anti-PD1 immune checkpoint inhibitor, as second-line therapy for advanced NSCLC, demonstrated the combination is safe and induces a higher frequency of good anti-EGF antibody responses compared to the historical experience with CE alone (Figure 1). In addition, promising efficacy was observed in patients with PD-L1 low (< 1%) tumors. These results led to the initiation of this multi-arm phase II trial.

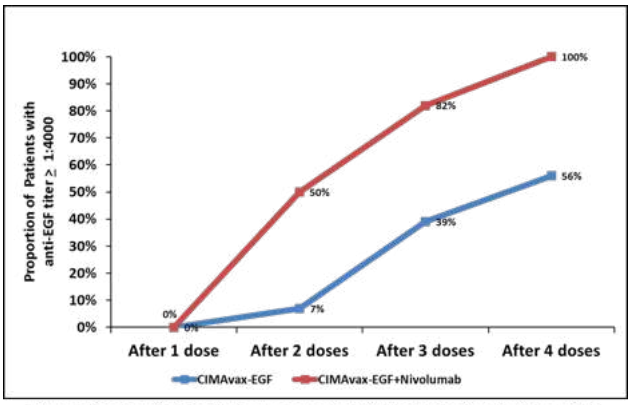

Figure 1. Good anti-EGF antibody response (>1:4000) elicited at earlier time points during induction for patients receiving CIMAvax-EGF in combination with Nivolumab compared to CIMAvax-EGF monotherapy experience in a phase 3 NSCLC study.

Method: CIMAvax-EGF (2.4 mg IM every 2 weeks x 4 doses, then every 4 weeks thereafter) in combination with Nivolumab (240mg IV every 2 weeks) is being evaluated in this multi-arm phase II study (NCT02955290) as second-line therapy in patients with advanced NSCLC (cohort A), advanced/recurrent head and neck squamous cell cancer (cohort B) and is also being tested as first-line therapy in combination with pembrolizumab (200 mg IV every 4 weeks) in patients with advanced NSCLC with PD-L1 ≥ 50% (cohort C). The primary and secondary endpoints are to evaluate 12-month OS and PFS in cohorts A and B, and to evaluate objective response rate, PFS and 12-month OS in cohort C. Exploratory objectives include characterizing tissue-based immune and EGFR signaling as well as serum EGF levels, anti-EGF antibody levels and other blood-based biomarkers in relation to clinical outcomes. **Result:** A total of 10 patients have been enrolled to this ongoing study with a planned enrollment of up to 127 patients. An update on accrual along with interim safety, efficacy and correlative data will be presented. **Conclusion:** To date, the combination of CIMAvax-EGF with anti-PD1 therapy has been safe and well tolerated. Enrollment to the phase II portion of this study is ongoing at Roswell Park and is in the process of being expanded to additional U.S. sites.

Keywords: CIMAvax-EGF, anti-PD1, Immunotherapy

EP1.04-24 SMOKING HISTORY MAY HELP PREDICT IMMUNOTHERAPY RESPONSE IN PDL1+ LUNG CANCER PATIENTS

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Background: Tumour PD-L1 expression is a key predictor of benefit from anti-PD-1 therapy in NSCLC. Clinical factors associated with benefit include smoking status. We explored the additional predictive impact of smoking status added to tumour PD-L1 expression. **Method:** A prospective cohort of 125 patients with advanced NSCLC treated at a single institution with anti-PD-1 therapy and outcome data including treatment response was explored. Ordinal logistic regression was performed to test factors associated with treatment response, including age, sex, ethnicity, pathology, PD-L1 expression (>=1%) and smoking status. **Result:** Median age of the cohort at the time of anti-PD-1 therapy was 65.3 years (range 28-88.2); 55.2% were male, 21.2% were East Asian, 76.8% had adenocarcinoma (11.8% *EGFR* mutant, 15.2% squamous, 8% other). In univariable analysis, smoking status was associated with higher response rate (current versus never smoker: OR 3.73, 95% CI 1.40-9.97, p=0.004; past versus never: OR 1.09; 95% CI 0.52-2.30, p=0.09). Patients with *EGFR* mutant lung cancer were unlikely to respond (OR 0.25; 95% CI 0.07-0.83, p=0.02). In multivariable analysis, smoking remained significantly associated with response in patients with positive tumour PD-L1 expression (current vs. never smoker OR 4.01; 95% CI 1.31-12.27, p=0.01). **Conclusion:** Clinical factors such as smoking status may enrich our ability to select patients with PD-L1 positive lung cancer that respond to immunotherapy.

Keywords: predictive; immunotherapy; smoking

EP1.04-25 INCREASED PD-L1 EXPRESSION IN MET AMPLIFIED (AMP) ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS (P)

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Background: MET amp has been reported in a subset of NSCLC p and treatment with crizotinib has proved clinical activity in cases of MET exon 14 alterations and MET amp. Recently, immunotherapy has emerged as a new approach to treat NSCLC. The development and success of programmed cell death 1 (PD-1)/program death-ligand 1 (PD-L1) checkpoint inhibitors has been correlated with PD-L1 status, particularly in NSCLC p whose tumors express high PD-L1 levels by tumor proportion score (TPS) ⩾ 50%. In this study we have reviewed the PD-L1 status in a cohort of advanced NSCLC p with a METamp. **Method:** PDL1 expression has been evaluated in a retrospective cohort of NSCLC p with MET amp and wild type for EGFR, KRAS, BRAF mutations and ALK and ROS1 rearrangements. Overall Survival (OS) was evaluated with Kaplan-Meier curves and groups were compared using log-rank test. Clinical and tumor characteristics, as well as treatment details, were evaluated. MET amp was analyzed by FISH, while PD-L1 status was assessed by immunochemistry by SP 263. antiboby **Result:** A total of 50 p were included, 15 p has high or intermediate Met amp and 35 p had low or negative Met amp. Median age were 66 years old. 39 (78%) p were male, 43 (86%) p were smokers or former smokers, 37 p (74%) were ECOG PS 0-1, 37 p (74%) were stage IV. PD-L1 were negative (< 1%) in 21 p (42%), positive (>1%) in 26 p (52%). PD-L1 highly positive in 18 p (36%). Statistically significant more p had PD-L1 positive (TPS > 1%) in high or intermediate Met amp p versus low or negative (92.9% vs 39.4%; p 0.001). And high or intermediate Met amp p had PD-L1 high expression (TPS > 50%) than negative or low Met amp p (64.3% vs 27.3%; p 0.020). No differences in PD-L1 expression was observed by gender, ECOG PS or smoking status. Median OS was 16.367 m (2.295-30.438). No differences in OS were seen by PD-L1 expression or Met amp status. **Conclusion:** PD-L1 expression in NSCLC p is positively correlated with MET amp, especially in p with PD-L1 > 50%. Our data suggests that MET amp may play a direct role in up-regulating PD-L1 expression in NSCLC p. Additionally, combination therapy targeting MET and checkpoint inhibition should be considered as a potential therapeutic strategy for NSCLC p with high and intemediate MET amp.

Keywords: PD-L1, MET amplification

EP1.04-26 EFFICACY AND SAFETY OF ANTI-PD-1 INHIBITORS IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Recently, the proportion of elderly patients with advanced non-small cell lung cancer (NSCLC) has increased. However, those patients cannot occasionally continue to receive systemic therapy due to adverse events (AEs) or decreased performance status (PS). There are few reports which address efficacy and safety of anti-PD-1 inhibitors as the second line therapy for such elderly patients. The purpose of this study is to evaluate the efficacy and feasibility of anti-PD-1 inhibitors for elderly patients with advanced NSCLC are controversial. **Method:** We retrospectively evaluated the efficacy and feasibility of anti-PD-1 inhibitors in 14 elderly patients (≥ 75 years old) with advanced NSCLC, comparing with 53 non-elderly patients (< 75 years old). All patients received anti-PD-1 inhibitors as the second line therapy or later. **Result:** Of the 14 elderly patients, 11 patients had PS score 0 or 1. Anti-PD-1 inhibitors included nivolumab in 11 patients and pembrolizumab in 3 patients, and the median courses of anti-PD-1 inhibitors was 7 (1-27). There was no difference in patient background between the elderly group and the non-elderly group. The objective response rate (ORR) was 43% in the elderly group, while the rate was 30% in the non-elderly group (p = 0.33). The median progression-free survival (PFS) was 12.1 and 11.1 months in the elderly and non-elderly group, respectively (p = 0.86). The median overall survival (OS) was 14.3 and 29.6 months in the elderly and the non-elderly group, respectively (p = 0.53). Immune related AEs (irAEs) of grade 2 or higher were significantly observed in 50% of the elderly group, comparing with 17% of the non-elderly group (p = 0.048).

Immune-Related Adverse Events

Age	<75 (%)	75≦ (%)	
Any (≧G2)	9 (17.0)	7 (50.0)	p=0.048
Skin Reaction	0 (0)	2 (14.3)	
Pneumonitis	3 (5.7)	2 (14.3)	(G5 IP:1)
Hepatitis	2 (3.8)	0 (0)	
Colitis	2 (3.8)	1 (7.1)	
Nephritis	0 (0)	0 (0)	
Neuropathy and Myositis	1 (1.9)	1 (7.1)	
Endcrinopathy	1 (1.9)	1 (7.1)	

Conclusion: The anti-PD-1 inhibitors led to good prognosis for the elderly patients with advanced NSCLC while the rate of irAEs was higher. The follow-up or management of irAE should be careful.

Keywords: Anti-PD-1 inhibitor, Elderly patients, immune related adverse event

EP1.04-27 EXPRESSION ANALYSIS OF PROGRAMMED DEATH-LIGAND (PD-L) 1 IN LARGE CELL NEUROENDOCRINE CARCINOMA

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Background: Programmed death (PD)-1/PD-ligand-1 (PD-L1) signaling is main target of immune-checkpoint therapy for lung cancer. Since PD-L1 expression level is known as an important indicator for patient selection of PD-1/PD-L1 blockade therapy, immunohistochemical analysis using anti-PD-L1 antibody were largely performed in various lung cancer tissues. However, there was few evidences regarding expression pattern of PD-L1 in large cell neuroendocrine carcinoma (LCNEC). In this study, we aimed to clarify the tissue distribution of PD-L1, and gene expression pattern between PD-L1-positive and negative cells in LCNEC. **Method:** Lung cancer tissues were derived from patients with LCNEC (n=10) and adenocarcinoma (n=8). All tissues were stained with anti-PD-L1 (SP142, Ventana/Roche), CD8 (T lymphocytes), and PD1 antibody using OptiView DAB IHC systems. To investigate the molecular mechanism of overexpression of PD-L1 in LCNEC, we have also performed microarray analysis of PD-L1-positive and -negative cancer cells in the identical LCNEC patient. **Result:** From immunohistochemical staining data, while 25% of adenocarcinoma were PD-L1 positive, 80% of LCNEC were strongly stained by anti-PD-L1 antibody. Invasion of PD-1-positive lymphocytes were also seen around PD-L1 positive lung cancer cells. Microarray data showed that antigen-presenting related genes were dominantly up-regulated in the PD-L1-positive cells. **Conclusion:** Our data concluded that the patients with LCNEC might be targets for immune-checkpoint therapy using anti-PD-1 neutralizing antibody.

Keywords: LCNEC, PD-L1, Immune-checkpoint therapy

EP1.04-28 THE ABSCOPAL EFFECTS OF THE COMBINATION OF RADIOTHERAPY AND GM-CSF FOR PATIENTS WITH METASTATIC THORACIC CANCERS

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Background: An absopal response was defined as distal tumor regression out of irradiated field induced by radiotherapy and mediated by immune system. Golden EB et al reported a benefit with the use of Granulocyte-macrophage colony-stimulating factor (GM-CSF) with local radiotherapy in a subset of chemotherapy or hormone therapy in patients with metastatic solid tumors. However, the contribution of systemic therapy to abscopal effects couldn't be defined. Therefore, we conducted the study aiming to evaluate the abscopal effects of the pure combination of local radiotherapy and GM-CSF in patients with metastatic thoracic cancers. **Method:** Patients who met the following criteria were included for this study: (1) Pathologic confirmation of thoracic cancer by histology; (2) at least three distinct measurable sites of metastatic disease; (3) received at least one line of previous chemotherapy and had stable or progressing disease to the last chemotherapy or refused to receive chemotherapy; (4) received the combination of GM-CSF and radiotherapy; (5) no previous malignancies; (6) no previous immunotherapy. **Result:** A total of 30 consecutive patients who were treated between March 31, 2016 and March 31, 2019 were included in this study. In the 16 patients with lung cancer, 2 partial abscopal responses, 9 stable and 5 progress were observed. In the 10 patients with thymic cancer or thymoma, 2 partial abscopal responses (thymic cancer), 6 stable and 2 progress were seen. Neither of the two patients with esophageal cancer had progressive diseases within 3 months. The patient with tracheal adenoid cystic carcinoma had partial response to the treatment, whereas the other patient with malignant pleural mesothelioma had stable disease. Twenty-four patients (80%) received GM-CSF of 125ug/m2 d8-22, which was the same as Golden EB et al reported. However, 8 patients had high fever (33.3%), 4 patients (16.7%) had edema (Grade 2: 3, Grade 3: 1), 4 patients (16.7%) had dyspnea of Grade 2, and one patient had dermatitis of Grade 3. Another one patient underwent cerebral infarction during the third day of GM-CSF injection. The other 6 patients who had GM-CSF of 70% dosage (87.5ug/m2) had no obvious side effects. No evidence showed that the reduced dosage of GM-CSF may have negative influence on the effect of the treatment. **Conclusion:** In conclusion, pure combination of local radiotherapy and GM-CSF may increase the incidence of abscopal responses, and bring benefits to patients with thoracic cancers except esophageal cancer. Lower dosage of GM-CSF is recommended to Asian patients.

Keywords: GM-CSF, Abscopal effect, radiotherapy

EP1.04-29 KHORANA SCORE: A POTENTIAL NEW BIOMARKER FOR REAL LIFE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: PD-L1 tumor proportion score is presently the only biomarker used for selecting incurable NSCLC patients for immune check point inhibition (ICI). Performance score (ECOG) and comorbidities are useful, but no specified guidelines exist in this regard. New objective biomarkers are warranted. Khorana score (KS) is a validated tool used to predict venous thromboembolisms (VTE) in out-patients with cancer prior to chemotherapy. For NSCLC patients undergoing chemotherapy KS has recently been associated with prediction of early mortality and not VTE. KS has not previously been investigated in patients undergoing ICI. **Method:** Retrospective data from 118 incurable advanced/metastatic NSCLC patients treated with ICI in a single center during the period of September 2015-April 2018 was gathered. Baseline platelet count (PC), leucocyte count (LC), and hemoglobin count (HC) were registered. Baseline body mass index calculations were performed as well as KS (a minimum of KS ≥ 1 due the primary lung cancer disease). Based on follow-up data Kaplan Meier curve estimates of overall survival (OS) and progression free survival (PFS) were performed. **Result:** For patient, tumor and treatment characteristics see Table 1. Fourteen percent had known VTE prior to ICI. Two patients died from pulmonary embolisms. KS correlated significantly to OS but not to PFS. A median OS of 18.1 months [CI 12.8-23.4] and 8.4 months [CI 4.3-12-6] was found for groups with KS=1-2 and KS≥3, respectively (log-rank test, p=0.017).

Table 1.

Age, median (years)	66
Interquartile range	[59-71]
PD-L1 tumor proportion score (TPS), n (% of pts)	
< 1%	3 (3)
>=1% but < 50%	16 (14)
>= 50%	80 (68)
NR	19 (15)
ECOG score at baseline, n (% of pts)	
0	31 (26)
1	75 (64)
>=2	12 (10)
Charlsons Comorbidity Index Score, n (% of pts), range	[0-8]
0	35 (30)
1	37 (31)
2	22 (19)
>=3	24 (20)
Khorana Score (KS), median, range, n (%) (n=107)	2 (1-4)
1	51 (43)
2	37 (31)
3	27 (23)
4	2 (2)

Conclusion: Baseline Khorana Score may represent a new clinical applicable prognostic biomarker for incurable NSCLC patients undergoing ICI. A KS ≥ 3 may be a predictor for early mortality but large prospective studies validating or rejecting this are warranted.

Keywords: Biomarker, Checkpoint inhibitors, Non small cell lung cancer

EP1.04-30 RECIST AND IRECIST COMPARISON IN A COHORT OF PATIENTS WITH ADVANCED NSCLC TREATED WITH IMMUNOTHERAPY: PRELIMINARY STUDY

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Background: Nivolumab, Pembrolizumab and Atezolizumab are anti-programmed death-receptor-1 (PD-1) and anti-programmed-death-ligand 1 (PD-L1) immunotherapy agents used in the treatment of advanced non-small cell lung cancer (NSCLC). However, its radiological evaluation is challenging because of atypical patterns of response and immune-related adverse events. This study aims to (i) compare the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, with the Immune RECIST (iRECIST) and (ii) explore the association of response patterns and clinical outcome. **Method:** We conducted a retrospective study of previously treated patients with advanced NSCLC who received Nivolumab, Pembrolizumab or Atezolizumab (first and second line). All CT scans were reviewed by two radiologists specialized in immunotherapy evaluation (1 senior, 1 junior). Tumor response was assessed according to both RECIST v1.1 and iRECIST C. **Result:** Were included 39 patients (27 male, 12 female) between November 2014 and December 2018 with advanced NSCLC. Median of age was 64 years (range 43 to 86). 13 patients (33,3 %) were treated with Nivolumab, 18 patients (46,1 %) with Pembrolizumab and 8 patients (20,5 %) with Atezolizumab. Among of 100% of patients included, 35,9 % showed partial response (PR),

20,5% stable disease (SD) with RECIST and iRECIST criteria. 43,6 % of patients showed progressive disease (PD) with RECIST criteria but only 4 of them were confirmed progressive disease (iCPD) with iRECIST criteria (2 truly progressed and died, 1 showed PR with the treatment and 1 reached SD). 8 patients with PD (20,5 %) could not be confirmed with iRECIST, remaining as unconfirmed progressive disease (iUPD), 5 of them because of patient's death, 1 because a change of therapy was performed and 2 because they reached SD within the treatment. The remaining 4 patients with PD presented improvement within the treatment after the initial progression (pseudoprogression). **Conclusion:** In our study, both RECIST 1.1 and iRECIST criteria were valid for measuring the effectiveness of the treatment with Nivolumab, Pembrolizumab and Atezolizumab. No differences were found in the assessment of PR and SD. 13 differences were detected between RECIST and iRECIST in the assessment of PD. RECIST criteria underestimated more the benefit of the treatment compared with iRECIST, but was better detecting true PD resulting in patient's death than iRECIST (which could not always confirm the progression). Given the relatively small number of patients studied, further study is warranted on whether RECIST and iRECIST criteria are equivalent to evaluate new immunotherapy treatment in NSLC.

Keywords: Immunotherapy, RECIST, iRECIST

EP1.04-31 IMMUNOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER PREVIOUSLY TREATED: REAL WORLD DATA

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Background: Immunotherapy has changed the paradigm of the treatment and prognosis of Non-Small Cell Lung Carcinoma (NSCLC). Pembrolizumab and nivolumab are monoclonal antibodies that blocks PD-1, both approved in advanced NSCLC. The aim of this study was to evaluate the demographic, histological characteristics, response and toxicities of these drugs. **Method:** This is a retrospective cohort of patients with metastatic NSCLC that had been treated with pembrolizumab or nivolumab in our institution, who began treatment until 12.2018. **Result:** 60 patients were included in this study. In pembrolizumab group (N27), 81.5% (22/27) were men, 53.8% (14/26) ex-smokers, median age 68 (45-79). Histologically, 81.5% (22/27) were adenocarcinomas, EGFR negative, one with ALK translocation and 48.1% (13/27) with PD-L1 levels > 50. At diagnosis 66.7% (18/27) was in stage IV. 1st line palliative chemotherapy was platinum/pemetrexed in most patients (59.3% 18/27). 81.5%(22/37) were treated with pembrolizumab in 2nd line. ECOG at the start of pembrolizumab was 1 in 74.1% (20/27). Median number of cycles was 8 (1-34). 42.3% (11/26) had toxicity, grade 3 in 4 patients, the most common being asthenia, anorexia and hypothyroidism. Treatment discontinuation occurred due to clinical deterioration in 33.3% (9/27) or 25.9% (7/27) disease progression. 7 patients (25.9%) maintained treatment. 12 patients die due to NSCLC (mortality: 44.4%). In nivolumab group (N 33), 78.8 % were men (26/33), median age 62 years (46-73), 54.5% (18/23) smokers. Histologically, 69.7% (23/33) were adenocarcinomas, EGFR positive in 2 patients, no ALK translocation and PD-L1 negative in all patients. 60.6% (20/33) were diagnosis in stage IV. 1st line palliative treatment was platinum/pemetrexed in most cases (63.6%, 21/33). 84.8% (28/33) were submitted at least to 2 lines of treatment before nivolumab. 81.8% (27/33) had ECOG1 at the start of nivolumab. Median number of cycles was 9 (1-50). 54.5% (18/33) of patients had toxicity, grade 3 in 5 patients, with asthenia and rash being the most common. Disease progression (42.4%; 14/33) and clinical deterioration (27.3%; 9/33) are the most reason for treatment discontinuation. 21 patients die due to cancer (mortality: 63.6%). At 12 months, progression-free survival was 33.3% in pembrolizumab and 64% in nivolumab. **Conclusion:** Immunotherapy brought higher survival rate to NSCLC, with good tolerability in most cases, maintaining and improving the quality of life. However, given the disparities between responses, acknowledgment of new targets and biomarkers will make the patient selection for immunotherapy more accurate.

EP1.04-32 SUCCESSFUL CORNEAL TRANSPLANTATION IN A PATIENT TREATED WITH NIVOLUMAB FOR METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Survival improvement in metastatic non-small cell lung cancer has been achieved with the use of checkpoint inhibitors. PD1/PD-L1 pathway is related to immune response and tolerance, so its blockage could predispose to graft rejection. In the pivotal studies of novel immunotherapy, patients submitted to organ transplantation were classically excluded, and scarce data on medical literature exits about graft and patient outcomes in a scenario of use of checkpoint inhibitors in this patientes. **Method:** We report the case of a 58 years old man treated with nivolumab for metastatic non-small cell lung cancer, after received platinum-based doublet chemotherapy, docetaxel and erlotinib and that was submitted to a corneal transplantation during the nivolumab treatment. **Result:** The patient received Nivolumab 3mg/kg intravenously every two weeks and had stable disease accessed by RECIST 1.1 after 54 cycles and keeped ECOG 0 performance status. This man had a previous history of vision impairment on right eye because of bullous keratopathy after vitrectomy for vitreoretinal disorder, whose treatment of choice is corneal transplantation. After multidisciplinary discussion, the nivolumab was stopped 2 weeks before the corneal graft was successfully performed. The patient received systemic corticosteroid treatment with prednisone at 10mg daily dose for 10 days and topical dexamethasone for 45 days after procedure. Nivolumab was initiated 3 weeks later. The patient has currently received 68 cycles of nivolumab, CT scan shows stable disease. In the recent ophthalmologic examinatio, there were no sign of chorneal rejection and ocurred an improvement of visual function on right eye (counts fingers in a 2 metes distance). In the literature, there are with few reports of graft outcomes in a scenario of threatment with chekpoint inhibitors, since this patients were not included in clinical trials. Diverse outcomes are reported ,with a substancial risk of rejection, specially with the use of PD-1/PD-L1 inhibitors in comparison with agents anti -CTLA-4. In our knowledge, this is the first reported case of a graft transplantation during checkpoint inhibitors therapy. **Conclusion:** Immunotheray in this special popullation is usually not recommended and under studied. In a context of immunotherapy, corneal graft transplantation can be associated with favourable outcomes due to devoid of vasculature and lymphatics in this tissue, that can facilitate immunological tolerance. So, although the risk of rejection must be taken into account, the treatment with anti-PD1 could not be considered an absolute contraindication to corneal transplantation, specially in patients with amaurosis, whose the risk of rejection of a graft cannot induce more damage than is already installed.

Keywords: Non-Small Cell Lung Cancer, Immune Checkpoint Inhibitors, organ transplant

EP1.04-33 PEMBROLIZUMAB WITH HIGH PD-L1: WHO ARE NON-RESPONDERS?

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Background: Pembrolizumab is a programmed death-1 (PD-1) blockade which is approved for non-small cell lung cancer (NSCLC). It has been reported that programmed death-ligand 1 (PD-L1) high patients are more effective than low patients to pembrolizumab. It has not been clear what factors decide responsiveness to pembrolizumab in PD-L1 high patients. **Method:** NSCLC patients who had been given pembrolizumab from April 2017 to October 2018 in Nagoya Medical Center and whose PD-L1 tumor proportion score (TPS) was ≥50% were included. A double cancer case was excluded. The non-effective group was made of patients who had stable and progressive diseases, and the effective group was made of patients who had complete and partial response. We compared the non-effective group with the effective group. **Result:** Data were extracted retrospectively from patients' medical records. In total, 34 patients received pembrolizumab. One patient who had double cancer and 7 patients whose PD-L1 TPS was <50% were excluded from this analysis. Twenty-six patients were included. In 26 patients, 19 men (73.1%), 22 current or former smokers (84.6%). The median age was

69 (ranged 48–88). Patients with adenocarcinoma, adenosquamous, squamous, not otherwise specified, and pleomorphic carcinoma were 15/1/ 8/1/1. Stage IIIA, IIIB, IV, and recurrence after surgery were 1/2/16/ 7. Performance status (PS) 0, 1, 2, 3, and 4 were 7/9/7/ 2/1. First, second, and fourth lines of chemotherapy were 18, 7, and 1, respectively. Differences between pembrolizumab effective and non-effective group in gender, smoking history, age, tissue type, proportion of stage IV, and treatment line were not statistically different. In terms of PS, all PS 3 or 4 patients were non-effective. **Conclusion:** In NSCLC PD-L1 high patients treated with pembrolizumab, PS 3–4 might be a factor, which indicated poor response to pembrolizumab.

Keywords: NSCLC, Immune Checkpoint Inhibitors, Pembrolizmab

EP1.04-34 IMAGING CHALLENGES IN THE IMMUNOTHERAPY TREATMENT OF NON SMALL CELL LUNG CANCER (NSCLC): PROGRESSION VS. PSEUDO PROGRESSION

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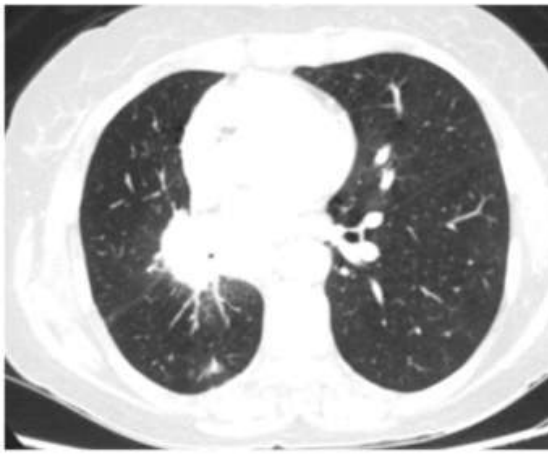
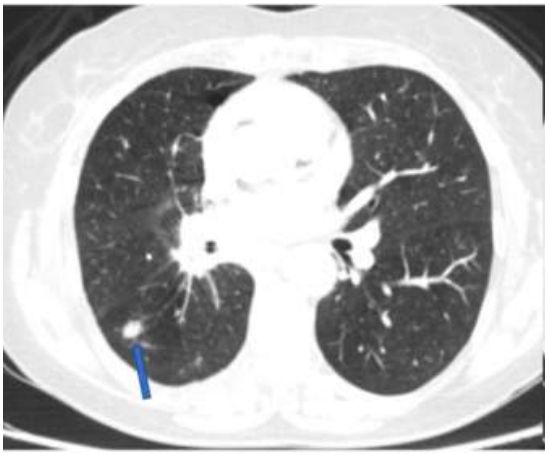
Background: Immunotherapy has revolutionized treatment of squamous NSCLC. Along with the superior efficacy physicians have to face new side effects and response criteria. Initial tumor growth or new lesions followed by tumor response is called pseudo progression and can be seen in up to 10 % of patients. **Method:** This education exhibit aims to show how the treatment response was evaluated in a series of cases of the clinical research of our institution using both RECIST and irRECIST, comparing the two methods and the multidisciplinary team consensus with correlation with the clinical status of the patient. Demonstrate the importance of the concept of unconfirmed progression and pseudo progression in the imaging evaluation of these patients. Illustrate with practical cases the diverse treatment outcomes. **Result:**

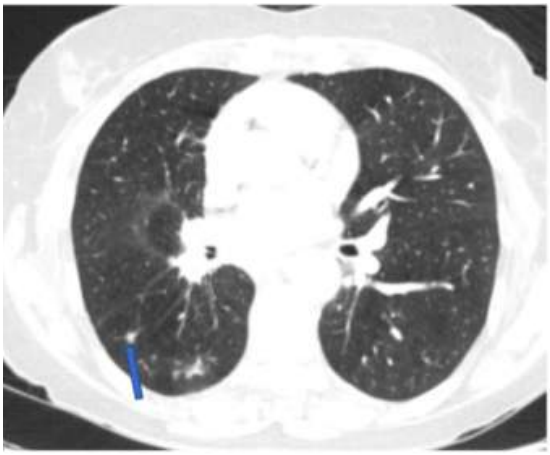
Pseudo Progression



Baseline



Control 1



Control 2

A 65 yo female patiente receive atezolizumab in the second line treatment for NSCLC stage IV, after a pulmonar progression with carboplatin + paclitaxel treatment in first line. PD-L1 was unknown. EGFR and ALK was negative. After 3 cicles of treatment wih anti PD-L1 agent (radiological control 1) the RECIST 1.1 evaluation identified a pattern of progression of disease, becouse there was a new pulmonary nodule. The patient was improving clinically, with weigh gain and cough reduction and in the immune-related response criteria (irRC) a stable disease was the response in that moment, besides the new lesion appearance. She does not have any remarkable side effect with the treatment, thas was susteined becouse of the clinical benefit. In order to get a close follow up of the disease, after 2 months she did a new radiologic evaluation (control 2), that show the involution of that new lesion in the right inferior lobe as well as happen to other pulmonary lesions at the same time, what could be characterized by a pseudoprogression pattern of response. **Conclusion:** We need to take care in the radiologic and clinical evaluation of response in immunotherapy. Besides thrue pseudoprogression pattern ir rare in NSCLC and it is not able to be captured by convencional RECIST evaluation, it need to be reminded. Is necessary to combine clinical evaluation and immune-related response criteria (irRC) in doubtful cases in order do not underestimate the benefit of immunotherapy and prevent premature cessation of treatment.

Keywords: Pseudoprogression, NSCLC immunotherapy

EP1.04-35 IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC) – EXPERIENCES FROM CLINICAL PRACTICE – SWEDEN

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide, with NSCLC accounting for over 85% of all cases. Until recently, chemotherapy – characterized by some benefit but only rare durable responses – was the only treatment option for patients (pts) with NSCLC whose tumors lacked targetable mutations. By contrast, immune checkpoint inhibitors have demonstrated durable responses and represent the opportunity of a new treatment approach for pts with NSCLC. **Method:** A chart review was conducted of incident cases of all pts who had been treated with immune check point inhibitor during the last 3 years in 4 hospitals. Data was retrospectively collected: pts characteristics, tumour characteristics, treatment details, tumor stage, adverse events, survival. **Result:** In total, 244 pts, 114 (46.8%) males were given immunotherapy. Mean and median age was 70.11, 72.3 yrs. 219 (89.6%) were smoker or former smoker. 168 (68.9%) with PS 0-1, 61 (24.9%) PS 2. Most of the pts had stage IVA 119(48.6%), IIIB 34 (13.9%), IIIA 31 (12.7%). Adenocarcinoma in 151 (61.6%) and squamous cell carcinoma in 70(29.6%) of the pts. PDL1 < 1% in 30(12.2%), 1-49% in 66(27.3%) and ≥50% in 92 (37.6%). Pembrolizumab was given either as 1st or 2nd line in 120 (49.0%) ,nivolumab as 2nd, 3rd or 4th line in 85 (34.7%) and atezolizumab 31 (12.7%) as 2nd or 3rd line. 76(31.1%) had partial response, 3 (1.2%) complete response, 41 (16.8%) stable disease, 64 (26.2%) progressive disease. 60 (24.5%) still on treatment. Most adverse events (AE) was pneumonitis 13 (5.2%), *colitis 10 (4.1%), Thyroiditis 8 (3.2%).* **Conclusion:** Pembrolizumab has been given mostly in first line treatment due to high PD-L1 but nivolumab or tecentriq most in 2nd or 3rd line. Overall responses was 49.1%. Very few AE mostly pneumonitis and colitis More data will be presented during the conference

Keywords: Non-Small Cell Lung Cancer, Survival, Immunotherapy

EP1.04-36 AGGRAVATION OF DEPIGMENTATION FOR A NSCLC PATIENT WITH PRE-EXISTING VITILIGO USING IMMUNE CHECK POINT (PD-1) INHIBITOR: A CASE REPORT

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Background: Immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1/CTLA4 antibody can enhance the antitumor activity of the immune system by mainly promoting CD8+ T lymphocyte immune function. While, they can also induce immune-related adverse events (irAEs), especially the skin toxicity, such as maculopapular rash, lichenoid reactions, vitiligo and pruritus. However, the effectiveness and safety of ICIs in cancer patients who are also suffered from autoimmune diseases are still unclear. **Method:** In our present report, we described a newly diagnostic non-small cell lung cancer (NSCLC) patient who suffered from the focal vitiligo for about ten years, her vitiligo lesions were localized in eyes and mouth circumference. **Result:** The patient's vitiligo was aggravated rapidly with depigmentation of the whole body skin in just half a year. Meanwhile, lung cancer focus was still in a stable status for over 14 months. The efficacy evaluation is stable disease (SD), but as the treatment time prolonged, the tumor density gradually decreased, suggesting that the immunotherapy continues to benefit. **Conclusion:** Vitiligo, as one kind of autoimmune diseases, should be paid more attention as using with ICIs at the same time. Meanwhile, ICIs may bring more irAEs and more benefit in the pre-existing autoimmune disease population, compared with that normal population.

Keywords: Non-Small Cell Lung Cancer, pd-1, vitiligo

EP1.04-37 BIOMARKERS IN NON-SMALL CELL LUNG CANCER: EXPRESSION OF PD-L1 PROTEIN AND P16 IN SQUAMOUS CELL CARCINOMA HISTOLOGIC SUBTYPE

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Background: Squamous cell carcinoma(SCC), 30% of Non-Small Cell Lung Cancer(NSCLC), cigarette is its mayor etiology. >50% NSCLC are diagnosed in advanced/stage, 10–15%EIIIB, 40%E-IV. In terms of survival, NSCLC is heterogeneous and variable. Survival at 5 years is <15%, treatment is not curative. In cancer, the evasion of the immune system and the uncontrolled tumor proliferation is important. The programmed-cell-death-ligand(PD-L1) is a lymphocyteT protein. The union PD-1/PD-L1 inhibits the lymphocyteT's activity. Overexpression of PD/L1 in CD8+lymphocytes inhibits apoptosis, reduces survival. In NSCLC, PD-L1 is a predictor of successful immunotherapy. Inhibition PD:PD-L1 is an effective antitumoral therapy. The p16INK4a intervenes in pulmonary carcinogenesis, localized in chromosome 9p21(locus CDKN2A), its codes suppressor/tumoral proteins:p16INK4a-p14ARF. P16 inhibits D1-dependent quinases4-6(CDK4/6,ciclinaD1) which regulate the retinoblastoma protein through phosphorylation. Dysfunctional p16 inactivates Rb through hyperphosphorilation and progression of the cell cycle. Its expression contributes to the therapeutic response and to survival in NSCLC. We describe the clinical, pathological and survival characteristics in SCC based in expression of PD-L1/p16. **Method:** Descriptive study, 24 patients with SCC, 2009–2013. PD–L1 studied with antibody 22C3 pharmDxkit(Agilent, Santa-Clara, CA,USA) in Autostainer Link/48DAKO® with murine monoclonal antibody(Clone/E6H4™) in BenchMark/Autostainer(Ventana®). PD-L1 was classified with TPS(Tumor/Proportion/Score), high expression TPS>50%, low expression TPS1-49%, or negative TPS=0%. P16(+) with expression >70% in nuclei, tumoral membranes. STATAv.14®, ShapiroWilk, Chi squared, Fisher, t-Student or U/Mann/Whitney were used. Survival with Kaplan-Meier. **Result:** Age 67±14, 63%men. 54% of smokers, 7% had COPD. E-IV54%, E-IIIA25%, E-IIIB13%, E-IIB y E-IIA4%. PD-L1(+) more in smokers (85%)p=0.001. Treatment: palliative/care(25%), chemotherapy/surgery(17%); chemotherapy/radiotherapy/surgery(12%); radiotherapy/surgery(8%), only surgery(4%). PD-L1, high-expression survival 33m, low expression/negative 66m (log-rank test p=0.0041), Figure1: p16(+) in 10(41.6%), survival 36.2m, p16(-) survival 66.8m, p16/PD-L1(-) survival 66.8m, p16/PD-L1(+) survival 36.2m. **Conclusion:** SCC with PD-L1 TPS>=50%, p16(+), smokers with high/tumor/burden had lower survival rates. Immunotherapy against programmed cell death(PD-1) is a promising alternative impacting survival in advanced/metastatic NSCLC.

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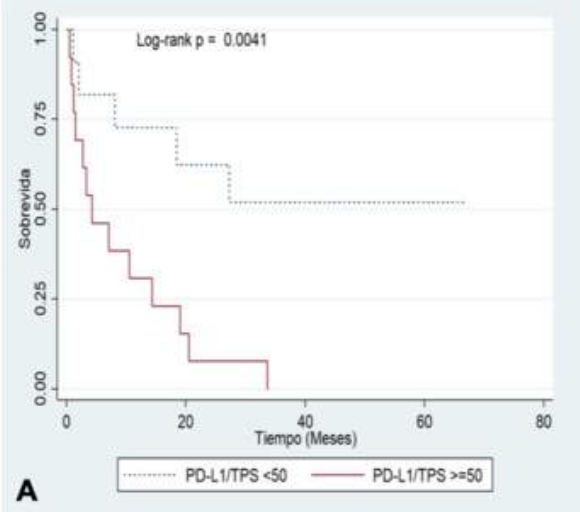

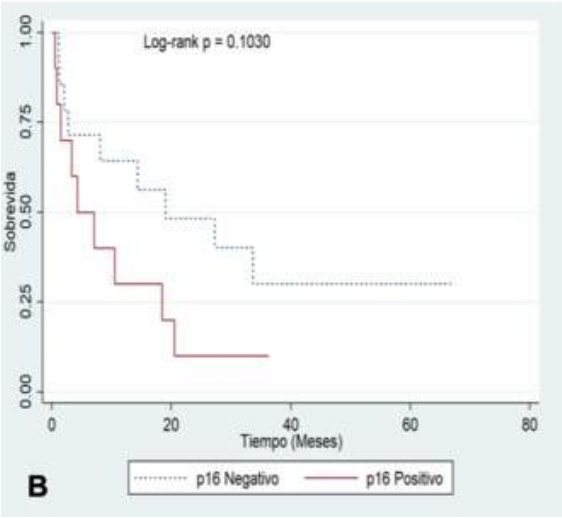

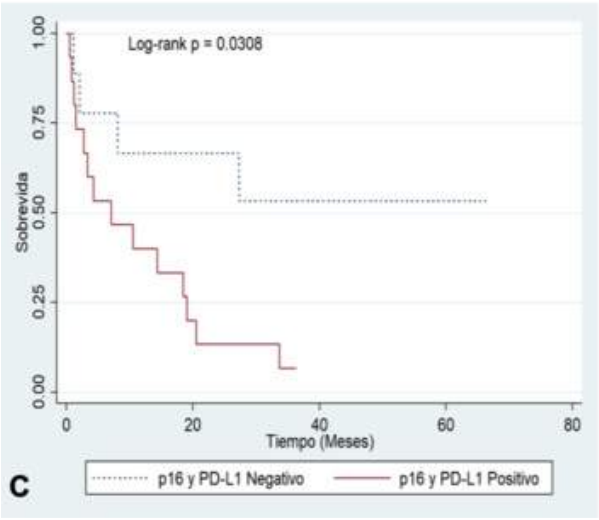

A. Survival analysis according to PD-L1. B. Survival analysis according to p16 status. C. Survival analysis according to PD-L1 and p16 status

Keywords: Squamous cell carcinoma, PD-L1 protein, p16

EP1.04-38 A CASE OF LICHENOID REACTION AS LATE AND UNCOMMON IMMUNE-RELATED SKIN TOXICITY DURING NIVOLUMAB TREATMENT

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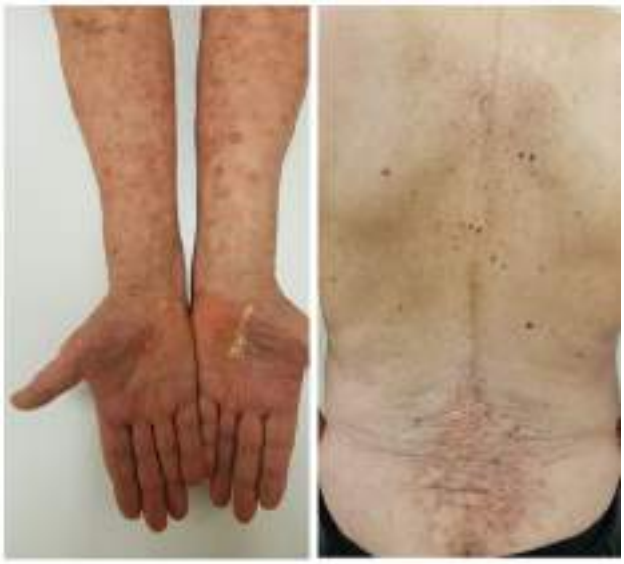
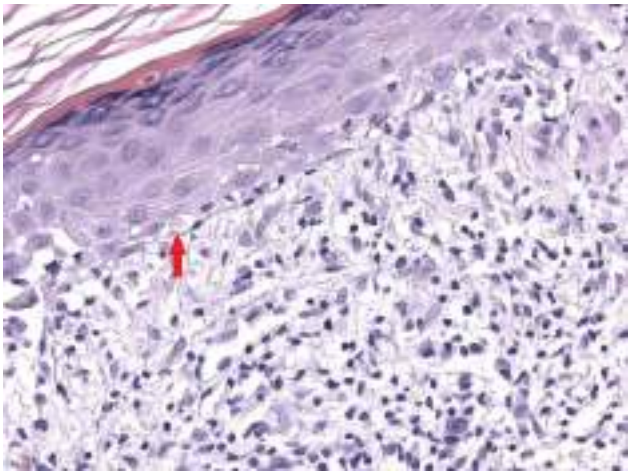
Background: Immune-checkpoint inhibitors have shown remarkable activity in advanced Non-small cell lung cancer (NSCLC). An increasing number of immune-related skin toxicities has been reported, also heterogeneous and unusual. So, these reports could be useful to manage such events. Lichenoid dermatitis (LD) identifies a group of dermatoses clinically and histologically reminiscent of idiopathic lichen planus (LP). Pharmacologycal, chemical and viral causes agents can induce skin lichenoid reactions. **Method:**



We report the case of a 81-years-old man with stage IV non-small cell lung cancer treated with Nivolumab developing a hitchy, recurrent and polymorphous lichenoid eruption after 36 cycles of treatment (Figure 1). **Result:** A skin biopsy (Figure 2) showed an area of parakeratosis associated to a dense lympho-histiocytic infiltrate of the papillary derma that obscures the basal membrane and causes vacuolization of the basal layer of the epidermidis with an isolated Civattes body (red arrow), (40X, H&E).



The temporary interruption of Nivolumab, together with short and low-dose cycles of corticosteroids repeated for several times due to the wave evolution of the lichenoid reaction, allowed for the partial recovery of the skin toxicity and the resumption of treatment. **Conclusion:** Unlike the classic appearance of lichenoid reactions, this patient showed a more polymorphous lesions as compared to the

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classic forms. The correct and early recognition of these uncommon effects is useful to optimally manage and safely continue a treatment while achieving a therapeutical response of neoplastic disease

Keywords: lichen planus, immune-related skin toxicity, advanced NSCLC

EP1.04-39 IS BODY MASS INDEX A PROGNOSTIC FACTOR IN PATIENTS WITH LUNG CANCER TREATED WITH IMMUNOTHERAPY?

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Background: Non-small cell lung cancer (NSCLC) is a prevalent disease with high mortality and poor response to traditional cytotoxic therapy. Immune checkpoint inhibitors (ICI) approvals were the landmark in the last years for the treatment of lung cancer. With these treatments, many patients with advanced disease are starting to see durable responses and longer survival rates. Several factors like obesity has been previously investigated for its role in cancer and promoting tumor growth, at least partially by inducing a chronic inflammatory state, but it's unclear how it links to immunotherapy, where inflammation has been linked to treatment response," High Body mass index (BMI) might have a positive impact in the outcomes of patients who are taking PD-1 or PD-L1 inhibitors, according to a recent study. In this study, we aim to determine if the body mass index (BMI) is a prognostic factor in patients treated with immunotherapy **Method:** We retrospectively evaluated the outcomes of 30 patients with NSCLC confirmed histology, aged 18 years or older, treated with anti PD-1/PD-L1 from 2016 to 2018. BMI was stratified unto 2 groups: 1) normal and under-weighted (BMI < 25 kg/ m2) and 2) over-weighted and obese (BMI ≥ 25 kg/ m2). Simple descriptive statistics were created for all covariates. After statistical analyses with Kruskal-Wallis equality-of-populations rank test were related to progression free survival (PFS). **Result:** A total of 30 lung cancer patients were enrolled in this study, divided by gender as 10 female-patients (33,33%) and 20 masculine-patients.(66,67%) The median age was 63 years (youngest 41-year-old and oldest 81 years old). According to histology 20 patients have adenocarcinoma (66,67 %) and 10 patients have squamous tumors (33,33%). Analyzing the mutational status, the majority was EGFR Wild type (WT). The majority of patients involved (43,33 %; 13 patients) were given immunotherapy in the third-line setting or beyond. More than half of patients had over-weighted and obese BMI (group 2 – 56,67% (n=17)). The median follow-up was 86 days (1 quartile 35 days and 3rd quartile 291 days (minimum 5 days, maximum 971 days). The median PFS in group 1 was 98 days (1 quartile 56 days and 3rd quartile 407 days (minimum 28 days, maximum 495 days) and in over-weighted and obese was 74 days (1quartil 26 days and 3rd quartile 127 days (minimum 5 days, maximum 971 days). There were no statistical differences in PFS (p= 0,249) between higher or lower BMI groups (group1 vs. group 2). **Conclusion:** In this single institution cohort, BMI hadn't a significant effect on outcomes of patients with lung cancer receiving anti PD-1/ PD-L1 agents. As a critic to this evaluation we have that is for now a small group of patients and we think it is important to maintain studies in this field as the number of patients under this therapy increases.

Keywords: body mass index, Immunotherapy

EP1.04-40 EXTRA-THORACIC METASTASIS INDICATED WORSE CLINICAL EFFICACY ON IMMUNE CHECKPOINT INHIBITORS IN CHINESE ADVANCED NSCLC PATIENTS

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Background: Immune checkpoint inhibitors (ICIs) have demonstrated inspiring effectiveness against lots of cancer types, including non-small-cell lung cancer (NSCLC). However, the individual therapeutic response varies and heterogeneous. The purpose of this study was to investigate the association of different metastatic sites with clinical outcomes after ICIs monotherapy in Chinese advanced NSCLC patients. **Method:** We retrospectively analyzed all patients receiving more than two circles of ICIs monotherapy (anti-programmed death 1 or anti-PD-L1) in Shanghai pulmonary hospital from January 2016 to December 2018. Detailed clinical characteristics, metastasis status and progress-free survival (PFS, calculated from the first day receiving ICIs until the disease progressed) was recorded. **Result:** 76 patients were enrolled in this study. 10 of them received immunotherapy in the first-line and 46 of them in the second-line. The rate of extra-thoracic metastasis was 50% (38/76), including brain metastasis (10/38), liver metastasis (11/38), bone marrow metastasis (30/38), adrenal metastasis (4/38), extra-thoracic lymph node metastasis (10/38) and others (5/38). Patients with extra-thoracic metastasis had a significantly shorter PFS than those without (median PFS 4.20 VS 7.10months; hazard ratio [HR] 1.939, 95% CI 1.221-3.389; p=0.0072). In subgroup analysis, patients with brain metastasis, liver metastasis or bone marrow metastasis showed significantly shorter PFS than those without (3.35 vs 4.60m, p=0.0499; 2.50 vs 4.60m, p=0.0007; 3.70 vs 5.80m, p=0.0003 respectively). The disease control rate (DCR) is numerically lower in patients with extra-thoracic metastasis (66.7% vs 80%) comparing with those without, even though not statistically significant. **Conclusion:** The current study suggested that advanced NSCLC patients with extra-thoracic metastasis indicated worse clinical outcomes on ICIs monotherapy and more clinical strategies should be considered to improving treatment efficacy for them.

Keywords: Immune Checkpoint Inhibitors, no-small-cell lung cancer, distant metastasis

EP1.04-41 EFFICACY OF IMMUNOTHERAPY IN ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER: A MULTICENTRIC EXPERIENCE FROM ARGENTINA

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Background: Immunotherapy (IO) has become a standard of care in NSCLC. Aging is associated with structural and functional changes in the immune system; hence, elderly patients could obtain less benefit from IO. Although randomized clinical trials showed benefit regardless of age, elderly are underrepresented, though its role in this population remains uncertain. **Method:** We conducted a retrospective analysis of patients (pts) with NSCLC treated with IO at six centers between Nov 2013 and Feb 2019. We categorized patients in two groups (≥ 75 and < 75 years old) and evaluated overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Correlations were assessed using Fisher's exact tests. Kaplan-Meier was used to estimate survival rates and compared using log-rank testing. Cox proportional hazard models were used to evaluate prognostic factors for PFS and OS. **Result:** A total of 269 NSCLC pts treated with ICIs were included, 49 pts were ≥ 75 years old. Among them, 27 pts (55.1%) were male, 42 (85.7%) current or former smokers and 39 (79.5%) had PS 0-1; baseline brain metastases were present in 5 pts (10.2%). PDL-1 tumor proportion score (TPS) was ≥ 50% in 13/32 pts (41%), 31% received IO in first-line. There were no statistical significant differences in baseline characteristics between both groups. There was similar rate of G3-4 adverse events (18.4% vs. 17.7%, p=1.00) and treatment discontinuation (8.2% vs. 11% p=0.15, respectively) for ≥ 75 and < 75 years respectively. ORR was 18.4% (9/49) vs. 33.2% (73/220) p=0.06, DCR was 47% (23/49) vs. 65.9% (145/220) p=0.01, for ≥ 75 and < 75 years respectively. Median follow-up from IO was 15.9 months [95%CI 12.1 – 19.7]. Median PFS was 3.5 months [95%CI 2.4 – 4.6] vs. 9.8 months [95%CI 7.35 – 12.3] p<0.001 and median OS was 8.7 months [95%CI 5.4 – 12.0] vs. 18.8 months [95%CI 11.8 – 25.8] p=0.008, for ≥ 75 and < 75 years pts respectively. Histology (p=0.032), baseline corticoid treatment (p<0.001), first-line (p=0.004) and G3-4 toxicity (p=0.005) were significantly associated with OS in multivariate analysis. **Conclusion:** In our cohort, immunotherapy demonstrated to be safe for elderly pts showing similar toxicity profile compared to their younger counterparts; however, elderly pts achieve less benefit than younger patients. Further assessment in larger cohorts is warranted, considering the high prevalence of lung cancer among this subset of patients.

Keywords: Inmunotherapy, elderly, NSCLC

EP1.04-42 USING A MULTIPLEXED IMMUNOFLUORESCENCE APPROACH TO COMPARE IMMUNE CELL POPULATIONS IN SUBTYPES OF NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of all lung cancer cases, and is characterized by a poor response to chemotherapy and a low survival rate. Treatment targeting the immune checkpoint inhibitor pathway PD-1/PD-L1 has been found to be effective against NSCLC with manageable side effects, but with only 20-25% of patients showing a positive response there is an urgent need for additional immunotherapy options for this group of patients. NSCLC is a very heterogeneous disease with the two most common types being adenocarcinoma (ADCA) accounting for about 70% of all NSCLC cases, and squamous cell carcinoma (SCC) accounting for about 20% of all cases. In a study profiling the molecular signatures of these two NSCLC subtypes the existence of specific molecular networks and subtype-specific differences was reported (1), while a study using flow cytometry to analyze NSCLC on protein level reported the immune cell composition to be fundamentally different in ADCA compared with SCC (2). However, to the best of our knowledge this study is the first of its kind performing an extensive analysis of NSCLS immune cell composition in tissue. 1. Kargl et al. Nature Commun, 2017 Feb 1;8. 2. Daraselia et al. Am J Cancer Res, 2012 2(1). **Method:** In order to perform a comprehensive immunoprofiling of ADCA and SCC we used MultiOmyx™, an immunofluorescence (IF) multiplexing assay that utilize a pair of directly conjugated Cyanine dye-labeled (Cy3, Cy5) antibodies per round of staining. Using a 16-marker panel we have analyzed the proportion of B cells, T cell subtypes, M1/M2-type tumor-associated macrophages, as well as the expression of not only PD-1 and PD-L1, but also of more novel immunotherapy targets LAG-3, TIM-3, ICOS, and OX40 in 20 samples from patients with NSCLC (10 ADCA and 10 SCC). **Result:** While we found LAG-3 expressed mainly on T cytotoxic cells in both subtypes, the overall density of LAG-3 was increased from 130 cells/mm^2 in ADCA to 239 cells/mm^2 in SCC. Likewise, we found the density of TIM-3 to be increased from 413 cells/mm^2 in ADCA to 1100 cells/mm^2 in SCC, while the density of PD-L1 was decreased from 1626 cells/mm^2 in ADCA to 1089 cells/mm^2 in SCC. **Conclusion:** It is our hope that these data will help provide new insights into the biology of ADCA and SCC that can ultimately be used to explore novel immunotherapeutic interventions for lung cancer treatment.

Keywords: NSCLC, Multiplexing, MultiOmyx

EP1.04-43 THE SIGNIFICANCE OF NY-ESO 1 SEROPOSITIVITY AND INFLUENCE ON NSCLC PATIENTS SURVIVAL

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Background: Lung cancer is the leading cause of cancer mortality worldwide. Understanding biological processes of specific antitumor immune response remains of an eminent interest and represents necessity for designing successful antitumor immunotherapeutic strategies. In our previous study published in JTO 2017, we focused on the humoral component of the specific antitumor response and prospectively analysed serum frequencies of antitumor antibodies against NY-ESO-1, Her2/neu and MAGE-A4 antigens in 121 patients with NSCLC. Here it was shown for the first time that tobacco smoking significantly increases the frequency of NY-ESO-1 antibodies in sera of smokers in comparison to ex-smokers and non-smokers. In our current follow-up study, we plan to describe the significance of NY-ESO 1 seropositivity and influence on NSCLC patients survival. We suppose to have data completed during June 2019 (we are waiting for the 5-year observation period). We would like to apply for Late-Breaking Abstract privileges and the opportunity to present these novel promising data. **Method:** Between 2009 and 2014 we prospectively analyzed the serum frequencies of NY-ESO-1 antibodies and corresponding antigen expression in tumors of 121 non-small cell lung cancer (NSCLC) patients undergoing surgery without prior neoadjuvant chemotherapy and compared them with 57 control age-matched patients with no history of malignant disease, each with no sign of malignancy on chest X-ray. In addition to pulmonary X-ray, a panel of tumor markers (CEA, TPA, NSE, SCC, CYFRA 21-1) was used to compare the group of cancer patients and the group of control patients. The complete set of samples for NY-ESO-1 analyses which includes serum, tumoral and non-tumoral tissue was obtained only for 40 patients. Nowadays we are finishing a 5-year observation period after surgery for primary tumor and we plan to complete a statistical analysis of all data by June 2019. We would like to present results of our follow-up study on WCLC 2019. **Result:** We suppose to have data completed during June 2019 and we apply for Late-Breaking Abstract privileges. Thank you for considering our request. **Conclusion:** We suppose to have data completed during June 2019 and we apply for Late-Breaking Abstract privileges. Thank you for considering our request.

Keywords: NY-ESO-1, NSCLC, Survival

EP1.04-44 EXPLORATION OF FACTORS RELATING TO PARADOXICAL IMMUNE RESPONSE IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS FOR NSCLC

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Background: Although the introduction of immune checkpoint inhibitors (ICIs) has yielded substantial benefits in terms of survival in the treatment of Non-Small Cell Lung Cancer (NSCLC), the possibility of activation of dormant autoimmune diseases or onset of immune mediated toxicities is a reality. The objective of this study was to explore intrinsic immunological factors associated with poor outcomes. **Method:** In a retrospective cohort study of 48 patients, without any prior medical history of autoimmunity, treated for advanced/metastatic NSCLC with ICI´s were assessed. Determination of HLA-A*02011 as well as acute phase reactants and antiphospholipid antibodies was performed. Additionally, evaluation of survival in a time to event manner was conducted using the Kaplan Meier method and Cox regressions **Result:** Median follow-up was 27.3 months, of the included patients 26 were male (54%) with a median age of 62 years old and there were no individuals with and ECOG performance score >1. Median overall survival (OS) was reached at 22.47 months. When analyzing the presence of the HLA-A*02011 serotype, 6 patients tested positive (12.5%). Additionally, all presented with borderline or abnormal B2glycoprotein IgM and IgG, 2Bmicroglubulin and elevated C reactive protein. Four patients (66%) experienced reactive lymphadenopathy during treatment and all suffered some form of venous thromboembolism. When analyzing OS, this group of patients had a significantly worse outcome (6.53 vs 22.47 months, HR= 4.47, [95%CI 1.47 – 13.61], p<0.001) compared with their counterparts. Overall response rate for the whole was superior for the HLA-A*02011 positive patients achieving 41.4% and 33%, p<0.001, respectively. **Conclusion:** The presence of the HLA-A*02011 could potentially predispose to a paradoxical and pathological activation of the immune system without offering any benefit in terms of tumor control. Larger studies validating these findings are warranted.

Keywords: Non small cell lung cancer, Inmunooncology, HLA-A

EP1.04-45 RELEVANCE OF ANTIBIOTIC USE ON CLINICAL ACTIVITY OF IMMUNE CHECKPOINT INHIBITORS IN HISPANIC PATIENTS WITH ADVANCED NSCLC (CLICAP-ABS)

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Background: The composition of gut microbiota affects antitumor immune responses, as well as preclinical and clinical outcomes following immune checkpoint inhibitors (ICI) in cancer. Antibiotics (ATB) alter gut microbiota diversity and composition leading to dysbiosis, which may influence the effectiveness of ICI. **Method:** We examined patients with advanced non-small-cell lung cancer (NSCLC) treated with anti-programmed cell death ligand-1 mAb monotherapy alone or in combination in three different countries of Latin America. Those receiving ATB within 30 days of beginning ICI were compared with those who did not. Objective response, progression free survival (PFS) and overall survival (OS) were assessed. **Result:** 18 of 140 (13%) NSCLC patients received ATB. The most commonly used ATB were b-lactam or quinolones for pneumonia or urinary tract infections. In NSCLC patients, ATB was associated with 4 cases of primary PD (28.6% versus 31.5%, P=0.818), non-significant decreased PFS (median 2.66 versus 1.94 months, HR 1.63, [95% CI 0.71-3.72], P=0.247) and significantly deleterious OS (median 12.42 versus 2.04 months, HR 2.3, [95% CI 1.08-4.95], P=0.03). In multivariate analyses, the impact of ATB remained significant for OS. **Conclusion:** ATB were associated with reduced clinical benefit from ICI in Hispanic patients with NSCLC. Modulation of ATB-related dysbiosis and gut microbiota composition may be a strategy to improve clinical outcomes with ICI.

Keywords: Non small cell lung cancer, antibiotics, Inmunooncology

EP1.04-46 IMMUNOTHERAPY AT ANY LINE IMPROVES SURVIVAL IN HISPANIC PATIENTS WITH ADVANCED METASTATIC NSCLC COMPARED TO CHEMOTHERAPY (QUIJOTE-CLICAP)

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Background: Immunotherapy for NSCLMC offers a significant advantage to chemotherapy in selected cases. This benefit starts to disapear as the patients start two progress and requiere change in medication or even chemotherapy. The objective of this study was to compare survival outcomes of patients with advanced or metastatic NSCLC who received immunotherapy at first, second or beyond versus matched patients receiving standard chemotherapy. **Method:** A retrospective multicenter international cohort study of 296 patients with unresectable/ metastatic NSCLC treated with immunotherapy either as first, second, third or fourth line was conducted. A matched comparison with a historical cohort of first line chemotherapy was conducted. **Result:** Median age was 64 years (Range 34-90) and 40.2% were female patients. 91.2% of patients had an ECOG performance score ≤ 1. Immunotherapy as first line was given to 39 patients (13.7%), second line to 140 (48.8%), and as third line and beyond to 108 (37.6%). Median overall survival was 19.9 months (95% CI 14.5-22.7 months) and progression-free survival was 3.73 months (95% CI 2.8-4.2). Factors associated with increased survival included treatment as first-line (p < 0.001), type of response (p < 0.001) and PD-L1 status (p = 0.0039). Compared with the historical cohort, immunotherapy proved to be superior in terms of OS (p= 0.05) but not PFS (p= 0.2). **Conclusion:** Patients who receive immune checkpoint inhibitors as part of their treatment for NSCLC have better OS compared with matched patients treated with standard chemotherapy, regardless of treatment line.

Keywords: Non small cell lung cancer, Inmunooncology, Chemotherapy

EP1.04-47 CHRONIC AND SEVERE NON-LICHENOID ORAL ULCERS INDUCED BY NIVOLUMAB: DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Background: Due to the widespread use of immune checkpoint inhibitors and the growing research efforts in this area, immune mediated toxicity is well recognized. Nonetheless, few severe cases of oral or upper gastrointestinal tract mucosal involvement have been documented. In this case, report we present the case of a patient who developed severe oral ulcers that were refractory to steroidal support. We also developed a few hypotheses regarding the pathological findings and the implications of microbiomal environment seen in this patient. From a therapeutic point of view, a strategy based on the management given to both Behcet´s disease and Graft versus Host Disease is described. **Method:** A 93-year-old male was diagnosed with T2N1M0 squamous cell carcinoma of the pharynx with partially involvement of the base of the tongue. Due to comorbid conditions, hypofractionated radiotherapy (40 Gy) plus cetuximab (loading dose of 400 mg/m2 5-7 days before radiotherapy initiation, followed by cetuximab 250 mg/m2 weekly for 5 doses (total 1.650 mg/m2) was administered. A partial response was achieved. Local progression occurred within 12.4 months. The patient received Nivolumab 200 mg IV q15 days. A complete response after 4 months of initiation was observed. After 10 cycles, multiple painful erythematous ulcers in the buccal mucosa and tongue were seen. No test evidence of herpes virus, mycotic, Ebstein Barr virus or cytomegalovirus infection was found. Treatment with Nivolumab was halted. He was started on sucralfate, magic mouthwash (oral mucoadhesive) a 14 day course of oral prednisone (1 mg/kg q/day) and topical triamcinolone acetonide, with minimal response. Two weeks later, the patient reported progressive dysphagia, severe pain and rapid weight loss (≈8 Kg). Initial blood tests showed a normal white cell count 8.4×109/L (neutrophils 6.87× 109/L, lymphocytes 0.940×109/L, eosinophils 0.5× 109/L) and platelets at 296.000×109/L. Intravenous methylprednisolone 2 mg/kg/day was started without improvement and increased pain. Due to refractory behavior of the oral ulcers and based on the histological findings, a chronic GVHD reaction was considered. **Result:** It was hypothesized that the ulcers were caused by a pathologic immune system reactivity against the oral mucosa. Based on this, oral cyclophosphamide was initiated in a metronomic schedule: 50 mg q/day by 21 days in a regimen of 28 days for 2 cycles. Additionally, and extrapolating the use of colchicine used for Behcet´s disease ulcers, treatment was initiated with a solution of 1 mg in 150 ml q/8h. Shortly after, an almost complete remission of the lesions and optimal pain control was achieved. Simultaneously, metagenomic evaluation of oral microbiome was also performed. High throughput sequencing

of bacterial 16S rRNA was used. A significant reduction in bacterial diversity was observed. The bacterial species most commonly found were Prevotella melaninogenica, Veillonella dispar and an enrichment in the concentration of Prevotella melaninogenica and Haemophilus parainfluenzae was noted. At 3 months of follow up the patient maintains an oncologic complete response with no evidence of new ulcers or other ICIs derived complications. **Conclusion:** In conclusion, treatment of oral lesions as an adverse reaction to ICIs is a therapeutic challenge.

Keywords: Inmunooncology, Ulcers

EP1.05 INTERVENTIONAL DIAGNOSTICS/ PULMONOLOGY

EP1.05-01 "LIQUID WITHDRAW" TECHNIQUE IN CT-GUIDED CUTTING NEEDLE LUNG BIOPSY DECREASE INCIDENCE OF COMPLICATIONS: PROSPECTIVE STUDY

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Background: CT-guided percutaneous biopsy is a minimally invasive technique used for obtaining enough tissue samples in the diagnosis of pulmonary lesions and genetic testing related to drug efficacy. The common complications of CT-guided percutaneous lung biopsy include pneumothorax, hemoptysis etc. Coaxial technique makes it much easier to repeat sampling and obtain adequate specimens, still it makes no change to the high incidence of pneumothorax. For all this, it is particularly urgent to find some technique to reduce the incidence of pneumothorax. Basic on the research De Filippoet al. had done about complications of the biopsy technique, we hypothesis that when the inner chuck of coaxial guiding needle was removed and the cutting needle was placed inside the guiding needle, the injection of a small amount of liquid (a mixture of lidocaine and hemocoagulase) through the syringe while withdraw of the guiding needle may help to prevent the incidence of pneumothorax for which close the needle track with liquid. **Method:** From August 24th, 2018 to April 1th ,2019, a total of 32 CT-guided percutaneous transthoracic biopsy procedures performed in 32 patients were retrospectively evaluated. The patients were divided into groups regarding the lesion from pleural surface: <30 mm or ≥30 mm. The rates of complications such as pneumothorax and pneumorrhagia were analyzed. And the complications were graded as mild/very mild, moderate, and severe. Different complications between the two groups were analyzed using Pearson's Chi-squared test for categorical values. **Result:** Pathology results were malignant in 28 patients (17 cases were adenocarcinoma, in which10 patients consented EGFR mutation test), benign in 4 patients.7 cases (21.9%) happened pneumothorax (4 very mild pneumothorax, 2 mild pneumothorax, 1 moderate pneumothorax),13 cases (40.6%) happened pneumorrhagia (12 mild pneumorrhagia, 1 very mild pneumorrhagia). No infection, tumor implantation or aeroembolism happened. And there was no statistically significant between pneumothorax and the depth of lesion to pleural surface (P>0.05). **Conclusion:** Compared to co-axial technique only, CT-guided percutaneous lung biopsy using co-axial combined with "liquid withdraw" significantly reduced the incidence of pneumothorax, which has been confirmed what we found in earlier retrospective study. The new technique provided a more accurate, secure and reliable way to obtain adequate tissue samples in the diagnosis.

Keywords: Lung biopsy, PNEUMOTHORAX, CT

EP1.05-02 ENDOBRONCHIAL ULTRASOUND AND TRANSBRONCHIAL NEEDLE ASPIRATION EBUS-TBNA: IN A UNIVERSITY HOSPITAL IN LATIN AMERICA

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Background: Endobronchial Ultrasound and Transbronchial Needle Aspiration (EBUS-TBNA) nowadays it has a primordial role in the workup of malignant and nonmalignant pulmonary disease. It's the most important advancement in pulmonary medicine in the last 20 years.EBUS-TBNA is a minimally invasive technique, well tolerated, cost efficient, for real time visualization of the airways with ultrasound and for sampling the mediastinum and hilum. Its indications: diagnosis, staging, restaging of lung cancer, evaluation of metastatic lesions and non-malignant diseases. It requires multidisciplinary evaluation with image analysis, general condition of the patient, risks and benefits, also close work with pathology, performing a Rapid On-Site Evaluation (ROSE) to improve the diagnostic performance. We describe the EBUS-TBNA in Fundación Valle del Lili a University Hospital of Reference in Latin America. **Method:** Prospective, descriptive study, period June/2015-June/2018. The indications were staging and restaging of lung tumors, diagnosis of lung or mediastinal masses, abnormal ganglia in CT or PET/CT equal or greater than 1cm. 108 patients were evaluated under general IV anesthesia, with a standardized protocol in the endoscopy room. The equipment used was Olympus® bronchoscope + US probe + 22G FNA. **Result:** Average age of 63,5 +/- 12,9, women 53(49%), men 55(50,9%). The quality of the sample was adequate in 105 (97,22%), positive of malignity 63(60%) negative 42(40%), inadequate samples 2(1,8%) and in one case a complete evaluation of the mediastinum was made without evidence of lesions, so no samples were taken. The ganglionary stations most frequently evaluated were 7 40(37%), 11R 22(20,3%), 11L 14(12,9%) and mediastinal mases 11(10,1%). The malignant lesions were non-small cell pulmonary carcinoma (NSCLC) 26(41,2%), metastasis head and neck tumors 10(15,8%), small cell pulmonary carcinoma 9(14,28%). 97,22% of the smears with Diff-Quick staining presented lesion, 5 dips were performed in each station, and immunohistochemistry was made in cellblocks as well as DNA extraction for EGFR mutation studies and EML4/ALK gene rearrangements in 50% of cases of NSCLC and PDL1 in 19,2% of these cases. 10(9,26%) of the series was taken to mediastinoscopy with a 100% correlation with the results of EBUS-TBNA. **Conclusion:** EBUS-TBNA is the recommended technique for lung cancer mediastinal staging. Our results adjust to international results; it is safe, minimally invasive, in many cases an outpatient procedure and a good performance when accompanied with ROSE.

EBUS-TBNA	108
Age*	63.5 ± 12.98
Sex n(%)	
Female	53 (49.07)
Male	55 (50.93)
Total samples, n(%)	
Adequate	105 (97.22)
Not adequate	2 (1.81)
No puncture	1 (0.93)
Samples suitable for study, n(%)	105 (97.22)
Negative	42 (40)
Positive	63 (60)
Stations, n(%)	
7	50 (46.3)
11R	23 (21.3)
11L	16 (14.8)
Mediastinal masses	11 (10.2)
Diagnosis , n(%)	n =63
non-small cell pulmonary carcinoma (NSCLC)	26 (41.27)
Metastasis	10 (15.87)
Small cell pulmonary carcinoma	9 (14.286)
* Promedio ± sd	

Keywords: endobronchial ultrasound, Transbronchial Needle Aspiration, Staging in Lung Cancer

EPOSTERS

EP1.05-03 THERAPEUTIC BRONCHOSCOPY IN MULTIMODAL THERAPY FOR THE MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION

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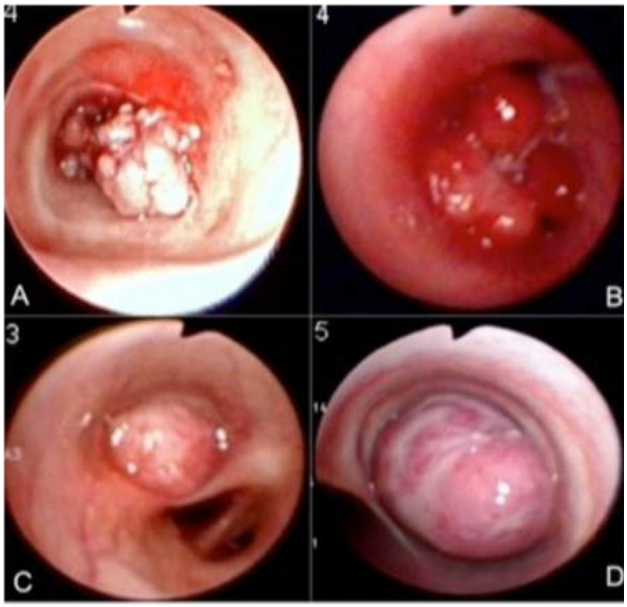
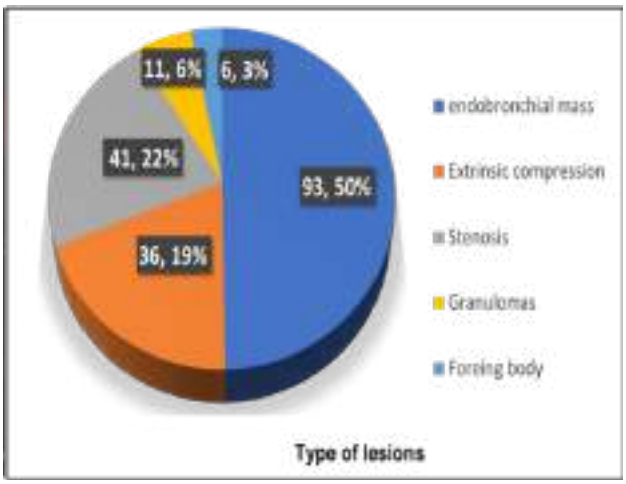
Background: Central airway obstruction may be due to malignant and non-malignant causes. The malignant obstruction of the airway is an important cause of morbidity and mortality in lung cancer. Intervention with therapeutic bronchoscopy decreases symptoms and allows time to employ treatments like surgery/radiotherapy or quimotherapy. In benign pathology prior intubation or complications related to lung/transplantation are common. Patients usually have cough and dyspnea that can progress to respiratory failure. Therapy should be oriented to secure and restore the airway. Best technique choice depends on etiology, type and severity of lesion, technological availability and operators skills. Nowadays, a multimodal therapy is implemented, including different intervention methods for the management. We aimed to describe therapeutic bronchoscopy in Fundación Valle del Lili a University Hospital in Latin America. **Method:** Descriptive retrospective study, April-2013/June-2018. 151 procedures were performed. Symptoms, etiology, localization, severity, diagnosis, type of anesthesia, interventions and complications were analyzed. The device was a therapeutic flexible and rigid bronchoscope Olympus® and specific intervention instruments. **Result:** 56.9+/-16.9-years. 58(38%)women and 93(61,5%)men. Malignant lesions were found in 91(60.26%). Symptoms were cough 122(80.8%), dyspnea 122(80.8%), hemoptysis 51(33.8%) and chest pain 41(27.2%). General anesthesia was used in 147(97.35%), the most common approach was the use of laryngeal mask 112(74,17%) then an endotracheal tube 22(14.57%). In 108(71,52%) a severe airway obstruction was present. 93(61,59%) had an endobronchial mass and 36(23,84%) external compression. Lesion location was: left-stem bronchi 73(48,34%) right-stem bronchi 64(42,38%), trachea inferior 23(15,23%), trachea superior 18(11,92%), carina 18(11,92%), trachea media 11(7,28%) and intermediate bronchus 11(7,28%). Most common malignant etiology was non-small cell lung cancer 39(42,85%), followed by typical/atypical carcinoid tumor 11(12,08%), sarcoma 9(9,89%) and metastatic tumors of gastrointestinal origin 8(8,79%) and head and neck tumors 6(6,59%) among others. Benign pathology was found in 60(39,7%) included granuloma 11(18,33%), stenosis 41(68,3%) which are related in most with airway complications after lung/transplantation and foreign bodies were found in 6(10%). Procedures were debridement 104(68,87%), electrocoagulation 95(62,91%), argon plasma 39(25,83%), stent colocation 5(3,31%), balloon/dilatation 42(27,81%) and cryoprobe 29(19,21%). Multiple interventions were made in various patients. Obstruction resolution was complete for 56(37,09%) and there was residual stenosis in 42(27,81%) or residual mass in 53(35,1). Complications included mild hemoptysis in 8(5,38%) and scaling in the attention room in two cases. No reported deaths associated with the procedure. **Conclusion:** Central airway obstruction is a complex situation that requires multidisciplinary approach. Currently, multimodal therapy is recommended combining different options of intervention, through flexible or rigid bronchoscopy, to achieve optimal results.



Examples of endobronchial lesions.



Type of lesions.

Keywords: Multimodal Therapy, Therapeutic Bronchoscopy, Central Airway Obstruction

EP1.05-04 RESULTS AFTER RETROSPECTIVE STUDY ABOUT COEXITENCE BETWEEN BRONCHIAL CARCINOMA AND ACTIVE TUBERCULOSIS IN ENDEMIC AERA

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Background: Morocco is an endemic country of tuberculosis (TB); the coexistence of active pulmonary tuberculosis in patients with lung cancer is not uncommon and may delay the management of bronchial carcinoma. To clarify the features and risk factors of cases with coexistence cancer and active TB, the aim of this study is to evaluate the clinical and radiological features through a retrospective study of cases with establishment of a diagnostic score to overcome conflict situation. **Method:** The medical records of 70 cases between 2008 and 2018 in which lung cancer and active pulmonary tuberculosis are intermingled in the same lobe of the lung were collected using our hospital database. We evaluated demographic data, the ways diagnosis of TB cases, the location of TB and cancer using the serial chest radiographs available for all patients; results of bronchoscopy with sampling for mycobacterial culture were reviewed. The CT findings; size, shape, border and location of the lesions and the possible causes of delay in the diagnosis of lung cancer were analyzed. **Result:** The findings of 70 patients (62 males and 08 females, aged 36-82 years), there are

47 smokers versus 23 never-smokers, in whom pulmonary TB and bronchogenic carcinoma coexisted in the same lobe were analyzed. Fifteen patients had history of tuberculosis. Isolated upper lung field were involved in 75 % patients. Sixty five per cent of cases had respiratory infection symptoms with presence of air-fluid levels in the affected lung with cavitation. Bronchoalveolar lavage (BAL) was performed with the positivity of smears and cultures in all patients. With regards to chest X-ray features, smokers presented with more advanced, and cavitating lung lesions. The average delay in diagnosing lung cancer was 12 (range, 6-18) months, and the causes of this were misinterpretation of lung cancer as active tuberculosis with cavitation in 92% of cases. **Conclusion:** Pulmonary TB and lung cancer may mimic each other especially in the aspect of the clinical and radiological features. We mainly discussed the diagnostic points to detect the coexistence of lung cancer and pulmonary tuberculosis at early stage.

EP1.05-05 THE OPTIMAL SEQUENCE OF BRONCHIAL WASHING AND BRUSHING FOR DIAGNOSIS OF NON-VISIBLE LUNG CANCER DURING NON-GUIDED BRONCHOSCOPY

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Background: The optimum sequence of obtaining bronchial washing and brushing samples in lung cancer patients with non-visible tumor during conventional bronchoscope is uncertain. Recent advanced diagnostic bronchoscopy use only is feasible in a few institutions and can be expensive. The aim of the study was to investigate the diagnostic yield of washing performed after brushing in patients with non-visible tumor during non-guided flexible bronchoscopy (FB). **Method:** We performed a retrospective review of prospectively collected data of suspected lung cancer patients who were performed washing after brushing in non-visible tumor during non-guided FB from 2010 to 2015. Total 166 patients with histologically confirmed primary lung cancer were enrolled in the study. **Result:** The overall diagnostic rate was 52.4 %, and the diagnostic yield of bronchial brushing and washing were 37.3 % and 46.4 %, respectively. We compared the diagnostic yield of brushing with washing using McMemar's test. Washing had a better diagnostic yield, 46.4 % (77/166) vs. 37.3 % (62/166) (p=0.017, kappa index=0.570). Comparison of intra-individual agreements between the positive cytology of brushing or washing and the final pathologic diagnosis were a concordance rate of 89.6 % and 90.3 %, with a kappa value of 0.791 (p<0.001) and 0.801 (p<0.001), respectively. The presence of a bronchus sign, tumor size, and higher standardized uptake value on positron emission tomography scan were predictors of a higher diagnostic yield. **Conclusion:** In institutions where advanced diagnostic bronchoscopy is unavailable, the sequence of washing after brushing in the diagnosis of non-visible lung cancer during non-guided FB may help improving the diagnostic yield.

Keywords: bronchial washing, bronchial brushing, non-visible tumor

EP1.05-06 BENEFITS OF 18F-FDG PET/CT-GUIDED CORE-NEEDLE BIOPSY IN NECROTIC OR RECURRENT CHEST TUMORS

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Background: In case when we have deal with necrotic chest masses and recurrent tumors histological verification become challenged. This happens because CT and ultrasound imaging don't give us enough information about vital and necrotized part of tumor. CT-guided core-needle biopsy give us possibility to take sample from almost any part of tumor but only with information about density of tissure. On the other hand, ^{18}F-FDG PET/CT give us information about tumor vitality. But usually, ^{18}F-FDG PET/CT performs after morphological verification and we don't use PET/Ct benefits for biopsy. **Method:** We analyzed 6 patients with chest malignancies: 3 with primary mediastinal lymphoma, 1 – recurrent Hodgkin's lymphoma, 1 – lung cancer and 1 thymoma. All of them had had at least non-diagnostic core-needle biopsy followed by non-diagnostic thoracoscopic biopsy (1 patient) of Chamberlain procedure (1 patient). We performed PET/CT in all the patients to define the viable target area for subsequent core-needle biopsy. One patient had the biopsy immediately after PET/CT scanning, using the CT-part of PET/CT scanner for navigation. In 5 patients the biopsies were taken within 1 week after PET/CT scanning under normal CT-control. The imaging data obtained from CT and PET/CT scanning were analyzed and compared using the axial slices and MPR reconstructions with OsiriX MD software. 14G and 16G needles were used for mediastinal and lung tumors respectively. All procedures were performed under local anesthesia on outpatient basis. **Result:** We received tissue confirmation in all cases. No complications occurred during or soon after the biopsy. **Conclusion:** Uptake zone of the radiotracer on ^{18}F-FDG PET/CT image correlates with informative biopsy specimen taken from that part of the tumor. We may recommend performing of ^{18}F-FDG PET/CT prior to the repeated core-needle biopsy to get information on viable and necrotic tumor compounds to define the target areas.

Keywords: Core-needle biopsy of chest tumors, PET/CT-guided core-needle biopsy, Biopsy of necrotic tumors

EP1.05-07 EXAMINING ENDOBRONCHIAL ULTRASOUND (EBUS) UTILISATION IN LUNG CANCER DIAGNOSIS AND TREATMENT DELAY. A RESTROSPECTIVE OBSERVATIONAL STUDY

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Background: Introduction • EBUS has high diagnostic yield in the assessment of mediastinal lymphadenopathy, staging and diagnosis of lung cancer. (1) • FDG PET/CT scans can be used in the initial assessment of hilar and mediastinal nodes, EBUS-TBNA has a higher sensitivity and specificity for staging these lymph nodes in patients with lung cancer. (2) • The provision of high quality EBUS demands that procedures are delivered in a manner which is demonstrably evidence based, effective, equitable, safe, patient-centred and timely. • Timeliness in EBUS provision will ensure a minimum in patient related anxiety and minimal prolongation of the referral to diagnosis and referral to treatment intervals. Objective To examine the impact of EBUS wait time on diagnosis and treatment delay in evaluating lung cancer and mediastinal lymphadenopathy within the Alfred Hospital. **Method:** A retrospective chart review of diagnosed lung cancer patients undergoing EBUS (linear and radial) at the Alfred Hospital between August 2013 and September 2018 was conducted. We recorded the waiting interval between EBUS referral and procedure and examined impact on lung cancer management timeliness from lung cancer referral to lung cancer diagnosis and first treatment based on electronic records. Electronic records were also used to gather baseline patient characteristics. **Result:** 103 EBUS procedures were completed on 96 patients with the below characteristics. Lung cancer referral to diagnosis interval had mean 23.2 days (30.5 SD), diagnosis to treatment interval had mean 24.1 days (21.2 SD), and referral to treatment interval had mean 47.4 days (35.9 SD).

EBUS within one week of EBUS referral, n(%)	70 (79%)
EBUS within two weeks of EBUS referral, n(%)	85 (96%)

EBUS waiting time was compared for lung cancer referral to diagnosis interval (within vs delay of greater than 28 days), and diagnosis to treatment interval (within vs delay of more than 14 days). There was a trend towards diagnosis delay with prolonged wait for EBUS (p=0.052). Significantly, EBUS wait time was greater for delayed referral to treatment interval (more than 42 days), than within 42 days (p=0.012). **Conclusion:** Delay in investigation has the potential to delay key management issues including lung cancer diagnosis and treatment. Prolonged wait for EBUS lead to a trend towards diagnosis delay and significant delay in referral to treatment interval in this cohort. Further assessment of causes in EBUS delay warrants further investigation.

Keywords: EBUS, staging, Timeliness

EP1.05-08 OBTAINING DIAGNOSTIC LUNG BIOPSIES IN SUSPECTED LUNG CANCER PATIENTS

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Background: Lung cancer screening programs will inevitably increase demand for lung biopsies, therefore best practice and standardised investigation pathways need to be well established. This study was designed to determine current practice in obtaining diagnostic lung biopsies in patients with suspected lung cancer. **Method:** A retrospective study of CT-guided lung biopsies and frozen section biopsy procedures performed in 10 hospital trusts over 3 years. All pathology results were reviewed for patients with suspected lung cancer. The number of procedures performed, and the proportion of cancerous, benign and indeterminate findings were ascertained and compared for the two biopsy techniques. Relevant imaging was reviewed (by an experienced interventional thoracic radiologist) to determine whether patients met the criteria for a percutaneous CT-guided biopsy. **Result:** 607 frozen sections and 204 CT-guided biopsies were performed over three years in 10 hospital trusts for suspected lung cancer. Pathology results demonstrated that 23% of frozen sections were benign, 2% were indeterminate and 75% were cancerous. In comparison, 16% of CT-guided lung biopsies were benign, 30% indeterminate, and 54% cancerous. Trends showed a gradual increase in the number of CT guided biopsies over 3 years, and a decrease in the number of frozen sections performed. There was a reduction in indeterminate CT-guided biopsy results and in benign frozen section results over the three-year period. Most patients met the criteria for percutaneous CT-guided biopsy, based on size and location of the lesion and background lung function, yet frozen section biopsy frequently remained the first line approach. **Conclusion:** Advancements in imaging and biopsy techniques promotes percutaneous CT-guided biopsy - the more favourable, less-invasive approach for obtaining lung tissue. However, many patients are still undergoing frozen section biopsies as the first-line option. A review of individual trust pathways is recommended to ensure standardisation of practice and that patients are offered the most appropriate investigation.

Keywords: CT-guided lung biopsy, Lung cancer diagnosis, lung cancer screening

EP1.05-09 WELL-DIFFERENTIATED LIPOSARCOMA CAUSING ENDOBRONCHIAL OCCLUSION: A CASE REPORT

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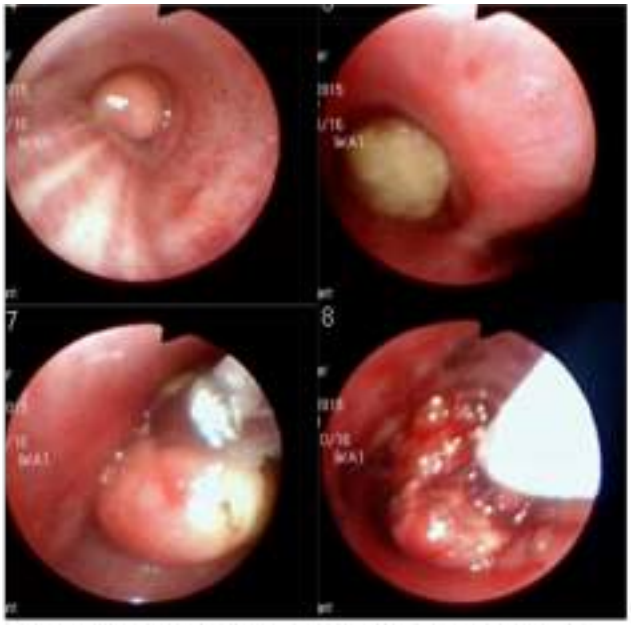
Background: Endobronchial well-differentiated liposarcoma(WDL) is an uncommon benign entity which corresponds to 0,1-0,5% neoplasms affecting the bronchial tree. 60% patients are men with a median age of presentation of 60-years-old. Smoking and obesity are known risk factors. Its treatment implies resection of the tumor only or part of the lung too. Endobronchial WDL is associated with favorable prognosis, particularly when distant compromise from the lungs is absent. In consequence, timely diagnosis is pivotal. We present the case of a endobronchial occlusion due to WDL. **Method:** Review of the Clinical History. **Result:** 74-years-old man former smoker of 54.8 packs-year, with COPD and family history of gastric and bladder cancer. Attends medical assistance with constant expectorant cough and repeated pneumonias without dyspnea. Chest-CT evidence a great size, exophytic tumoral lesion in left main bronchus, complete ipsilateral atelectasis and mediastinal lymphadenopathies. Bronchoscopy is performed, revealing a mass of tumoral appearance from the left inferior lobe. Mass resection is performed in two times with electrocoagulation and cryoprobe under general anesthesia, leaving permeable the lumen of the main left bronchus and all its segments without complications. Histopathological studies with hematoxylin-eosin stain showed a lesion of mesenchymal origin, compound by different size adipose tissue and fibrous stroma covered by respiratory epithelium. Immunohistochemistry expressed vimentin, within fibrous septa nuclear marker CDK4 was expressed, KI67 of 2% without evidence of mitosis according to pHH3 assessment. Morphological pattern and immunophenotypic expression profile. compatible with WDL. Periodic follow-up evaluations of the airway with bronchoscopy were recommended. **Conclusion:** WDL is a benign but uncommon neoplasm arising at the tracheobronchial tree. Despite its benignity, endoluminal polypoid growth can cause endobronchial occlusion and destruction of distal parenchyma. Cough, progressive dyspnea, hemoptysis and recurrent pneumonia are common clinical manifestations, yet bronchoscopy and histopathologic assessment are essential to confirm diagnosis and avoid irreversible parenchymal changes.



Endoscopic aspect of the mass in the left main bronchus, handled with electrocautery and cryoprobe

Keywords: Endoscopic resection, Liposarcoma, Endobronchial Occlusion

EP1.05-10 METASTASIS FROM A PRIMARY MELANOMA OF THE SINONASAL CAVITY: A CASE REPORT

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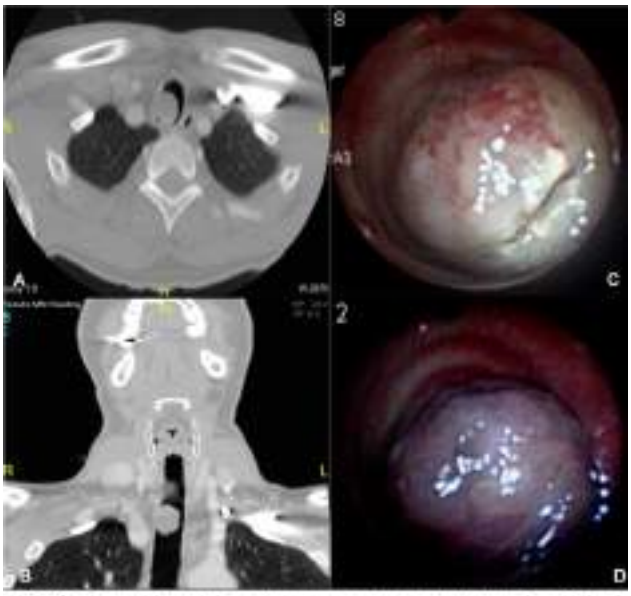
Background: Metastatic extension to tracheobronchial tree from non-lung primary neoplasms is a common clinical problem. Endoluminal compromise is estimated to be present in 2-28% of metastatic disease cases. Melanoma's high metastatic potential can affect lung in 71% of cases, turning it into a frequent cause of relapse, however, endobronchial metastases by this entity corresponds to 4,5% of all metastatic lesions from the tracheobronchial tree. Mucosal melanoma (MM) is a rare entity that encompasses 1.3% from all cases of melanoma. Sinonasal cavity and conjunctiva are the most frequent locations. Liver metastasis from primary sinonasal MM has been described but endoluminal airway spread is extremely uncommon. We report the case of primary MM from sinonasal cavity with endotracheal metastasis and severe obstruction of the central airway. **Method:** Review of the Cinic History. **Result:** 47-year-old man with previous diagnosis of nasal melanoma attended the hospital for a FBC indicated due to one month of dyspnea and chest discomfort. His medical history included surgical resection from inferior turbinate lesion with positive borders, followed by adjuvant radiotherapy as part of the therapeutic management for his melanoma. Subsequent PET-CT scan evidenced hypermetabolic lesion in VII hepatic segment and pre-cava adenopathy. On the FBC, a 1-cm tumoral lesion in right nasal fossa was observed in addition to a complex mass located in the fourth tracheal ring, obstructing 90% of the lumen. ICU hospitalization was indicated due to respiratory failure high risk. Complete lesion resection was performed via therapeutic FBC with electrocautery and cryoprobe under general anesthesia. Pathological report: Neoplastic lesion compatible with metastasis of MM with non-mutated BRAF. Chemotherapywasinitiated. **Conclusion:** Primary MM is an uncommon tumor. Although endoluminal airway metastases are extremely rare from primary sinonasal MM, they are a differential diagnosis to consider in a patient with respiratory symptoms within the context of this primary neoplasia.



A,B. CT-Scan: Metastatic melanoma endotracheal obstruction 90% of light of the tracheal. C,D. Endoscopic appearance of the mass prior to resection

Keywords: Melanoma, Tracheal Occlusion, Endoscopic resection

EP1.05-11 INTEGRATING RADIOLOGICAL FEATURES TO CT GUIDED LUNG BIOPSY RESULTS; THE EXPERIENCE OF AN ARGENTINEAN UNIVERSITY TEACHING HOSPITAL

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Background: To analyze the radiological findings and the diagnostic accuracy of percutaneous transthoracic needle biopsies (CT-PTNB) performed for the evaluation of patients with lung lesions derived to our center. **Method:** We describe a retrospective review of 206 consecutive patients undergoing CT- PTNB of lung lesions performed between 2016 and 2019 at a single oncological referral center. Clinico-pathological data, including: age, smoking status, and previous cancer was described. Radiologic lesion´s characteristics on CT; multiple or solitary , location, mean diameter (mm), type (mass^{3}30 mm, nodule < 30mm, other), mean distance to pleura, presence of consolidation, nodule edge, calcifications, presence of radiologic emphysema, ground glass component and PET-CT SUVmax were used to compare with lung biopsy results. The rate and factors associated with complications was also be reported. **Result:** From 105 patients who underwent CT- PTNB and fulfilled inclusion criteria; 85 (81%) had pathologic confirmed cancer diagnosis, 3 (3%) had benign findings and 17 (16%) had inadequate samples for accurate diagnosis. The majority of patients were: male (57%) and the mean age was 63 years (32–88). Lung cancer was the main diagnosis (49/85; 58%) achieved through CT-PTNB; 71.2% of these cases had adenocarcinoma histology and 29% (14/49) had previous cancer diagnosis (35%: breast cancer) being the majority of them smokers (86%). Metastatic lesions (36/85; 42%) were: 44% melanoma-sarcoma, 38%: breast, colorectal, renal and cervix cancer and 18%: lymphoma, cervix, head and neck, lung and urothelial cancer. Primary lung cancer compared to lung metastases showed on CT images: mass presentation (63%vs33%; p=0.002), right superior lobe localization (47% vs 33%; p=0,016), solitary lesion (77% vs 53%; p=0,016), consolidation (22% vs 5%; p=0,033), central calcification (12% vs 0%; p=0,024), emphysema (55% vs 28%; p=0,009), mean major diameter (mm) (61±33 vs 36±24; p=0,000), mean distance to pleura (mm)(32±78 vs 86±12.7; p=0,014) and PET-CT mean SUVmax (8.8±10.63 vs 4.7±6.8; p=0.045). The complication rate of CT- PTNB was 18.5% (half of them practiced through right upper lung lobe , being pneumothorax the most common. Mean distance between pleura to CT- PTNB site was 10.54 vs 3.81 mm in complicated and non-complicated cases, respectively. **Conclusion:** Primary and metastatic lung lesions were safely pathologically evaluated by CT-PTNB. Radiological characteristics of the lesions can help in patient´s initial assessment to predict their nature.

Keywords: lung-nodules GGO

EP1.06 MESOTHELIOMA

EP1.06-01 AMRUBICIN TREATMENT AS PALLIATIVE-INTENDED CHEMOTHERAPY FOR PREVIOUSLY TREATED MALIGNANT PLEURAL MESOTHELIOMA

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Background: Treatment options for non-naive malignant pleural mesothelioma (MPM) are limited. Few phase II trials have provided evidence for the treatment. Till date, antineoplastic activity has been observed in phase II trials in patients with MPM treated with anthracyclines, doxorubicin, or pegylated-liposomal doxorubicin. However, few studies have reported on these treatments because of severe toxicities. Conversely, amrubicin (AMR) is an anthracycline drug that is commonly used for treating thoracic tumors; therefore, we know that the treatment is generally well tolerated. We performed this phase II trial to determine whether AMR monotherapy is a promising treatment approach for non-chemotherapy naive patients with MPM. **Method:** Non-randomized phase II trial Patients diagnosed with MPM based on the histological and cytological examination of specimens, with disease progression after pemetrexed/platinum, 1–2 prior regimens, age 18–74 years, AMR naïve status, and performance status (PS) 0–2 were enrolled. Patients received 35 mg/m2 AMR (days 1–3) every 3 weeks until tumor progression and had unacceptable toxicities. The primary endpoint was tumor response rate, and secondary endpoints were progression-free survival, overall survival, and toxicity rate. **Result:** From September 2013 to July 2018, five patients with MPM were enrolled, and the treatment responses were evaluated. All subjects in this case series were men with a median age of 65 (range, 49–76) years; the mean number of treatment cycles was 3 (range, 2–11). Stable disease was observed in three patients (60%) and progressive disease in two (40%). The median progression-free survival was 2.4 (range, 1.2–11.2) months, and the median overall survival was 9.1 (range, 6.2–22.0) months. Grade 1/2 toxicities, such as nausea and malaise, were reported in all subjects, and most of the toxicities were controllable. Grade 3/4 neutropenia occurred in four patients (80%), and there was no case of febrile neutropenia. **Conclusion:** Three of our patients achieved stable disease with AMR treatment. These data suggest that AMR is a promising treatment for previously treated MPM in the absence of another treatment. Moreover, AMR is associated with modest toxicities, similar to that in previous reports.

Keywords: malignant pleural mesothelioma, amrubicin, case series

EP1.06-02 ASSOCIATION OF INFLAMMATORY BIOMARKERS WITH OVERALL SURVIVAL IN PATIENTS WITH ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

L. Gutiérrez Sainz, P. Cruz, S. Martínez Recio, I. Esteban, F. Arias Lotto, D. Viñal, J. Villamayor, D. Sanchez Cabrero, O. Higuera, J. De Castro Carpeno

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Background: The inflammation process has been proposed as a mechanism of immunoresistance in patients with cancer, promoting cancer growth and dissemination. Derived neutrophil to lymphocyte ratio (dNLR) greater than 3 and lactate dehydrogenase (LDH) level greater than upper limit of normal (ULN) are associated with poor outcomes in patients with advanced non–small cell lung cancer. The aim of this study is to determine whether pretreatment levels of dNLR and LDH as well as PD-L1 status are associated with overall survival in patients with malignant pleural mesothelioma. **Method:** We conducted a retrospective study, which included all patients with malignant pleural mesothelioma diagnosed in a tertiary referral hospital from December 2009 to March 2019. PDL1 status, complete blood cell counts and LDH levels were collected. A descriptive analysis was carried out, followed by a survival analysis using the Kaplan-Meier estimator. **Result:** We selected 25 patients. No correlation was found between dNLR and LDH levels. 5 patients (20%) had a dNLR greater than 3, of which 3 patients had stable disease and 2 patients received supportive care. Patients with a dNLR greater than 3 had a median overall survival (mOS) of 8,5 months, whereas patients with a dNLR less than 3 had a mOS of 17,0 months, with statistically significant differences (P:0.038). 2 patients (8%) had a LDH level greater than ULN, of which 1 patient achieved

a partial response and 1 patient had stable disease. Regarding the LDH level no difference in overall survival was found. Regarding to the PD-L1 status, 10 (40%) of 25 patients had PD-L1 ≥ 1%, 8 (32%) had PD-L1 < 1% and 7 (28%) had unknown PD-L1. Patients with PD-L1 ≥ 1% had a mOS of 8,5 months, whereas patients with PD-L1 <1% had a mOS of 15,7 months, with no statistically significant association (P> 0.05). **Conclusion:** In our sample, pretreatment levels of dNLR greater than 3 were correlated with worse overall survival in patients with malignant pleural mesothelioma. Furthermore, pretreatment levels of LDH greater than ULN and PD-L1 greater than or equal to 1% could be correlated with worse overall survival, although due to the size of our sample we are not able to conclude statistical significance. Further studies are needed to explore this relationship.

Keywords: Malignant pleural mesothelioma, inflammatory biomarkers, PDL1 status.

EP1.06-03 THE MESOTHELIOMA OUTCOMES, RESEARCH AND EXPERIENCE (MORE) SURVEY. USING REAL WORLD RESEARCH METHODOLOGY

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Background: Malignant mesothelioma is a locally invasive neoplasm arising from the mesothelial surfaces of the pleural cavity & a smaller number of cases affecting the peritoneum. Annually approximately 2,700 are diagnosed with mesothelioma in the UK with approximately 2,500 deaths.(CRUK 2019) In 2012 Mesothelioma UK (MUK) undertook a patient experience survey enabling MUK to inform healthcare providers what was done well, what could be improved & to demonstrate where there were variations in care. As a primary objective MUK are replicating the 2012 survey to update recommendations representing the patient experience & to circulate these to the mesotheloma community and healthcare providers. A secondary objective will deliver data to support regulatory discussions for new medical interventions. This will include the collection of treatment histories, patient reported outcome measures, NHS resource use & non-medical patient costs. This will provide a comprehensive evidence portfolio, from which the understanding & burden of disease in mesothelioma can be identified/quantified, so that the provision of services for individuals can be deployed. The survey will provide cost effective utility assessments assisting in the approval for new therapeutic interventions. **Method:** The survey is anonymous, prospective, cross sectional & non-interventional. Recruitment of mesothelioma patients is via a number of methods coordinated & led by MUK. The research will collect circa 600 participants over 26 weeks from January to June 2019. Participants are given a survey that includes questions on standard demographics, experience of care (questions adapted from the 2012 Mesothelioma Experience Survey), HRQol and previous/current clinical management. On completion of the survey, the participants are asked to provide consent for the CNS to review /validate the clinical section & the information provided on their clinical management. **Result:** A full statistical analysis plan will be developed and disseminated following completion of the survey and review of the data. **Conclusion:** MUK believes the data being collected using this unique methodology will be the only data of its kind to examine real world patient demographics, occupational histories, treatment pathways, individual experience and the burden of disease.

Keywords: Unique, Outcomes, Experience

EP1.06-04 DIFFERENCES IN HEALTH STATE PREFERENCE VALUES FOR MALIGNANT PLEURAL MESOTHELIOMA AND GLIOBLASTOMA MULTIFORME

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Background: Malignant pleural mesothelioma (MPM) is an invasive and generally fatal malignancy of the pleura mainly caused by exposure to asbestos fibers. Glioblastoma (GBM) is the most aggressive and similarly fatal form of primary brain cancer in adults. It was recently shown, that both rare cancers are treateable with tumor treating fields (TTFields). Novel cancer treatment modalities are subject to comparative economic evaluation using health state preference values or heath utilities, in addition to clinical trial endpoint data. Utilities have a value range between 0 and 1, with "1" representing a state of perfect health and "0" death. Clinical results of TTFields treatment show a comparable effect on median overall survival (OS) for both MPM and GBM. The EF-23 STELLAR trial in MPM demonstrated a median OS increase of 6.1 months for TTFields treatment compared to historical control. The EF-14 trial showed a median OS increase of 4.9 months in GBM. Differences in health state preference values however, could significantly influence the adoption of a treatment independent of its clinical efficacy and safety in the respective indication. **Method:** We reviewed the structure and results of the trials using TTFields treatment in GBM and MPM from a health economic standpoint. Three health states (stable disease, progressed disease and death) were determined appropriate for both, the EF-14 trial in GBM and for the EF-23 STELLAR trial in MPM. A comprehensive review of the published literature adressing health state preference values or health utilities was performed using a boolean search of the PubMed database. The results were compiled separately for both diseases and then compared to each other. **Result:** Estimates of health states preference values or utilities in GBM all refer to one single publication. Healthy members of the NHS Value of Health Panel (VoHP) rated a total of nine descriptive health state scenarios using the standard gamble method for preference elicitation. There are no published preference values for descriptive health states scenarios or disease states in mesothelioma. Uilities published for MPM were elicited at individual patient level as derived from the EQ-5 questionnaire data collected during the trial. Other publications do not use specific mesothelioma heath state preference values but assume applicability of utilities derived from a non small cell lung cancer (NSCLC) population. **Conclusion:** Although both are rare cancers, health state preference values for GBM and MPM are different. GBM health state preference values are elicited from a single source, while utilities used in MPM are more diverse. Published utilities for GBM allow for use in a health state disease model, while there are no similar published values for MPM. MPM utilities derived from the EQ-5 questionnaire however describe more adequatly the individual utilities and their change during the course of the disease. This difference in structure, elicitation methods and sources of health state preference values in GBM and MPM could lead to disparities in the assessment of cost effectiveness of new treatments like TTFields in different indications, despite similar costs and clinical efficacy.

Keywords: Mesothelioma, TTFields, health state preference value

EP1.06-05 THE BRITISH LUNG FOUNDATION MESOTHELIOMA RESEARCH NETWORK: AN INTERNATIONAL COLLABORATIVE RESEARCH PLATFORM

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Background: The British Lung Foundation's Mesothelioma Research Network (MRN) brings together basic science and clinical researchers in the field of mesothelioma to share knowledge, skills and resources. It aims to facilitate research progress and improve patient outcomes. International researchers are encouraged to join. **Method:** The MRN was launched in October 2017. Success is measured against performance indicators including member numbers and member feedback. Member surveys were conducted in July and December 2018. **Result:** • The MRN has over 130 members ranging from PhD students to departmental heads and includes non-UK based researchers. • In May 2018, 4 early-career MRN members were financially supported to attend the International Mesothelioma Interest Group (iMig) conference. • The first annual MRN Research Day (held June 2018, London, UK) was attended by 85 researchers. Evaluation showed that 85% of responders rated the programme as excellent or good and 86% felt the event would impact positively on their future research. • In the December 2018 members survey: - 77% of responders felt that being a member of the MRN helped them in their work as a researcher and 95% would recommend being an MRN member to a colleague. - 9 responders had contacted other members of the Network to access expertise or resources, and 5 of the 9 felt this contact had formed or could form research collaborations. • In December 2018, a British Lung Foundation collaborative grant call was launched exclusively for MRN members. The award, which will pump-prime new ideas in mesothelioma research, will be made in June 2019. **Conclusion:** A year and a half since launch, the MRN has

established itself as a valued resource for UK researchers. There will be a significant drive to increase international members in 2019. The MRN is supported by the Victor Dahdaleh Charitable Foundation.

Keywords: Mesothelioma, network, collaboration

EP1.06-06 RETROSPECTIVE ANALYSIS OF CLINICAL FEATURES AND NONSTANDARD TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA IN A GENERAL HOSPITAL

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Background: Malignant pleural mesothelioma (MPM) is a relatively rare disease and there are not many cases at a single institution. However, our hospital is closed to the industrial area, so there were relatively many MPM patients who visited our hospital. On the other hand, MPM is disease with poor prognosis, and its standard treatment is also limited. Only two regimens; cisplatin + pemetrexed and nivolumab are approved as standard treatment in Japan. But in clinical practice, other drugs are also used for various reasons. Therefore, it is necessary to clarify the actual condition including nonstandard treatment. **Method:** We extracted patients of MPM who visited our hospital during the twelve-year period from April 2007-March 2019. And we carried out a retrospective analysis of the both data of patients who received standard therapy only and nonstandard therapy based on the medical records. And more summarized the clinical course, outcome and various factors. **Result:** There were a total of 41 MPM patients, of which 80.5% were male and 19.5% were female, and median age was 72 years old. Sixty-one percent of patients had a history of asbestos exposure. The most common clinical symptom at the first visit was dyspnea (48.8%). In 92.7% patients, pleural effusion was present. Their performance status (PS) at the time of diagnosis was as follows: "0" in 4 cases (9.8%), "1" in 23 cases (56.1%), "2" in 7 case (17.1%), "3" in 7 case (17.1%), and "4-5" in 0 case (0%). By histology of MPM, 17 cases (41.5%) were epithelioid type, 10 cases (24.4%) were biphasic type, 3 cases (7.3%) were sarcomatoid type, and there were 11 other cases (26.8%) (including unknown); classified by the disease stage (IMIG Ver.8), 43.9% patients had "1A", 7.3% patients had "1B", 14.6% patients had "2", 9.8% patients had "3A", 12.2% patients had "3B", and 12.2% patients had "4". Radical surgery could be performed in only 3 cases (7.3%). Chemotherapy was administered in 25 cases (61%), and 16 cases (39%) also received chemotherapy with unapproved drugs and regimens, e.g., pemetrexed only, carboplatin, gemcitabine, vinorelbine, and bevacizumab, etc. The median overall survival (OS) of all patients was 13.8 months. The median OS for patients who received only standard treatment or only palliative treatment was 7.6 months, while the median OS for patients who received unapproved treatment was 16.9 months. The group of patients who received unapproved treatment included 3 cases with PS 2 or more, and also included 47 months of long-term survival cases. **Conclusion:** Although it is data of one general hospital, 41 MPM patients could be extracted and analyzed. Nevertheless, it is difficult to show statistically significant differences due to an insufficient number of cases, and factors such as stage and PS are related. However, it can be said that survival tends to be longer in patients who also received unapproved treatment. We will analyze more cases, including patients under observation, and will report these detailed data at the venue.

Keywords: malignant pleural mesothelioma, nonstandard therapy, overall survival

EP1.06-07 IN VIVO STUDIES OF TUMOR TREATING FIELDS TO UPPER TORSO IN COMBINATION WITH CHEMOTHERAPY SHOW NO ADDITIONAL TOXICITIES

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Background: Tumor Treating Fields (TTFields) are low intensity, intermediate frequency alternating electric fields targeting rapidly dividing cells. TTFields (200 kHz) are FDA-approved for the treatment of glioblastoma based on phase 3 studies demonstrating efficacy and a high safety profile. TTFields are currently being tested as a treatment option for other solid tumors in the brain, abdomen, and torso. We evaluated if the safety profile of TTFields is maintained at various frequencies in the upper torso. **Method:** TTFields (150 kHz) were applied for 1-4 weeks using the Novo-TTF 100 system to rat and rabbit torso at 2-3 V/cm, which are intensities and frequencies known to be effective for the treatment of NSCLC and mesothelioma. The safety of TTFields in combination with liposomal doxorubicin and cyclophosphamide or paclitaxel was tested in animals. Throughout the treatment course, all animals underwent daily clinical examination by a certified experienced veterinarian and their body weight was determined on a weekly basis. Extensive blood workup, ECG, and temperature measurements were performed in the rabbit experiments. At the end of treatment, animals were euthanized and an experienced independent pathologist performed histological comparative evaluation of all major internal organs. **Result:** No changes in the following parameters were observed in activity level, food intake, drinking, stools, motor neurological status, and respiration. Further, no changes in weight were observed between the TTFields treated and relevant control groups. No significant changes were observed in complete blood count and differential between TTFields treated animals and relevant control groups. Histological analysis did not reveal any increase in pathological findings in the TTFields treated animal groups. **Conclusion:** These results demonstrate the safety of TTFields application at frequencies of 150 kHz to the torso. No additional toxicities were observed with the combination of TTFields and chemotherapy agents vs chemotherapy agents alone. This work further supports the safety profile of TTFields and offers opportunities for combining TTFields with various chemotherapy agents in lung cancers.

Keywords: Tumor Treating Fields, Safety, In Vivo

EP1.06-08 A RETROSPECTIVE ANALYSIS ON SARCOMATOID MESOTHELIOMA TO IDENTIFY IF CHEMOTHERAPY PROVIDES GREATER OVERALL SURVIVAL COMPARED TO BSC

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Background: Sarcomatoid is the least common, but most aggressive type of mesothelioma (1) accounting for approximately 11% of all malignant pleural mesothelioma (MPM) (2). However, unlike lung cancer which has different treatment depending on histology, Mesothelioma has the same treatment, regardless of cell type (3, 4). Current data suggests patients with Sarcomatoid Mesothelioma have an average of 5.3 months survival from diagnosis. (5). **Method:** Method A retrospective analysis was undertaken on 9 Sarcomatoid Mesothelioma patients diagnosed and treated from March 2017 to November 2018. The aim of the audit was to identify if patients who received chemotherapy had better overall survival when compared to those patients' who received best supportive care (BSC). All of the 9 patients were PS 0/1 at time of diagnosis. 5 patients had platinum doublet chemotherapy 4 patients had best supportive care partly due to age and concerns of the patient about impact of chemotherapy on quality of life. **Result:** 2 patients who received chemotherapy died within 8 months of diagnosis. 2 patients who had BSC died within 5 months of diagnosis. 1 patient had 1 line of chemotherapy and then on PD recruited to PROMISE Trial and received Pembrolizamab. Still on treatment at C20. 3 patients who had chemotherapy are still alive on average 1yr 6 months post diagnosis with continuing stable disease. 3 of the patients who had first line chemotherapy went on to receive 2nd line chemotherapy either in or out of a clinical trial. 2 patients BSC still alive with average 6 months progression free survival. **Conclusion:** The results do suggest that patients who have chemotherapy do have an OS benefit when compared to those with BSC only. Overall patients tolerated chemotherapy well and have gone on to either receive second line oral Vinorelbine or be recruited into a clinical trial. Due to small numbers of patients it would be good to undertake a formal research study in multiple centres to recruit larger numbers of patients to assess if these results are mirrored nationally. It would also be of interest to identify if Sarcomatoid patients are routinely offered chemotherapy as first line treatment or whether the majority of patients are advised to accept BSC only.

Keywords: Sarcomatoid Mesothelioma, chemotherapy, best supportive care, overall survival.

EP1.06-09 MESOTHELIAL TUMORS REGISTRY IN SPAIN: A RETROSPECTIVE MULTICENTER STUDY

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Background: Malignant mesothelioma is an unusual tumor associated with poor prognosis. Currently, there are no effective treatments after the progression to the first line. The aim of this study is to analyze the experience in 7 spanish centers. **Method:** We conducted a retrospective analysis including patients with malignant mesotheliomas of 7 centers in Spain. Demographic, clinical and pathological variables, tumor response, progression date and death were collected. **Result:** We enrolled 63 patients with diagnosis of malignant mesothelioma. The average age was 70 years. 73,4% were men and 26,4% women. The most frequent location was the pleural (78,1%) and biopsy was the main diagnostic method (92,2%). 76,6% were diagnosed as epitheloid mesothelioma subtype, whereas sarcomatoid and mixed subtypes were less frequent. Tumor in stage IV was presented at diagnosis in 75 % cases. The most frequent first treatment was chemotherapy, 95,2% of patients received treatment based on platinum doublet with pemetrexed, followed by pemetrexed maintenance. Best response was partial response in 20,6%, stable disease in 41,3%, complete response in 22,2% and progressive disease in 15,9%.The median progression free survival of the sample was 8,8 months, and the median overall survival was 12 months. **Conclusion:** The demographics and baseline characteristics as well as the survival data obtained in our sample are consistent with the previously reported.

Keywords: Malignant mesothelioma, retrospective study.

EP1.06-10 MALIGNANT PLEURAL MESOTHELIOMA DIAGNOSIS: AN 18-YEAR-OLD EXPERIENCE

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Background: Malignant pleural mesothelioma (MPM) is a rare malignant tumour derived from the embryonic mesoderm, whose most frequent location is the pleura. It regularly occurs between the ages of 60 and 80, and it is strongly related to an asbesto exposure. This work compiles the joint experience of both the thoracic surgery and the pathological anatomy services of the General Interzonal Hospital for Acute and Chronic Cases "San Juan de Dios" from the city of La Plata, Argentina. **Method:** A retrospective analysis was carried out in all the patients with a MPM diagnosis registered in the database of San Juan de Dios Hospital, during the time period from January 2000 to December 2018. All diagnoses were performed through pleural biopsies, analized by means of a routine haematoxylin-eosin test and confirmed by an immunohistochemistry study (two positive and two negative indicators). **Result:** 118 cases were analized, and ages ranged from 17 to 89 years (62 years old was the average), 70% were male while 30% female. The biopsy was taken through videothoracoscopy or thoracotomy, except for a case in which Abrams needle was used. In 14% of the cases a second biopsy was necessary to confirm the diagnosis. The histologic patterns were: epithelioid (65%), sarcomatoid (11%), desmoplastic (3%), and biphasic (12%); in 6% of the cases the histologic type was not determined. **Conclusion:** We could observe that most cases apply to men elder than 70 years of age and that the most frequent histologic pattern is the epithelioid one. Moreover, we could see that the average size of the useful sample for diagnosis and the one which did not require a new biopsy sample was 0.8 cm.

Keywords: Mesothelioma, size of pleural biopsies, diagnosis

EP1.06-11 ADVANCED MALIGNANT PLEURAL MESOTHELIOMA: A SINGLE INSTITUTION EXPERIENCE

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Background: Malignant pleural mesothelioma is a rare and highly aggressive tumor that typically presents with advanced disease. The prognosis of patients with malignant pleural mesothelioma is poor and there is currently a lack of effective treatment options. The aim of this study is to analyze the experience of our center in the management of this pathology. **Method:** We conducted a retrospective study, which included all patients with malignant pleural mesothelioma diagnosed in a tertiary referral hospital from December 2009 to March 2019. Data regarding baseline characteristics, treatment response and survival were collected. A descriptive analysis was carried out, followed by a survival analysis using the Kaplan-Meier estimator. **Result:** We selected 25 patients. Table 1 summarizes the main sociodemographic characteristics, the histological subtype and the stage.

Table 1	Nº (%)
Sex: Male/Female	19 (76%) / 6 (24%)
Age (years):	71 (51 – 89)
Histology: – Epithelioid mesothelioma – Sarcomatoid mesothelioma – Mixed mesothelioma	22 (88%) 1 (4%) 2 (6%)
Stage: – Stage III – Stage IV	4 (16%) 21 (84%)

22 (88%) of 25 patients received first line chemotherapy with platinum doublet with pemetrexed followed by pemetrexed maintenance and 3 (12%) received palliative care. The proportion of patients who received six cycles of platinum doublet with pemetrexed was 55%. 5 (20%) of 22 patients who received first line chemotherapy with platinum doublet with pemetrexed achieved a partial response, 15 (60%) had stable disease and 2 (8%) experienced disease progression. After a median follow-up duration of 15,17 months, 19 (76%) patients had died. The median progression free survival was 13,1 months (IC 95%: 6,7 – 19,5), and the median overall survival was 15,7 months (IC 95%: 11,3 – 20,0). The major cause of death was cancer in 18 patients (95%) and 1 patient dead of heart disease. **Conclusion:** Demographics and baseline characteristics as well as the survival data obtained in our sample are consistent with the previously reported. Further studies are needed to determine other treatment options to improve the prognosis of these patients.

Keywords: Malignant pleural mesothelioma, retrospective study.

EP1.07 NURSING AND ALLIED PROFESSIONALS

EP1.07-01 EFFECTIVENESS OF THERAPEUTIC MASSAGE FOR TREATING ANXIETY IN SUSPECTED LUNG CANCER PATIENT PRE-BRONCOSCOPIC PROCEDURES

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Background: Anxiety management rules important aspect during intervention procedures. Suspected lung cancer patients especially in diagnostic bronchoscopy procedures mostly experience mental and emotional problems including stress, anxiet and depression. Massage therapy as complementary and alternative medicines (CAM) are being used to help reduce tension and elicit feeling of calm and deep relaxation. **Method:** Our objective was to assess the effect of massage therapy on suspected lung cancer patients among pre-procedure of bronchoscopy. These are clinical trial placebo-controlled assesing pre and post anxiety quisionaire with massage therapy intervention. **Result:** Twenty eight patient with clinically diagnosed with suspected lung cancer were included in pulmonary ward divided into 14 subjek each massage group and control group. Based on anxiety quisionaire one hour post massage vs one to two hours pre-procedure there had been significantly decreasing anxiety score (p<0,05). Confounding factor are controlled by solo terapist

performing massage. **Conclusion:** Our results indicate that massage is effective to reduce anxiety before interventional procedures. Further well-designed, large studies with longer follow-up periodes are needed for better standard treatment managing anxiety.

Keywords: anxiety, massage, therapy, suspected lung cancer, pre-procedures bronchoscopy.

EP1.07-02 ROLE OF NURSE IN PATIENT CARE DURING IMMUNOTHERAPY TREATMENT THROUGH EXAMPLE OF CANADA AND POLAND

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Background: Immunotherapy is a rapidly growing field and is seen as an active cancer treatment strategy. Administration of immunocompetent drugs does not always take place in a stationary setting, so the level of education of the patient and his family is worth paying attention to. The knowledge of nursing staff plays an important role here. **Method:** The method of participant observation and analysis of the literature was used in the work. The materials utilized are the procedures and standards abided in Princess Margaret Hospital in Toronto, Clinical Hospital no. 1 of Poznan Medical University and the Medical University of Gdańsk. The observations were made during the participation in the Personalized Learning Program in Nursing-Clinical Research at Princess Margaret Hospital in Toronto on 17-21 September 2018, and at Polish centers in 2018. **Result:** Observations confirm that the analysis of the work structure, the functioning of observed centers, the availability of treatment methods and the scope of nurses competence in both countries vary. The level of education presented in Canada can serve as a model to follow for each country, where the method of treatment with immunocompetent drugs is transformed from the level of clinical trials into therapeutic programs. **Conclusion:** Polish Nursing should use the experience of Canadian nurses in the education of patients treated with immunotherapy.

Keywords: Immunotherapy, patient education

EP1.07-03 PREPAREDNESS IN PROMOTING AND SELF-ASSESSMENT OF NURSES ABILITY TO PROMOTE HEALTH AWARENESS IN LUNG CANCER PREVENTION

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Background: Aim: The aim of this study was to analyze the self-assessment of nurses' knowledge regarding lung cancer, and to verify whether this group of professionals is prepared for promoting lung cancer prevention. Background:Lung cancer constitutes a health and epidemiological problem worldwide. Introduction: The complete elimination of exposure to the components of tobacco smoke is a primary prevention component of vital importance and should constitute extensive educational activities be undertaken by family nurses. However, according to available literature, the level of relevant knowledge represented by nurses remains insufficient. **Method:** This study included 490 nurses from Pomerania province. All the respondents completed the questionnaire verifying their knowledge of the etiology of lung cancer and their preparedness for promoting the prevention of this malignancy and self-assessed knowledge of the problems in question. **Result:** The average level of etiological knowledge of lung cancer was high. Preparedness for promoting health awareness in the prevention of lung cancer represented an intermediate level. The efficacy of screening is determined by its coverage. Nurses can provide a pivotal role in lung cancer prevention provided they are given training and responsibility for these additional duties. **Conclusion:** Many nurses, given appropriate training, have the potential for educating people in the prevention of lung cancer. However, full utilization requires education and reorientation of nurses towards primary prevention, especially in healthcare education. Nursing professionals may require additional training and increases in staffing to adequately respond to the increase in responsibility for patient care. Implications highlight a need for additional training and consultancy to improve knowledge and preparedness of nurses to address concerns in lung cancer prevention.

Keywords: lung cancer, prevention

EP1.07-04 INCOMPLETE FIRST TREATMENT COURSE AND RELATED FACTORS OF SURVIVAL RATE ANALYSIS FOR LUNG CANCER PATIENTS

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Background: Cancer case managers not only provide clinical care for cancer patients and management, but also make sure patients receive continuous, correct and complete integrated care, in order to have good survival rate.To investigate reasons for lung cancer patients with incomplete treatment course and their survival rate analysis **Method:** The retrospective study enrolled patients with lung cancer from the case manager system according to the international classification disease(ICD-9:162) during 2013~2017 and analyzed the reason of incomplete first treatment course and related factors of survival rate. **Result:** Totally, 1489 lung cancer patients were enrolled in the study. Most of the patients were stage 4 disease, about 68.6%. There were 114 patients who incompleted their first treatment course (7.6%). In these patients, 41 patients(35.9%) were transfered to other hospital; 8 patients (7%) did not want to receive treatment anymore because they felt better; 27 patients (23.6%) refused treatment due to side effects; 36 patients (31.57%) received hospice care due to poor performance, and 2 patients (1.7%) incompleted their treatment due to old age. **Conclusion:** Case management interventions can provide health education of treatment, improvement of side effects, and social resources to the patients. Through the connection of nursing cares, case management can offer continuous follow up and support to reduce incomplete therapy course and increase patient survival rate by helping patients to return to hospital to complete their therapy course.

Keywords: Lung cancer, case manager, survival rate

EP1.08 OLIGOMETASTATIC NSCLC

EP1.08-01 WHOLE-BRAIN RADIOTHERAPY PLUS SEQUENTIAL OR SIMULTANEOUS INTEGRATED BOOST FOR THE TREATMENT OF LIMITED NUMBER OF BRAIN METASTASES IN NSCLC

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Background: There has been no definitive regimens on how to integrate whole brain radiotherapy(WBRT) and local boost for brain metastases(BMs). To compare the therapeutic effect and cerebral cognitive dysfunction in non-small cell lung cancer(NSCLC) patients with limited number of BMs (≤10) treated by WBRT plus sequential integrated boost (SEB) or simultaneous integrated boost(SIB). **Method:** A total of 52 non-small cell lung cancer patients with limited number of BMs who underwent IMRT from January 2013 to December 2016 were retrospectively analyzed. 20 cases in group A were irradiated by WBRT+ SEB (first 3Gy*10Fx for WBRT then 4Gy*3Fx for BMs) and 32 case in group B were irradiated by WBRT+SIB(3Gy*10Fx for WBRT and the same 4Gy*10Fx for BMs). All patients had complete MMSE scores before radiotherapy, at the end of radiotherapy, 1 month after radiotherapy, 3 months after radiotherapy, and 6 months after radiotherapy. The clinical efficacy and differences in cognitive impairment were compared between 2 groups. **Result:** The Cumulative survival rates of 1,2 and 3 years in 52 patients were 52.5%, 28.6% and 14.3%, respectively. The median survival time was 13 months. The Cumulative 1, 2 and 3-year survival rates of group A were 60.0%, 41.1%, 27.4%, respectively. The median survival time was 15 months. The 1,2 and 3-year survival rates of group B were 47.8%, 19.1%, 0%, respectively. The median survival time was 10 months. The effect difference between group A and B was significant (P=0.046). Subgroup analysis revealed that 1, 2 and 3 years survival rate and median survival time of group A were significantly superior to group B, especially to those patients with 1-2 BMs, male or age <60 years old (P<0.05). MMSE scores at the end of radiation and at 1 month after radiation were not significantly different from those before treatment in both group (P>0.05), however, the scores at 3 or 6 months after radiation were lower than before radiation, the difference was significant(P<0.05). There was no significant difference in MMSE scores in the 2 group before radiation, at the end of radiation, at 1 month after radiation and at 6

months after radiation (P> 0.05). The scores of group A at 3 months after radiation was higher than that of group B (P<0.05). Certainly, group A had longer radiotherapy time and more cost than group B (P<0.005). **Conclusion:** For limited number of BMs in non-small cell lung cancer, WBRT+SEB is likely to be better than WBRT+SIB, especially to 1-2 metastases, male or aged <60 years patients. The decline of cognitive function in both groups occurred after 3 months of radiation, and WBRT+SEB group seems to be less impairment of brain cognitive function than that WBRT+SIB group. It is worth further study to verify Which boost scheme will be better.

Keywords: Non-Small Cell Lung Cancer, Brain metastases, Neurocognitive

EP1.08-02 SURGICAL INDICATION FOR POSTOPERATIVE REGIONAL LYMPH NODE OLIGO-RECURRENCE IN NON-SMALL CELL LUNG CANCER

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Background: Currently, evidence-based guidelines for therapy to treat regional lymph node (LN) oligo-recurrence in post-resection non-small cell lung cancer (NSCLC) are limited. We investigated the clinical outcome of surgery for LN oligo-recurrence in post-resection NSCLC. **Method:** From 2008 to 2017, 14 patients received R0 resection for regional LN oligo-recurrence after initial NSCLC R0 surgery. Eligible patients met these criteria: A, no recurrences without regional LN by PET-CT and brain-MRI; B, LN recurrence within 3 regions. We investigated the characteristics of surgically curable NSCLC patients with postoperative regional LN oligo-recurrence, including recurrence-free survival (RFS) and overall survival (OS). **Result:** Ten patients were male and 4 were women. The median age was 69 years (62-86). Pathological findings in initial surgery was as follow; adenocarcinoma in 9, squamous cell carcinoma in 5, pathological stage I in 6, II in 4, and IIIA. The regional number of LN recurrence was as follow; 1 region in 11, 2 regions in 1, and 3 regions in 2. The median number of pathological metastatic LN were 2 (1-8). The median size of LN oligo-recurrence was 19 mm (14-38). All the oligo-recurrence LN had uptake in PET-CT. All the recurrent LN site was out of the dissection range at initial surgery. The median period from the initial surgery to oligo-recurrence was 18.1 months (7.0-66.5). The median operation time was 134 minutes (52-452), and median bleeding volume was 15 ml (2-2593). SVC reconstruction was performed in 1. Postoperative complication was detected in 3 cases; arrhythmia in 2 and graft occlusion in 1. There were no cases of perioperative death. EGFR mutation was detected in 4 cases. After LN dissection, 9 patients were followed up without treatment, and the other 5 patients underwent chemotherapy. Six patients (42.8%) out of 14 were recurrence-free after LD dissection. Compared recurrence-free patients with recurrence patients after LN dissection, pathological only one LN of oligo-recurrence ($p < 0.01$) and EGFR wild type ($p = 0.04$) were significant in the recurrence-free group. LN oligo-recurrence in only one region also tended to be more frequent in the recurrence-free group ($p = 0.09$). Pathological N or stage in initial surgery, size of LN oligo-recurrence, recurrence-free interval after initial surgery were no significant difference between recurrence-free and recurrent group. The median RFS and OS after LN resection in all 14 patients was 24.2 and 66.3 months. The 2-year and 5-year RFS rates after LN resection were 52.7% and 35.2%. Eight patients were recurrence after LN dissection; 4 were locoregional and the others were distant. Of the 8 relapsed patients, only 2 patients survive with EGFR-TKI. **Conclusion:** Surgery for postoperative regional LN oligo-recurrence in NSCLC should be indicated for the patients with only one LN of oligo-recurrence in only one region or EGFR wild type.

Keywords: oligo-recurrence, regional lymph node, Non-Small Cell Lung Cancer

EP1.08-03 RESULTS OF DEFINITIVE TREATMENT IN PATIENTS WITH SYNCHRONOUS OLIGOMETASTATIC NON SMALL CELL LUNG CANCER

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Background: To evaluate the prognostic factors and outcome of both thoracic radiotherapy (RT) and oligometastasis treatment with curative intent in cases with oligometastatic non-small lung carcinoma (NSCLC). **Method:** We retrospectively evaluated 18 synchronous oligometastatic NSCLC patients who underwent radical treatment in the thoracic and oligometastasis region between 2015 and 2018 in our center. **Result:** The median age of patients was 62 years. Only two of 18 patients had ≥2 organ involvement. Patients' clinical and treatment characteristics are summarized in Table-1 and Table-2. Median follow-up was 7 months. The median overall survival (OS) was 11 months and the median progression-free survival (PS) was 8 months. The one year OS and PS was found 45% and 50% respectively. In the univariate analysis, the localization of oligometastasis (brain vs other distant met) was found as an effective factor on OS. The median survival was found to be 7 months in patients with brain metastasis whereas 18 months in patients with other metastasis. Although treatment type (RT vs surgery) or RT technique applied for oligometastasis (Conformal RT (3DCRT)/IMRT vs Stereotactic RT (SRS/SBRT)) did not cause significant difference on OS in univariate analysis; in the multivariate analysis, the localization of oligometastasis (HR: 7.3, 95% CI 1.33-40.5) and the RT technique applied for oligometastasis (HR: 8.45, 95% CI 1.43- 49.9) were found to be prognostic factors on OS ($p = 0.012$). In the univariate analysis induction chemotherapy (CT) and RT tecnique were statistically significant for PS, but this significance could not be demonstrated in multivarian cox regression analysis.

Table.1: Demographic characteristics of patients and the results in univarian analysis

	Number (%)	p value (OS)	p value (PS)
Age (years) median (min-max) <60 years ≥ 60 years	61.5 (35.0-73.0) 7 (38.9) 11 (61.1)	0.725	0.355
Gender Male Female	16 (89.0) 2 (11.0)	0.786	0.876
Histology Adenocarcinoma SCC	12 (67.0) 6 (33.0)	0.145	0.785
T stage T1 T2 T3 T4 Unknown	3(17.0) 4(22.0) 4(22.0) 6(33.0) 1(6.0)	0.87	0.369
N stage No N1 N2 N3 Unknown	4(22.0) 5(28.0) 8(44,0) 0(0) 1(6.0)	0.169	0.222

Table 2: Treatment characteristics of patients and the results in univarian analysis

	Number (%)	p value (OS)	p value (PS)
RT region Brain Bone Surrenal Liver Other	7 (50) 3 (21) 1 (7) 1 (7) 2 (15)	0.299	0.021
Metastasis number 1 2 3-5	12 (66.0) 3 (17.0) 3 (17.0)	0.393	0.794
Metastatic organ Brain Other Bone Surrenal Liver Multiple Other	7 (39.0) 11(61.0) 3 (17.0) 3 (17.0) 1 (5.0) 2 (11.0) 2 (11.0)	0.031	0.421
Oligometastasis treatment Surgery RT Surgery and RT	4 (22.0) 10 (56.0) 4 (22.0)	0.412	0.534
Oligometastasis RT tecnique SRS/SBRT 1x20 Gy 5x5 Gy 3DCRT/IMRT 3x 10 Gy 3x 15 Gy	4 (28.5) 3 1 10 (72.5) 6 4	0.065	0.468
Thoracic RT Dose 45 60 64-66	4 (22.0) 5 (28.0) 9 (50.0)	0.194	0.536
Induction CT Yes No	11(61.0) 7 (39.0)	0.067	0.044
Concurrent CT No Yes	6 (33.0) 12 (67)	0.084	0.142

Conclusion: Results of treatment with thoracic RT and oligometastasis region in oligometastatic NSCLC seem promising. The localization of the oligometastasis and the technique of RT are important factors.

Keywords: oligometastasis, nonsmall cell lung cancer, treatment

EP1.08-04 LOCAL TREATMENT FOR PATIENTS WITH PULMONARY OLIGO-RECURRENCE OF NON-SMALL CELL LUNG CANCER

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Background: The concept of oligo-recurrence, which is theoretically curable by definitive local therapy, has been proposed in several cancers. But the efficacy of local therapy for patients with pulmonary oligo-recurrence of non-small cell lung cancer (NSCLC) is unclear. The aim of this study was to investigate the efficacy of local therapy for pulmonary oligo-recurrence of NSCLC. **Method:** We retrospectively analyzed the data on 35 patients who underwent lung resection or radiotherapy for pulmonary oligo-recurrence in our institution, between 2000 and 2016. We evaluated independent risk factors for overall survival and progression-free survival after local treatment for patients with pulmonary oligo-recurrence of non-small cell lung cancer. In this study, pulmonary oligo-recurrence was defined as local recurrences limited within lungs after local or systemic treatment for NSCLC. **Result:** There were 26 men and 9 women with median age of 72 years [interquartile range (IQR), 64-75]. The median follow-up time was 48.8 months [IQR, 16.3-66.7]. Previous therapies for NSCLC were pulmonary resections in 26 patients (74.2%), stereotactic radiosurgery for brain metastasis in 3 (8.6%), radiotherapy for lung tumors in 3 (8.6%), chemoradiotherapy in 2 (5.7%) and chemotherapy (ALK-TKI) in 1 (2.9%). The median progression-free interval between previous therapy and local treatment for oligo-recurrence was 29.0 months [IQR, 16.0-44.5]. Histopathology were adenocarcinoma in 26 patients (74.2%), squamous cell carcinoma in 7 (20.0%), adenosquamous carcinoma and large cell neuroendocrine carcinoma in 1 (2.9 %). Among 21 patients (60.0%) who underwent surgical resection for pulmonary oligo-recurrence, surgical procedures were wedge resection in 11 patients, segmentectomy in 3, lobectomy in 5 and pneumonectomy in 2. Among 14 patients (40.0%) who underwent radiotherapy for pulmonary oligo-recurrence, 11 patients (31.4%) underwent stereotactic body radiotherapy. There were no treatment-related death. Three-year overall survival and progression-free survival were 60.3% and 49.6%. Post-treatment recurrence occurred in 16 (60.4%) patients (local; 6, distant; 2, local and distant; 8). Univariate analyses identified progression-free interval between previous therapy and local treatment for pulmonary oligo-recurrence as independent risk factor for overall survival (HR 0.97 [95% CI 0.95-1]; p=0.039). **Conclusion:** Local therapy for pulmonary oligo-recurrence of NSCLC are feasible and the post-therapeutic survival is acceptable. But there are highly selective patients in our study, further study is needed for curative intent treatment.

Keywords: non-small lung cancer, Oligometastases, local therapy

EP1.08-05 LOCAL NON-SALVAGE RADIOTHERAPY FOR SYNCHRONOUS OLIGOMETASTATIC NSCLC: A MULTICENTER, RANDOMIZED, CONTROLLED, PHASE 2 STUDY

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Background: Previous studies had suggested that aggressive thoracical treatment, such as surgery, might lead to higher local control rate and better long-term survival in oligometastatic NSCLC. Radiotherapy (RT) is also an effective and less invasive local treatment. Therefore, we assessed the role of addition of aggressive thoracical RT to first-line systemic therapy in patients with synchronous oligometastatic NSCLC. **Method:** Stage IV patients with measurable primary tumor and distant metastases number ≤5, histologically or cytologically confirmed NSCLC and ECOG PS≤2 were included. All enrolled patients had not previously experienced local or systemic antitumor treatment, including surgery (biopsy is allowed), first line chemotherapy, targeted therapy or immunotherapy. Other inclusion criteria included adequate organ function and life expectancy of >3 months. Our study randomized patients at 1:1 ratio to receive systemic therapy plus radiotherapy(RT+) or systemic therapy alone(RT-). First-line regimens recommended by NCCN guidelines are allowed for systemic therapy, including standard platinum-based doublet chemotherapy, targeted therapy, antiangiogenic therapy and immunotherapy. Three-dimensional conformal radiotherapy(3D-CRT) or Intensity modulated radiotherapy(IMRT) to primary thoracic foci or remediable oligometastatic focus should be given no later than disease progression. Randomization was stratified by histological type (squamous cell carcinoma vs. adenocarcinoma), first-line systemic therapy (targeted therapy vs. non-targeted therapy), intracranial metastasis (yes vs. no), number of metastases (1 vs. 2-5) and local stage (I/II vs. III). Primary endpoint of this study is progression-free survival(PFS) based on RECIST v. 1.1 criteria. Secondary endpoint are local tumor control; oligometastatic foci control; thoracic progression-free survival(TPFS); overall survival(OS); toxicity and compliance. The study has 80% power to detect a greater effect of RT+ group in PFS at a 2-sided alpha level of 0.05. Assuming a 10% drop-out rate, randomization of 148 patients was planned. The trial opened in China in November 2017. To date, 14 patients have been randomized and 2 sites in China have activated the trial. Support: 81572279, 2016J004, LC2016PY016, 2018CR033. Clinical trial information: NCT03119519. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Non-Salvage Radiotherapy, Synchronous Oligometastatic NSCLC, Aggressive Thoracical Radiotherapy

EP1.08-06 POSTOPERATIVE OLIGO-RECURRENCE OF NON-SMALL CELL LUNG CANCER

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Background: Postoperative recurrences of non-small cell lung cancer (NSCLC) are usually disseminated and systemic. The concept of oligo-recurrence, defined as a small number of new lesions at a distant site theoretically curable by local therapy, has recently been proposed for several cancers. The aim of this study was to clarify clinical features and outcomes of patients with postoperative oligo-recurrence of NSCLC. **Method:** From 364 patients who underwent resection for NSCLC between January 2008 and December 2017 at our hospital. A total of 43 patients who developed recurrence were included in this study. Oligo-recurrence was defined as 1-2 loco-regional or distant recurrence lesions restricted to a single organ. Other recurrences were classified as poly-recurrence. Local therapy included surgery, stereotactic radiotherapy and radiotherapy. **Result:** Oligo-recurrence was identified in 12 (27.9%) patients, mainly as a solitary recurrence (n=11, 91.7%) in regional lymph nodes (n=1), surgical stump (n=2), brain (n=5), lung (n=1), bone (n=2) and liver (n=1). Primary tumor histopathological types included 9 cases of adenocarcinoma, one case of squamous cell carcinoma, one case of pulmonary pleomorphic carcinoma and one case of large cell neuroendocrine carcinoma.The patients with oligo-recurrence had a longer time to recurrence than those with poly-recurrence (median: 23.5 months, 11.0 months). A case of mediastinal lymph node recurrence was performed radiation therapy. A case of surgical stump recurrence underwent lobectomy and other case was performed concurrent chemo-radiotherapy. 4 case of brain metastasis were underwent tumor resection and were performed stereotactic radiotherapy, one case of brain metastasis was performed stereotactic radiotherapy only. A case of lung metastasis underwent wedge resection and was used EGFR-TKI. A case of bone recurrence was performed radiation therapy and was used EGFR-TKI, other case was performed concurrent chemo-radiotherapy. A case of liver metastasis underwent tumor resection. 7 of 12 cases confirmed re-recurrence after local therapy. But 9 patients were alive between 30.4 and 110.0 months after local therapy, whereas three of 5 brain metastatic patients died between 24.9 and 71.8 months. The 5 year overall survival rates after local therapy were 81.5%. **Conclusion:** The presence of oligo-recurrence can predict a favorable prognosis in patients with NSCLC treated with aggressive local therapy.

Keywords: oligo-recurrence, non-small cell lung cancer, local therapy

EP1.08-07 CORRELATION BETWEEN GENETIC PROFILING AND RESPONSE IN DANISH ALK-POSITIVE NSCLC PATIENTS TREATED WITH CRIZOTINIB

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Background: In 2011 Crizotinib received FDA approval for the treatment of *ALK*-positive NSCLC. Due to large diversity in clinical course of these patients, baseline genomic profiling at diagnostic biopsy was performed to find possible correlations with clinical features. **Method:** We performed a retrospective analysis of 28 consecutive patients receiving Crizotinib for metastatic, immunohistochemistry (IHC)- and fluorescens in-situ hybridization (FISH)-determined *ALK*-positive NSCLC, between September 2011 and DATE. Clinical data were collected by chart review. DNA/RNA genomic profile were performed using the patients' biopsy at the time of diagnosis or at initiation of therapy using targeted next-generation sequencing (NGS) Oncomine™ Focus (ThermoFisher Scientific) and Archer® Solid Tumor (ArcherDx) assays. Baseline clinical features and genetic information were correlated with overall survival and progression free survival. **Result:** The cohort included 15 women and 13 men, median age 56 (range 22-83). Median PFS was 5.2 months (CI 2.9-9.5), median OS was 17.3 months (CI 8.8-33.2). Favorable prognostic factors for both PFS and OS were PS 0-1 vs 2 (n=25), male gender (n=13), never smoking (n=18) and up-front brain metastasis (n=6). Fourteen patients were treated with Crizotinib as 2nd line therapy and had better OS, but similar PFS. Crizotinib-responders (CR+PR+SD) represented 71% and -no responders (PD) 29%. Most patients received further treatment after progression on Crizotinib (68%). The most common *ALK*-fusion-partner was EML4 (64%; of which 50% were variant v1, 28% v2, 22% v3). For 8 patients (28%) no fusion partner was identified. In 7 cases (25%) the FISH-detected *ALK*-rearrangement was not confirmed by IHC and NGS and 4 of them did not respond, 1 case (4%) was FISH-/IHC-positive but NGS-negative and responded. Four of 8 non-responders (all 4 IHC-negative, 3 NGS-negative) showed another *de novo* gene-alteration (in KRAS, ALK or EGFR). Two patients with another fusion-partner: KIF5B(17)-ALK(20) and TEMP3(6)-ALK(20) had an aggressive clinical course after short-term response. In contrast, a patient with pre-existing *ALK*-mutations F1174L and R1275Q, had the longest duration of treatment with Crizotinib (2.5 years). Patients with EML4 fusion-partner (n=18) were prone to achieve better OS than the others. Rebiopsies at progression for 8 patients showed different TKI-resistance mechanisms. **Conclusion:** *ALK*-positive NSCLC represents a heterogenous disease, which in most cases can be encapsulated by ALK-TKI. Although this small cohort does not allow to draw unambiguous conclusions, it does indicate that the efficacy of treatment may vary with different *ALK*-fusion-partners. Moreover, *ALK*-positive NSCLC should be validated and classified by NGS-testing at baseline to optimize the choice of ALK- TKI.

Keywords: ALK positive NSCLC, DNA-NGS, RNA-NGS

EP1.09 PATHOLOGY

EP1.09-01 SUITABILITY OF QUBIT RNA IQ TO DETERMINE THE RNA QUALITY OF FFPE SAMPLES IN CANCER GENOMIC MEDICINE

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Background: Nucleic acid evaluation of formalin-fixed, paraffin-embedded (FFPE) samples by next-generation sequencing (NGS) is essential in cancer genomic medicine. In this study, our aim was to examine the suitability of the Thermo Fisher Scientific Qubit RNA IQ Assay to evaluate RNA quality by using pigments selectively binding to large or small RNAs, and rapidly measuring fragment percentages with a fluorophotometer. **Method:** RNA was extracted from FFPE samples (n = 35) prepared in clinical settings. DV200 (low: 30-50%, medium, 50-70%, high: > 70%) and RNA IQ (low-high: 1-10) values, which are recommended as indicators of RNA quality, were determined and the correlation between them was examined. By using NGS analysis to obtain the overall percentage of aligned reads (%) and comparing this to the RNA IQ values (15 samples), the suitability of RNA IQ as a tool for RNA quality evaluation was determined. **Result:** The correlation coefficient (*r*) between DV200 and RNA IQ values was 0.72, indicative of a strong correlation. However, a scatter diagram revealed that 4-7 samples used to determine the RNA IQ values accounted for 11.4% of the DV200 values (< 30%) that were not recommended for use as NGS samples. In the scatter diagram showing the overall percentage of aligned reads (%) and the RNA IQ levels, the correlation coefficient between aligned reads (> 50%) and RNA IQ levels > 4 was 0.54, representing a moderate correlation. However, RNA IQ values > 4 accounted for 33.3% (false-positive rate) of the aligned reads (< 50%). **Conclusion:** NGS analysis demonstrated a high false-positive rate for RNA IQ values. Therefore, further optimization is needed prior to utilizing this method as an indicator of RNA quality for FFPE samples in cancer genomic medicine.

EP1.09-02 EXPRESSION OF INTRATUMORAL GFPT2 IN LUNG ADENOCARCINOMA

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Background: Cancer cells exhibit abnormal proliferation and require large amounts of nutrients. In cancer tissues, the observed changes in metabolism are associated with an altered metabolic pathway. Moreover, an elevated uptake of glucose has been demonstrated in proliferating cancer cells. Glutamine fructose-6-phospate aminotransferase 2 (GFAT2) - coded by the glutamine-fructose-6-phosphate transaminase 2 (*GFPT2*) gene – is a metabolic enzyme involved in the hexosamine biosynthesis pathway (HBP). In normal cells, the glucose used for the HBP is in small amounts. However, in cancer tissues, the activation of the HBP influences tumor progression. In this study, we investigated the expression of *GFPT2* in the tumor microenvironment of lung adenocarcinoma. **Method:** The expression of*GFPT2* in tumor cells and cancer-associated fibroblasts was examined through immunohistochemistry in 31 patients with surgically resected adenocarcinoma. Histopathological subtype, tumor stage, other clinicopathological conditions, and survival rate were compared with the level of *GFPT2* expression. **Result:** Expression of *GFPT2* in tumor cells and cancer-associated fibroblasts was detected in 87% of patients. In the tumor microenvironment, the expression of *GFPT2* was significantly lower in patients with AIS and MIA versus that observed in patients with invasive adenocarcinoma. Notably, overexpression of *GFPT2* in the tumor microenvironment was associated with a poor-5-year survival rate. **Conclusion:** Activation of the HBP is implicated in the development of lung adenocarcinoma. This result may be helpful in predicting worse prognosis, and the HBP may carry therapeutic potential in this setting.

Keywords: lung adenocarcinoma, GFPT2, hexosamine biosynthesis pathway

EP1.09-03 INTEROBSERVER VARIABILITY STUDY OF PD-L1 IMMUNOSTAINING IN NON-SMALL CELL LUNG CANCER

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Background: Pathologic assessment of programmed cell death ligand 1 (PD-L1) immunohistochemical staining now have been used for treatment of non-small cerll lung cancer in advanced stage. But, due to misinterpretation or unspecified staining pattern, interpretation of PD-L1 staining may be difficult. This study was to investigate interobserver variability between three different pathologists to see if the staining can be safely assessed in practice. **Method:** PD-L1 immunostaining (SP263 and SP142) was performed in representative sections of 70 adenocarcinoma cases and 58 squamous cell carcinoma cases which surgically resected at the chonnam National University Hwasun Hospital, Republic of Korea between 2013 to 2015. Three pathologists individually evaluated the percentage of positive tumor cells, scoring each sample applying cutoff levels used in clinical practice: < 1% positive tumor cells (score 0), 1–4% (score 1), 5–9% (score 2), 10–49% (score 3), and >50% positive tumor cells (score 4). **Result:** Three pathologists were in

agreement in 121 of 128 (94.5%) of scored cases in the SP263 test and 109 of 128 (85.2%) in the SP142 test. In 26 remaining cases, at least two pathologists were in aggrement of scored cases. Weighted kappa value for interobserver variability between pathologists was respectively 0.892 in the SP263 test and 0.837 in the SP142 test. The number of differently classified cases was significantly higher for the ≥1% cutoff value than every other cutoff value. Also, a significantly better agreement between pathologists was seen using ≥50% as cutoff. No statistically significant differences were seen between adenocarcinoma and squamous cell carcinoma. **Conclusion:** Interobserver agreement remains an important challenge, and the ≥1% cutoff value seems to be problematic. But, this may be overcome by training, longer experience and optimization of cutoff value.

Keywords: PDL1, Non-Small Cell Lung Cancer, Interobserver

EP1.09-04 GATA-3 EXPRESSION IS A POOR PROGNOSTIC MARKER IN RESECTED NON-SMALL CELL LUNG CARCINOMA

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Background: GATA transcription factors play a wide role in determination of cell differentiation and control of cell proliferation and movement. GATA binding protein-3 (GATA-3) is a member of the GATA family and it plays decisive roles in the differentiation and maintenance of normal luminal cells and the development of Th2 lymphocyte. Decreased GATA-3 expression is associated with poor prognosis in breast cancer. On the other hand, GATA-3 expression correlates with poor prognosis in peripheral T cell lymphoma. However, the correlation of GATA-3 expression with non-small cell lung carcinoma (NSCLC) remains unclear. The aim of this study is to examine the clinicopathological and prognostic value of GATA-3 expression in surgically resected NSCLC. **Method:** A total of 842 NSCLC were examined. The male:female ratio was 515:327; the age range was between 38 and 85 years of age and the mean age was 71 years. Pathological stage's ratio (0:I:II:III) was 37:553:151:101. Adenocarcinoma:Squamous cell carcinoma:Others' ratio was 602:200:40 in histology. Adjuvant chemotherapy was performed in 188 patients. The follow up duration was from 0.4 months to 168.7 months and the mean duration was 61.9 months. Tissue microarray was constructed and GATA-3 expression was analyzed using immunohistochemistry (clone L50-823, F. Hoffmann-La Roche, Ltd., Basel, Switzerland). The GATA-3 staining percentage in tumor cells were classified as follows: (Negative, 0-9%; Positive, 10%≤). The status of GATA-3 staining was correlated with clinicopathological backgrounds, molecular features and patient outcome. **Result:** The status of GATA-3 staining was as follows: Negative, 808 (96%); Positive, 34 (4%). GATA-3 expression status was associated with sex, smoking history, pathological stage, histology, pleural invasion, p53 protein expression, MIB-1 labeling index and *EGFR* mutation. Both overall survival (OS) and recurrent-free survival (RFS) were significantly worse in the patients with positive expression of GATA-3 in comparison with those with negative expression of GATA-3 (5-year OS, 55.7% vs. 74.8%, p=0.006; 5-year RFS, 51.5% vs. 66.8%, p=0.016, respectively). In multivariate analyses adjusting for sex, year, smoking history and pStage, positive expression of GATA-3 was found to be an independent predictive factor of both OS (HR=1.76, 95%CI: 1.02-3.05; p=0.042) and RFS (HR=1.66, 95%CI: 1.01-2.74; p=0.046). **Conclusion:** GATA-3 expression is correlated with poorer prognosis for both OS and RFS in resected NSCLC. Therefore, the evaluation of GATA-3 expression by immunohistochemistry is a potentially useful prognostic marker for postoperative period.

Keywords: GATA-3, NSCLC, prognosis

EP1.09-05 CORRELATION OF ROS1 (D4D6) IMMUNOHISTOCHEMISTRY WITH ROS1 FISH ANALYSIS IN LUNG ADENOCARCINOMA: IS IHC A RELIABLE SCREENING TOOL?

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Background: ROS1 gene rearrangement in the lung adenocarcinomas is a one of the targetable non- overalapping genomic alterations (1-3%) besides, EGFR mutation, KRAS mutation, ALK fusion, and many others in patients with non small cell lung carcinomas. Lung adenocarcinoma that exhibit ROS1 gene rearrangement, respond to the targeted inhibitor, crizotinib. Various techniques such as Fluorescent in situ hybridization(FISH), immunohistochemistry(IHC), next generation sequencing and RT Polymerase chain reaction are used to detect ROS1 mutations. We evaluated the correlation between ROS1 IHC and FISH analysis considering FISH as the gold standard method to determine the utility of IHC as a screening method for lung adenocarcinoma. **Method:** Twenty-nine lung adenocarcinoma patients were retrospectively analyzed for ROS1 rearrangement. Each case underwent IHC and FISH analysis. ROS1 IHC was performed using D4D6 antibody clone on Ventana Benchmark platform. A positive and a negative control were run with each case. The analysis was based on H score system that calculates a score from 0 to 300 according to both the intensity of tumor cells (cytoplasmic) staining and the percentage of cells stained. FISH analysis was performed on the tumor area marked on Hematoxylin and Eosin stained slides. Dual colour break apart probe was used and the hybridization pattern was considered positive when > 15% of the tumor cells scored showed a gene rearrangement involving the ROS1 gene. **Result:** Among a total of 29 cases, 17 cases were positive by IHC and FISH analysis (true positive) while seven cases were negative by both the techniques (true negative). Four cases were positive by IHC but were negative on FISH analysis (false positive by IHC) and one case was found to be negative on IHC but positive by FISH analysis (false negative). Subsequently various indicators were calculated as shown in table 1.

Indicator	Value	95% Confidence interval
Sensitivity	94.44%	72.71% to 99.86%
Specificity	63.64%	30.79% to 89.07%
Positive likelihood ratio	2.6	1.18 to 5.72
Negative likelihood ratio	0.09	0.01 to 0.62
Positive predictive value	80.95%	65.86% to 90.35%
Negative predictive value	87.50%	49.74% to 98.02%
Accuracy	82.76%	

Conclusion: 1. ROS1 IHC using antibody D4D6 has high sensitivity but the specificity of detection of ROS1 gene rearrangement is low. 2. All cases that are positive by ROS1 IHC, should be confirmed by FISH testing and this stands as a reliable and economic approach to screen ROS1 positive lung adenocarcinomas.

Keywords: ROS1, immunohistochemistry, FISH, screening

EP1.09-06 AN UNUSUAL DIAGNOSTIC CASE OF HYPOGLYCEMIA: A DIFFERENT PERSPECTIVE OF THE DOEGE-POTTER SYNDROME

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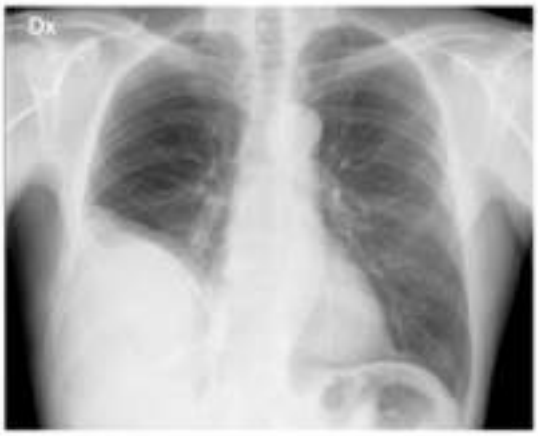
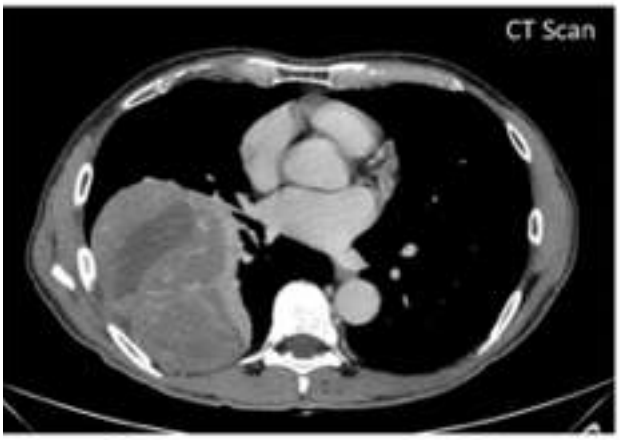
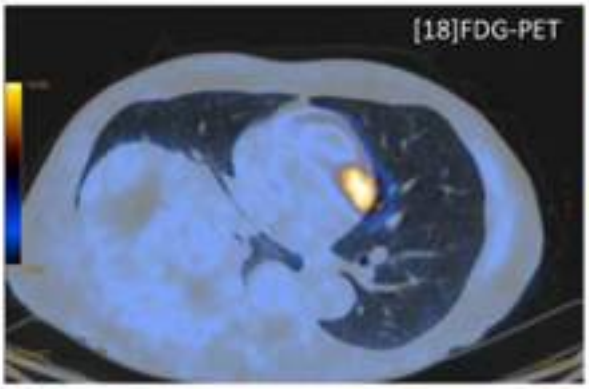
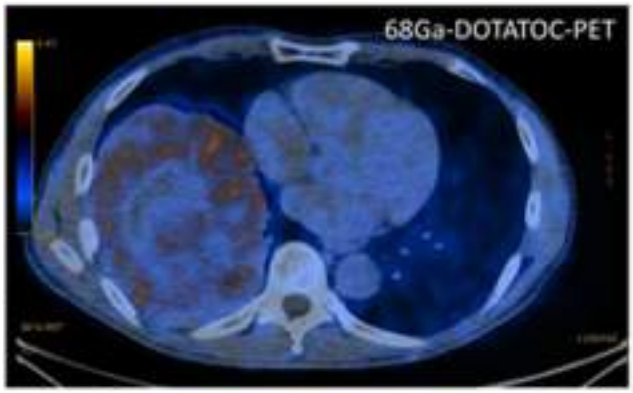
Background: Solitary fibrous tumor (SFT) is an uncommon type of mesenchymal tumor that can occur anywhere in the body. A typical molecular feature is a NAB2-STAT6 fusion, that enhances cellular proliferation. Symptoms are often related to the mass effect exerted by the tumor, but paraneoplastic syndromes can occur. Among them the Doege-Potter syndrome, characterized by refractory hypoglycemia, occurs in <5 % of cases. **Method:** A 60 years-old

male patient was admitted to the hospital because of a recent severe recurrent hypoglycemia and an episode of syncope during his tennis play. No clinical history of co-morbidities were identified at the time of E.R. admittance. Blood tests were performed and endogen insulin, C-peptide and ACTH levels were below the lower limit, serum cortisol was low-normal. Ca125.5 and NSE were slightly elevated. Total body CT-scan revealed, in the right lung, a large mass (cranio-caudal extension 17 cm) dislocating the adjacent structures. While [18]FDG-PET was almost negative (SUVmax=2.6) the 68Ga-DOTATOC-PET showed faint focal uptake in patchy areas of the tumor (SUVmax=3.6). During diagnostic workup, hypoglycemia was treated with steroid administration.

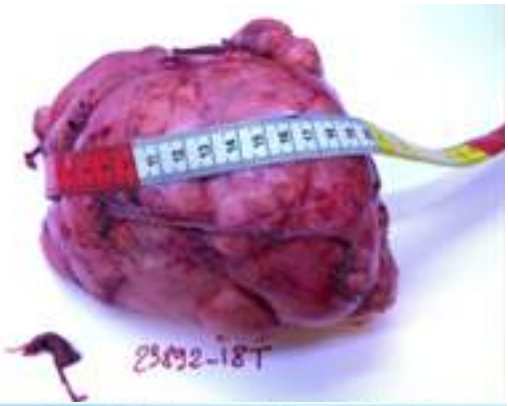


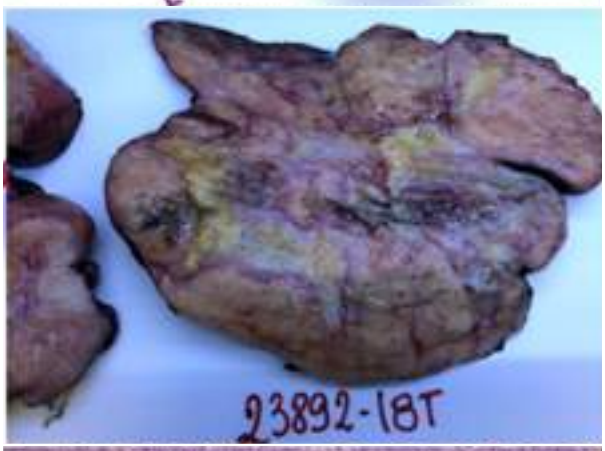


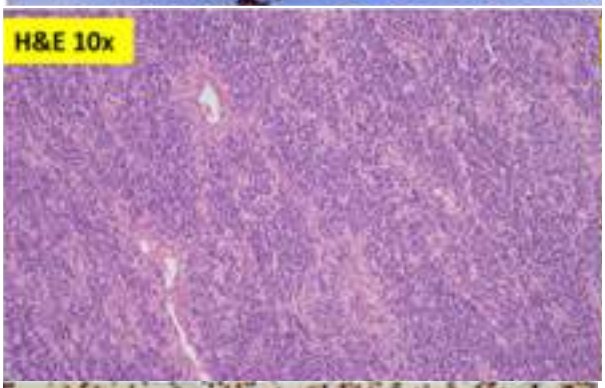


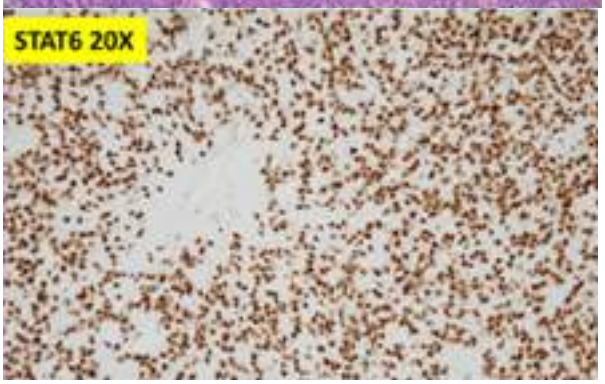


Result: The patient underwent surgical resection, through a right-sided postero-lateral ribs "bellows" spreading thoracotomy, for a 17x16cm sessile lesion originating from the visceral pleura of the middle lobe of the lung. The tumor cells did not express neuroendocrine(chromogranin), nervous(PS100), but showed CD34+ and STAT6+ cells, with a Ki-67<10%, confirming the diagnosis of SFT. Hypoglycemia resolved after tumor removal, coherently with the Doege-Potter syndrome. At 12 months from surgery the patient is alive with no evidence of disease.









Conclusion: Hypoglycemia can be the single symptom of malignant tumors, frequently seen with insulinomas, but in our case, it was associated with an SFT, a tumor with uncertain biological behaviour. Surgical resection of the tumor is the mainstay of treatment.

Keywords: Pleura, Doege-Potter syndrome, solitary fibrous tumor

EP1.09-07 DETECTION OF EGFR MUTATION BY AUTOMATED AND RAPID QPCR BASED BIOCARTIS IDYLLA™ SYSTEM IN LUNG CANCER PATIENTS

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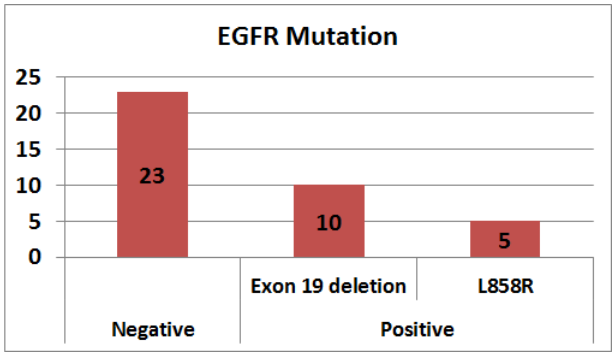
Background: Detection of EGFR mutations in subset of Non-small cell lung carcinoma (NSCLC) has significantly changed the therapeutic management strategies in lung cancer. The Biocartis Idylla™ EGFR detection system is used for the qualitative detection of EGFR mutations (exon 18 (G719A/C/S), exon 20 (T790M, S768I), exon 21 (L858R, L861Q) mutations, exon 19 deletions and exon 20 insertions). The system is unique as it covers the entire process from sample to result with an integrated sample preparation, followed by real time PCR amplification and detection of the targeted sequences. We present the data of series of 38 NSCLCs tested on this system with discussion on the advantages and disadvantages of the assay system. **Method:** A series of thirty-eight patients of NSCLC from July 2018 to March 2019 were included in the study. An H and E stained slide was prepared from the Formalin fixed paraffin embedded (FFPE) block to document the tumor content in each case. A cut off of 10-15% tumor content was set. About 10 sections were cut with a thickness of 10 micron. Using a new razor blade, the FFPE tissue sections were scrapped onto wet filter papers. Finally, the cartridges are loaded. The Idylla™ EGFR specific software (EGFR TTP) automatically analyzes the obtained PCR data. The test includes an integrated sample processing controls to verify adequate completion of the sample to the result process. The clinical and demographic data of these cases was analysed. **Result:** The median age of the population was 66 years. Male to female ratio was 1.5:1. Of total 38 cases, 15 were positive for EGFR mutation (39.4%). 10 cases were positive for Exon 19 deletion (66.6%) and 5 cases were positive for L858R mutation (33.3%).



Conclusion: 1. The Idylla™ mutation assay has an edge over conventional EGFR detection system of detecting 51 mutations and indels *versus* 21 mutations and indel. 2. Turn around time of this assay is average of 4 to 5 hours as compared to 12-48 hours of the conventional assay. 3. The system gains appreciation for minimum requirement of high end expertise required for the testing and interpretation of the results, making it valuable to reach to the masses and provide rapid treatment base for lung cancer patients. 4. The disadvantage of this system is the non-availability of extracted DNA for additional testing.

Keywords: Non small cell lung carcinoma, EGFR, IdyllaTM

EP1.09-08 PLASMA CIRCULATING FREE TUMOUR DNA IN ADVANCED LUNG ADENOCARCINOMA: EGFR TKI-NAÏVE

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Background: Molecular testing of tumour samples is therefore mandatory in routine clinical practice. Tumour DNA is also present as cell-free molecules in blood, which is therefore a very useful and convenient source of tumour DNA. Circulating tumour DNA (ctDNA) consists of short, double-stranded DNA fragments that are released into the circulation by tumour cell. With the advent of newer molecular platforms, ctDNA can be detected with high sensitivity and specificity in plasma. Aim of this study is to assess diagnostic accuracy of plasma circulating free tumour DNA (ctDNA) in advanced lung adenocarcinoma (EGFR TKI-Naïve) in several hospitals in Medan, Indonesia. **Method:** This was a cross-sectional study whose subjects were patients with adenocarcinoma obtained from histopathology and / or cytology and examined for EGFR mutations from plasma ct-DNA. Data analysis used *chi square test* and *fisher exact test*. **Result:** One hundred data have been collected, with male are 71 (71.0%), and 29 are female (29.0%). Found 20 mutations, single mutations from 19 tissue biopsies, del exon 19 as many as 12 cases (60.0%), deletion mutations in Exon 21 (L858R) 6 cases (30.0%), 1 case Exon L861Q (5.0%) and del Exon 19 and 21 L861Q double mutations 1 case (5.0%). From plasma ctDNA examination EGFR mutations were found 15 cases, del Exon 19:12 cases (80.0%), del Exon 21 (L858R) 3 cases (20.0%). Plasma ctDNA for detection of EGFR mutations has a sensitivity of 45.0%, specificity of 92.5%. It's means, all patients with EGFR (+) mutations, ctDNA managed to detect 45% of cases, while 55% of cases detected mutations (-). Then, all patients detected EGFR (+) mutations based on ctDNA, only 60% of cases have EGFR (+) mutations when examined by tissue will be EGFR (-) mutations. The positive predictive value of ctDNA is 60%. **Conclusion:** Plasma ctDNA can be used to detect EGFR mutations but cannot replace tissue biopsy as the gold standard.

Keywords: EGFR mutation, EGFR TKI-Naïve, lung adenocarcinoma

EP1.09-09 SURGICAL CASES OF PULMONARY PLEOMORPHIC CARCINOMA AT OUR INSTITUTION

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Background: Pulmonary pleomorphic carcinoma (PC) is rare with an incidence of 0.1% to 0.4% of all lung cancers. Because of its rarity, its exact characteristics are still unknown and standard treatment strategies have not been established. **Method:** The clinical features and prognosis of 19 surgical cases (1.5%) with PC among 1,247 cases of all resected lung carcinoma from August 2007 to September 2018 at Kanagawa Cardiovascular and Respiratory Center were retrospectively analyzed. **Result:** A total of 19 cases, 16 males (84.2 %) and 3 females (15.8 %) with a median age of 71±9.4 (range: 52-83) years was included in the analysis. The median of the brinkman index was 1060±662.8 (0-3000). Coexisting lung diseases included 1 case of chronic obstructive pulmonary disease (COPD) and 5 cases of interstitial pneumonias (IP). Tumors were located in the upper lobes in 10 cases and in the lower lobes in 9 cases. The median size of the tumors was 28 ± 22.9 (10-100) mm in diameter. The surgeries comprised 5 wedge resections, 2 segmentectomies, and 12 lobectomies, including 3 combined wedge resections, 2 combined angioplasties, and 1 double sleeve lobectomy. The epithelial components of PC were 11 adenocarcinomas, 5 squamous cell carcinomas (SQC), and 3 large cell carcinomas. There were 9 cases in stage I (IA1: 3, IA2: 3, IA3: 2, IB: 1), 4 in stage II (IIA: 2, IIB: 2), and 6 in stage III (IIIA: 5, IIIB: 1). All of the cases were followed-up, and the median follow-up period was 1124 ± 1066 (195-3845) days. After 5 years, 11 cases were alive (including 2 relapsed cases) and 8 cases had died (6 died from PC). The overall survival rate was 50.3% at 5 years in all cases. In univariate analysis, PC with both a SQC component and lymph node metastasis had a poor prognosis with a significant difference in the 3-year survival rate (component; SQC vs non SQC: 26.3% vs 73.7%, p=0.024) and in the 5-year survival rate (lymph node metastasis; positive vs negative: 36.8% vs 73.2%, p=0.026). In multivariate analysis, a SQC component (p=0.011) and lymph node metastasis (p=0.016) were independent prognostic factors indicating a poor OS. On the other hand, 8 of the 9 cases with a non SQC component and no lymph node metastasis were still alive. **Conclusion:** We found that PC generally had a poor prognosis even in surgical cases. A SQC component and lymph node metastasis were prognostic factors indicating a poor overall survival.

Keywords: pulmonary pleomorphic carcinoma, epithelial component, Lymph node metastasis

EP1.09-10 A DIAGNOSTIC PITFALL IN POSTERIOR MEDIASTINAL TUMOR: EXPRESSION OF CD117 IN ATYPICAL EWING SARCOMA MASQUERADING AS CLASSIC SEMINOMA

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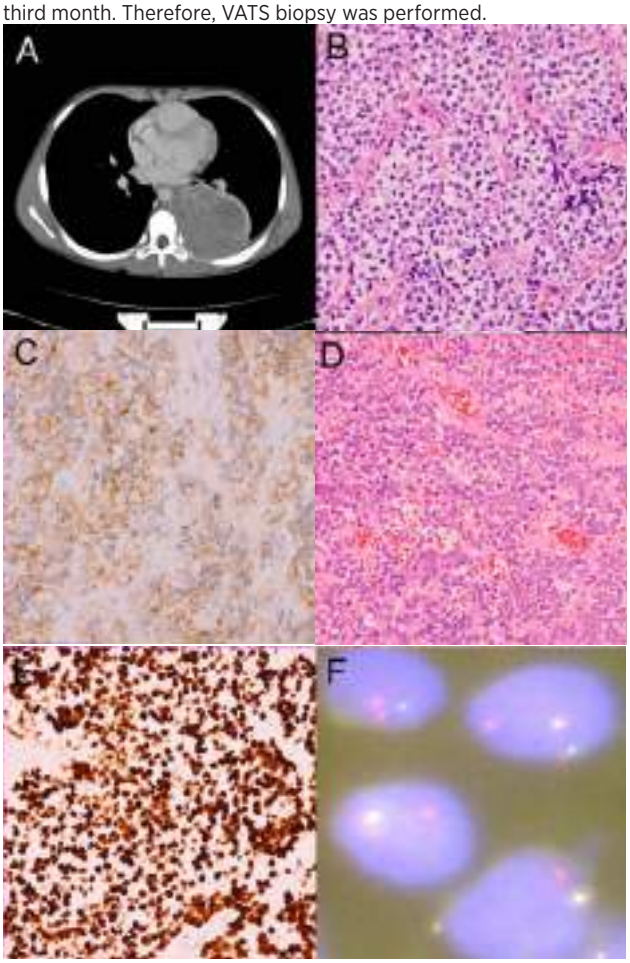
Background: Ewing sarcoma is a rare malignancy and occurs most commonly in metaphyseal-diaphyseal portion of long bones in children or young adults. Atypical Ewing sarcoma refers to unusual alterations at cell morphology and immunoprofile associated with atypical clinical presentation mimicking carcinomas, lymphomas, or other sarcomas, but still harbors *EWSR1* rearrangement. We recently encountered a case of atypical Ewing sarcoma involving the posterior mediastinum, which was initially misdiagnosed as seminoma based in part on CD117 expression by immunohistochemistry. **Method:** This 11-year-old boy without any systemic disease has been suffered from intermittent chest pain for months. CT scan showed a huge left thoracic tumor (7 cm, Fig 1A), centralized in the posterior-medial portion of mediastinum with adjacent rib destruction. The radiological findings were compatible with malignant neurogenic tumor or germ cell tumor. Microscopically, it showed tumor cell nests with oval nuclei, conspicuous nucleoli and abundant clear cytoplasm (Fig 1B). Immunohistochemically, the tumor cells revealed strong positivity for CD117 (Fig 1C). Based on the above findings, seminoma was diagnosed. A carboplatin-based regimen for malignant germ cell tumor, JEB (carboplatin, etoposide and bleomycin), was given and he finished two cycles. The tumor had initially decreased in size (4.5 cm) for the first two months but progressed again (7 cm) in the third month. Therefore, VATS biopsy was performed.



Result: Microscopically, it showed compact tumor cells in sheets, lobules or focal cord-like pattern with frequent necrosis, similar to the tumor cells seen in previous biopsy regarding both growth pattern and cell morphology. However, it also contained cells with high N/C ratio, finely dispersed chromatin (Fig 1D) and brisk mitotic activity (up to 24 mitoses per 10 HPFs) which were different from the cells of classic seminoma and prompted the consideration of atypical Ewing sarcoma and other small blue round tumors. After thorough immunohistochemical study, the tumor cells were positive for CD99 and NXK2.2 (Fig 1E), but also focally positive CD117. Fluorescent in situ hybridization demonstrated unbalanced *EWSR1* rearrangement (Fig 1F), confirming the diagnosis of atypical Ewing sarcoma. **Conclusion:** Atypical Ewing sarcoma could be present as a huge mediastinal mass with only partial rib destruction as well as strong CD117 expression, giving a false impression of primary mediastinal tumor and misdiagnosed as seminoma. Pathologists should always keep in mind this rare but lethal disease in the differential diagnosis. IHC of CD99 and NKX2.2 or even molecular test for *EWSR1* rearrangement would help pathologists make the right diagnosis.

Keywords: Seminoma, EWSR1 Rearrangement, Atypical Ewing sarcoma

EP1.09-11 LIPOID PNEUMONIA RESEMBLING BILATERAL LUNG CANCER: BE AWARE OF NASAL DECONGESTANTS!

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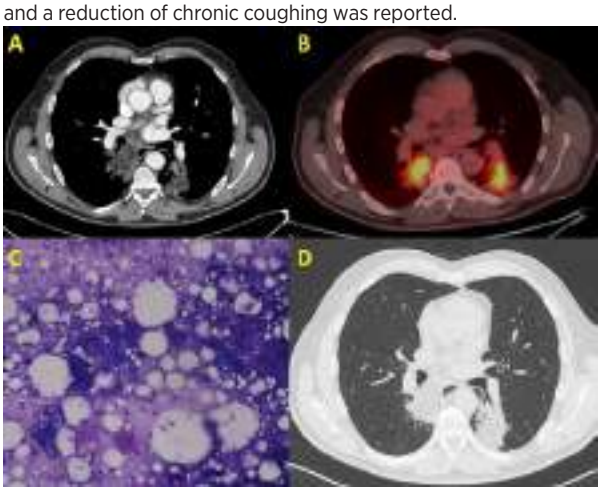
Background: To describe a case of bilateral exogenous lipoid pneumonia mimicking lung cancer in a patient affected by obstructive sleep apnea syndrome treated with decongestants mineral oils. **Method:** A 57 year-old male patient was referred to our surgical department for an incidental finding of a bilateral pulmonary mass during a chest X-ray made for chronic coughing. His past medical history was unremarkable; he was an everyday smoker with a 80pack/years and he was affected by obstructive sleep apnea syndrome. A chest CT and CT/PET scans was subsequently done and revealed the presence of a both pulmonary consolidations of the lower lobes bilaterally with increase in uptake of FDG (Fig. 1A-B): mediastinal lymph node was normal, no other lesions was found. Morphology of the lesions was strongly suspect for non small cells lung cancer, so the patient underwent a CT-guided lung biopsy. **Result:** A percutaneous CT-guided lung biopsy was done in the right lower lobe. The histological examination was consistent with pulmonary adenocarcinoma with signet-ring cell features (Fig.1C): therefore, the patient was addressed to conventional chemotherapy. At that point, a multidisciplinary discussion was done: a careful revision of the chest CT-scan was carried out and focal areas of fat attenuation within the lung consolidations were observed. According to that finding, a diagnosis of lipoid pneumonia was hypothesized. A more careful questioning about patient's medical history revealed the use of daily nasal decongestants during the last 4 years due to chronic rhinitis secondary to OSAS: the drug was composed of mineral oils. A further blind revision of the histological tissue samples was requested and confirmed the diagnosis of exogenous lipoid pneumonia. The patient was invited to discontinue the nasal oil decongestant. No other pharmacological treatment was started. Six months later, a chest CT-scan was performed but no significant changing of the pulmonary consolidations were observed (Fig. 1D). Currently, the patient is well and a reduction of chronic coughing was reported.



Conclusion: Exogenous lipoid pneumonia is a rare condition that might be misdiagnosed with lung cancer; for this reason it should be considered in the differential diagnosis of pulmonary consolidations, especially when occurring bilaterally. A precise medical history could be resolutive.

Keywords: Pathology, NSCLC, LIPOID PNEUMONIA

EPOSTERS

EP1.09-12 LUNG CANCER IN KENYA: QUANTIFICATION OF THE PROBLEM

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Background: Objective As part of MLCCP to establish a baseline of lung cancers in Kenya. **Method:** s Setting I: A Retrospective review of lung cancer diagnosis at Eldoret Cancer registry 1995-2017; 310 analyzed. Setting II: All those with lung masses at radiology unit from 2014- 2018 ;78 lung masses noted. Setting III: Data from a large private laboratory group- 514 cases that were biopsied, 279 malignant vs 235 others. **Result:** s Setting I: 310 lung malignancies. Primary lung 102 (32.9%). M: F was 1:1. Mean age, and range in years was 60.3±1.2 and 29-98. NSCLC 81.4% and SCLC 18.6%. Adenoca 62.7%, SCC 21.7%, large cell carcinoma 6.0%. Staging on 18 patients, 14 had stage IV disease. Age 55-74 accounted for 61.7% Setting II: From Rad unit Biopsies done mainly by CT-guidance (31/73), Ultrasound guidance (20/73), bronchoscopy (19/73) and Thoracotomy (3/73). Of 78 cases, 50 (64.1%) were malignancies. Lung cancer had 34 of the 50. Mean age 57.1 range 32-84 yrs with median 61. Males were 21 (67.8%) and females were 13 (38.2 %) NSCLC was 83.4% and SCLC was 17.6%. Adenoca accounted for 82.14% of NSCLC. Clinical data was available on 10 of the 34 cancer patients and indicated Stage IV in 80% of them. Setting III: Of the 279 malignant cases from the private lab facility, Primary lung cancer had 209 patients (74.9%). Other metastatic cancers;Metastatic carcinoma 4.7%, CUP 4.3%, Neuroendocrine 3.6%, Carcinoid tumor 1.8%, sarcoma, spindle cell tumor, lymphoma and others. M:F 116 (55.5%) vs 86 (41.2%). 61 av. age at diagnosis, range 23-94 yrs. NSCLC was 91.8% of all cases, SCLC was 8.2%. In NSCLC, Adenocarcinoma 129 (61.7%), SCC 20% and others 20% Others-TB, Pna, Aspergillosis, Benign tumors, Fibrosis, Bronchiolitis Obliterans etc. **Conclusion:** High index of suspicion, education and training is needed to improve diagnostics in Lung cancer in Kenya. Bio-banking of tissue and more research i.e Evaluation of mutations; EGFR, ALK, ROS1, MET, BRAF, HER2, PDL1, MAPK, PI3K signaling pathways may be useful to define mechanisms of drug sensitivity and potential molecular targets in our setting. There is a need to fully characterize, optimally treat and measure outcomes of lung cancer in Kenya. *MLCCP is a Multi-National Lung Cancer Control Program with Dr. Asirwa the overall PI for Kenya, Tanzania, Swaziland and South Africa. Funding for the program has been provided by Bristol Myers Squib Foundation (BMSF) *MLCCP Team is the Team for this Kenya Program Component

Keywords: KENYA, RETROSPECTIVE STUDY, Lung cancer

EP1.09-13 CLINIC-PATHOLOGICAL AND MOLECULAR FEATURES OF PD-L1 ANALYSES IN ADVANCED NSCLC: A REAL LIFE SINGLE CENTER EXPERIENCE

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Background: Programmed death ligand 1 (PD-L1) immunohistochemistry (IHC) is the most rapid, less expensive and routinely applied predictive assay for treatment with immune checkpoint inhibitors (ICI) in advanced non small cell lung cancer (NSCLC). We analyzed a real-life single center activity of PD-L1 characterization together with pathological features, molecular status determination and patients' clinical response to ICI. **Method:** From January 2017 to July 2018 all advanced NSCLC tumor tissue analyzed for PD-L1 expression and molecular status determination in the Pathology Unit of San Luigi Hospital, Orbassano (Turin) were selected. PD-L1 analysis was performed using 22C3 PharmDX on Dako Autostainer, while ALK rearrangement was assessed by FISH and EGFR mutations by direct pyrosequencing. Furthermore in a majority of cases (60%) a 22-gene panel was evaluated by Ion Torrent PGM™ Next Generation Sequencing (NGS). The PD-L1 IHC assay results were analyzed with cut-off values of >50% (strong positive), 1-49% (weak positive), and <1% (negative). Clinical data of response to ICI were acquired for 65 patients. **Result:** 510/532 (96%) cases were adequate for PD-L1 determination and molecular analyses; 169 (33%) were histological, 269 (53%) core biopsies and 72 (14%) cytological samples; 375 (74%) were from primitive lesion, while 135 (26%) were from metastatic sites. Of the 22 inadequate samples for PD-L1 analysis half of them were cytological specimens. PD-L1 was strong positive in 91 (18%) cases, weak positive in 137 (27%) cases and negative in 285 (56%) cases. Specimens with higher expression (>50%) derived preferentially from histological samples (e.g. surgical specimens) and from external hospitals referred to our Central Hub. EGFR and ALK positive cases were more frequently PD-L1 negative or weak positive (13% and 2%, respectively), although not reaching statistical significance. Instead, KRAS and TP53 mutated cases were significantly associated with negative or weak positive PD-L1 expression (14% and 22%, chi-square p=0.0006 and p=0.01, respectively). Among the 65 patients with clinical data of response to ICI, 37/65 (57%) were responders (partial response + stable disease) while 28/65 (43%) had progressive disease. No significant differences in terms of clinic-pathological or molecular features were found between these two groups, maybe due to the limited number of cases. **Conclusion:** Our analyses suggest that integration of PD-L1 testing in the pathological and molecular characterization of advanced NSCLC is feasible with a very high adequacy, enabling a wide ICI administration to these patients.

Keywords: Adequacy, molecular analyses, PD-L1

EP1.09-14 BEST PRACTICE SESSION ON LUNG CANCER MOLECULAR DIAGNOSTICS IN THE NETHERLANDS TO ENHANCE TESTING PROPORTIONS NATIONWIDE

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Background: Adequate and timely testing for genetic alterations in lung cancer is necessary to consider targeted therapy. Previously, we demonstrated that in the Netherlands molecular testing was suboptimal in 2015, as 25% (EGFR and/or KRAS and ALK) to 50% (ROS1) of patients were not tested according to the guidelines, and notable variation between laboratories was present. Results were fed back to individual laboratories. In a best practice session, we aimed to identify a process for best possible flow and highest possible testing proportions. **Method:** We invited pathologists, molecular biologists, pulmonologists, and technicians from six laboratories/hospitals with highest testing proportions to join a best practice session. Ultimately, four laboratories, two academic and two non-academic, joined. Following a questionnaire, we discussed their work flow and why they think their laboratory/hospital performs well. **Result:** We identified several stimulatory factors for molecular testing: 1. discuss all metastatic lung cancer patients at multidisciplinary meetings; 2. dedicated/specialized professionals; 3. short communication lines and clear agreements; 4. work culture of critical openness and honesty; 5. awareness and feedback on performance; 6. comprehensive request by the pulmonologist of all genes to be tested; 7. to obtain sufficient tumor tissue: a. perform CT-scan earlier in process, making it possible to collect larger biopsies in case a metastasis is detected, and b. embed cytological material. Costs, without reimbursement, were seen as a prohibitive factor. **Conclusion:** Several elementary steps (such as good communication) to improve adequate molecular testing were revealed. Initiatives will be taken to implement the outcomes nationwide, by starting a dialogue with health care professionals at a regional level.

Keywords: molecular pathology, best practice, metastatic NSCLC

EP1.09-15 UNUSUAL MALIGNANCIES OF LUNG-EXPERIENCE FROM A TERTIARY CARE CENTRE OF EASTERN INDIA

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Background: Carcinoma lung accounts for 12.3% of all malignancies globally and is the leading cause of deaths due to malignancies.Pathologically,among various types of lung carcinomas;adenocarcinoma,squamous cell carcinoma,small cell and large cell carcinoma are the common varieties encountered.However there are certain uncommon variants of malignancies arising in lung which require distinct diagnostic and management approach and hence pose a challenge to the oncologist.Hereby we present our experience with some of these unusual pathologic variants of lung malignancies with relevant literature review. **Method:** A retrospective

analysis was done from the hospital records of patients visiting at a tertiary cancer hospital of eastern India between June 2013 to December 2018. All patients with biopsy or cell block proven diagnosis of lung malignancies were included in the study. Common pathological types of lung carcinoma such as adenocarcinoma,squamous cell carcinoma and small cell carcinoma were excluded from the study. **Result:** Among a total of 216 lung malignancies presented during this time period, six patients presented with unusual pathological variants such as: synovial sarcoma,lymphoma(diffuse large B cell lymphoma),neuroendocrine carcinoma,mucoepidermoid carcinoma,basaloid squamous cell carcinoma and adenosquamous carcinoma(one case from each pathological type). All six patients in the study were male with age range 31-74 years(median-49 years). Out of these six cases,laterality was evenly distributed i.e three cases had malignancies on left lung whereas in other three cases right lung was involved. Three patients had distant metastasis during presentation(synovial sarcoma, adenosquamous carcinoma and DLBCL) whereas other three patients were nonmetastatic at presentation. The presentation,histopathological diagnosis and immunohistochemistry,treatment received and followup of the patients are briefly summerised in the table. Among these six patients,one has died(adenosquamous carcinoma),one has lost followup and four patients are on followup (range-2-24 months).

Conclusion: Unusual malignancies of lung pose a diagnostic and therapeutic challenge to the oncologist in clinical practise owing to paucity of relevant data and insufficient studies. However they are treated according to the specific histopathologic subtype and stage of presentation. More studies are needed to be conducted regarding this subgroup of malignancies and their management

Keywords: unusual malignancy, atypical lung pathology, carcinoma lung

Table showing clinicopathological and treatment details of patients

sl no	sex	Age (yrs)	laterality	histopathology	IHC	stage at presentation	mets	treatment	f/u
1	m	37	left	synovial sarcoma	Bcl-2,CD99+, CD34-,CK7-	III	no	3X(adriamycin+ifosfamide) --progressive disease	lost to f/u
2	m	67	left	adenosquamous carcinoma		IV	Bone (clavicle,rib)	6X(paclitaxel+carboplatin) --zolendronate,tab gefitinib	Death after 8 mnth f/u
3	m	48	right	neuroendocrine carcinoma	Synaptophysin, Chromogranin A+ve, TTF-1 weakly +ve	III	no	3XEP--excision of mediastinal mass with rt upper lobectomy	24 mnth
4	m	50	right	DLBCL	CD45,CD20,BCl2+	IV	adrenal gland	6XRCHOP--2XRituximab+prednisolone	2 mnth
5	m	74	right	basaloid squamous cell carcinoma	panCK,p40,p63+,-Mib-1>70%	IIIA	no	3X(gemcit+carbo) --partial response--CCRT	15 mnth
6	m	31	left	mucoepidermoid carcinoma	p63,CK5/6/7+, Her2neu+	IIIA	no	thoracotomy & resection--4XTCH--maintenance TrastuzumabX14	2 mnth

EP1.09-16 A CASE OF PULMONARY PRIMARY ENTERIC ADENOCARCINOMA DIAGNOSED PREOPERATIVELY

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Background: Pulmonary primary enteric adenocarcinoma(PEA) is a extremely rare subtype of lung cancer, which is defined in the new edition of 2015 WHO classification. Its histopathological and immunohistochemical feature is close to colorectal carcinoma, and it is important to distinguish between PEA and metastasis from colorectal carcinoma. In the paper, we present a case of PEA diagnosed before surgery. **Method:** Case report **Result:** A 72-year-old male was attending our hospital for rheumatoid arthritis, Thirty eight mm nodule in diameter was pointed out at the right S^9 lung area by follow-up CT of interstitial pneumonia. The patient was refered to our department and TBLB was performed. Histopathological examination revealed that the tumor formes ducts composed of tall columnar cells. Immunohistochemical stains demonstrated positive for CK20, Cdx-2 and negative for CK7, TTF-1 and NapsinA. These findings were suggested metastatic colorectal carcinoma of the lung. However, additional clinical examinations, including FDG-PET/CT, gastroscopy and colonoscopy, did not reveal any existance of tumor elsewhere. The CEA level was 20 ng/ml. The patient was given a diagnosis of primary lung cancer, Pulmonary primary enteric adenocarcinoma staged as cT2aN0M0 stageIB was considered and right lower lobectomy with systemic lymph node dissection was performed. Final histopathological findings of the tumor was same as colorectal carcinoma. Immunohistochemical examinations were also the same as TBLB specimens. The final diagnosis was PEA and the staged as pT2aN0M0 stageIB. **Conclusion:** PEA is difficult to confirm histopathologically or immunohistologically, and it is necessary to deny the existence of gastro intestinal carcinoma. At present, treatment of PEA should be conducted as primary lung cancer, including operation. It is thought that the biologic and clinical feature of PEA becomes crear by accumulation of more cases.

Keywords: Pulmonary primary enteric adenocarcinoma, histopathologically, immunohistologically

EP1.09-17 SPANISH LUNG CANCER BIOMARKER TESTING REGISTRY (LUNGPATH): DESCRIPTIVE ANALYSIS FOCUS IN ALK TRASLOCATION RESULTS

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Background: Oncogenic ALK gene rearrangements are found in approximately 4% of non-small cell lung cancer (NSCLC). Treatment options such as ALK tyrosine kinase inhibitors lead to improved progression free survival and overall survival. Thus, biomarker testing on pathology specimens is an essential requirement to properly treat lung cancer (LC) patients. *LungPath* is an on-line tool developed by the Spanish Society of Pathology (*SEAP*) with free and voluntary participation of differents Departments of Pathology to registry, monitor and trace biomarker results in clinical practice. After initial data reclutation step, first objective is to realize a descriptive analysis of *LungPath* focusing on ALK traslocation testing. **Method:** Descriptive analysis of the *LungPath* registry. Biomarkers determinations of LC patients were collected from March 2018 to January 2019, from 38 Spanish Departments of Pathology. **Result:** Based on this real clinical practice database, 19.332 biomarkers were tested over a total of 4.773 samples from LC patients. Small lung biopsies (60%), surgical resection specimen (16,3%) and cell block cytology (10,7%) were the mainly used samples in addition to fine needle aspiration cytology (5,1%), blood (2,5%) and other non lung biopsies (5,4%). NSCLC accounts for 95,1% of cases, principally adenocarcinoma (66%), squamous cell carcinoma (SCC) (19%), NOS (not otherwise specified, 6,1%), large cell neuroendocrine carcinoma (3,7%) and large cell carcinoma accounting for 0,3%. In non-squamous samples, ALK traslocation was one of the most frequently analyzed biomarker (80,1%), on the other hand, in SCC, ALK traslocation was shortly analyzed (53,1%), being PD-L1 expression the main biomarker realized (73,6%). From the adenocarcinoma samples were ALK was tested the positivity rate was 3,4%, whereas, 2,4% were not valit determinations due to several reasons. Used techniques plus further information has also been analyzed. **Conclusion:** Development of central biomarker databases, such as Lungpath, provide an opportunity to registry clinical practice data and in the future could be an useful tool to monitor, correlate results between different centers and improve the available knowledge regarding biomarkers in LC. According the international guidelines, EGFR mutation and ALK traslocation should be tested in all advanced NSCLC overall in lung adenocarcinoma. ALK traslocation was one of the main biomarkers tested in our database with 3,4% traslocation rate, similar with the literature reports.

Keywords: ALK, Targeted therapy, Biomarker

EP1.09-18 COMPARISON OF SAMPLE TYPES WITH SUCCESS RATES OF NEXT-GENERATION SEQUENCING

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Background: Precision medicine based on driver oncogenes is now developed for non-small cell lung cancer.Recent approval of next-generation sequencing(NGS)-based companion diagnosics has increased the need for use of high-quality specimens for diagnosis. **Method:** From December 2013 to May 2018,88 patients who were enrolled in a nation-wide genome screening, LC-SCRUM-Japan,from our institution were examined for the success rates of genetic analysis according to sample types. NGS analysis, NGS Ion Seq™,Oncomine Comprehensive Assay™,was performed using DNA and RNA extracted from lung cancer specimens. **Result:** The success rates of DNA and RNA analyses were 100% (88/88 cases) and 80% (70/88), respectively. Of the 88 samples analyzed, 85 (97%) were tissues and three (3%) were pleural effusions. The success rates of RNA analysis in the 85 tissue samples were 49/64 (77%) in bronchoscopic byopsy, 11/11(100%) in operation, 5/6(83%) in Percutaneous biopsy and 3/4(75%) in others. Of the 64 bronchoscopic samples, the success rates were 74% (20/27) in EBUS-TBNA, 90% (9/10) in EBUS-GS (large diameter), 69% (11/16) in EBUS-GS (small diameter) and 82% (9/11) in direct vision biopsy. In the 88 cases analyzed, a total of 55 actionable gene alterations (20 KRAS mut, 7 MET amp/mut, 6 EGFR mut, 5 RET fus, 5 ALK fus, 4 PIK3CA mut, 2 ERBB2 mut, 2 ROS1 fus, 2 FGFR1 amp, 1 BRAF mut, 1 FGFR3 fus) were detected in 50 cases (57%). Twelve of the 50 (14%) were registered in ongoing clinical trials of targeted drugs. **Conclusion:** All the samples were available for DNA analysis of the NGS. The success rates of RNA analysis were lower in samples obtained from EBUS-TBNA and EBUS-GS (small diameter), suggesting that the success rates depend on the sample size.

Keywords: NSCLC, Next-generation sequencing, sample size

EP1.09-19 MOLECULAR TESTING IN BRONCHIAL ADANOCARCINOMAS: RETROSPECTIVE ANALYSIS OF PARARFFINE BLOCKS ABOUT 100 PATIENTS IN EASTERN MOROCCO

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Background: The search for mutations in lung cancer has become a standard in the current management of this pathology; even more immunotherapy takes up more space in the therapeutic arsenal against this disease; in our department of thoracic surgery we became aware of this evolution; in this work which follows the creation of the electronic registry of lung cancer in our region which was also retained in the work presented at the IASLC summit in Tangier, Africa **Method:** This is a retrospective study of 100 patients treated between 2009 and 2017 in our center; only four patients benefited from this research (only EGFR mutation) in this period; the authors retrospectively screened all others patients who were diagnosed with stage IIIA through IV adenocarcinoma. We repredited the carefully preserved paraphine blocks. we present through this study the epidemiological profile of EGFR mutations; ALK; KRAS; as well as looking for PD-1 and PD-L1 checkpoints. The goal is to know the rate of these mutations in a region with a high incidence of 90% metastatic lung cancer. **Result:** Molecular testing was possible in 94.9% of the parrafine blocks obtained by excisional biopsy. Our results are being developed; preliminary observations shows the PD-L1 high expression rate was not associated with EGFR, ALK or KRAS molecular alterations. Higher stage (IV) was associated with higher PD-L1. The various proportional cut-offs used to interpret the results can be summarized in this study, which can be reproducibly assessed. **Conclusion:** To our knowledge this is the first epidemiological study of genetic mutations of lung cancer; with a significant number of patients in a region of high incidence of this metastatic disease; our results will make it possible to change the management towards targeted therapeutics and immunotherapy.

EP1.09-20 SOMATIC VARIANTS INTERPRETATION AND CLASSIFICATION IN LUNG ADENOCARCINOMA PATIENTS FROM A TARGETED GENE PANEL IN A MOLECULAR DIAGNOSTIC SETTING

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Background: The key driver mutations of lung adenocarcinoma are well described, and several targeted therapies have been developed. Personalized medicine with the availability of rapid and actionable clinical NGS-based genomic profiling has become a reality. But, as the molecular data continue to expand, we face a challenge to reliably estimate the pathogenicity of the identified variants. Thus, the aim of the present study is to interpret and classify somatic variants generated from next-generation sequencing of lung adenocarcinoma patients' samples in routine molecular diagnostic laboratory. **Method:** Variant call format files generated from next-generation sequencing of 150 lung adenocarcinoma patients'

samples, using Ion torrent hotspot panel of 50 oncogenes covering 207 amplicons, during a three year period (2014-2017) at Department of Molecular Pathology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, were retreived from the database. The variant classification and interpretation was done by an in-house generated bioinformatics pipeline based on the clinical and biological relevance of variants, levels of evidence available in the literature and *in-silico* pathogenicity prediction tools score. **Result:** A total of 125 VCF files were available from the 150 lung adenocarcinoma patients' samples. Variant annotation of the these files for the 50 cancer panel genes resulted in altogether 26,9180 variants. Application of variant filtering parameters to all the variants resulted in 117 unique variants. We classified these 117 variants into 3 categories: variants of strong clinical significance in lung cancer (55, 47%), varaints of potential clinical significance (19, 16%) and variants of unknown significance (43, 36.7%) which were further categorized into possible pathogenic (37) and unlikely pathogenic (6) based on their *in-silico* predicted pathogenicity scores and their effect on protein function. **Conclusion:** By using this classification system, we could classify 47% of variants as of strong clinical evidence and 16% variants of potential clinical significance in our cohort of lung adenocarcinoma cases. The VUS were further characterized into possibly pathogenic (31.6%) and unlikely pathogenic (5%), thus providing a structure and value to the interface between the oncogenic variants and non-oncogenic variants.The classification system proposed in the study is simple, robust and can be applied to a range of cancer panels in a clinical laboratory and will help in reducing the turn-around time to analyse and report variants. The variants identified in the study can be used to build an in-house database of VUS and the potential clinical significance of these variants could be assessed by correlating with patients' histopathological and clinical data.

Keywords: somatic variants, lung adenocarcinoma, Next-generation sequencing

EP1.09-21 SARCOMATOID CARCINOMA OF THE LUNG. ANALYSIS OF THE TUMOR IMMUNE-MICROENVIRONMENT AND SURVIVAL OF A CASE SERIES

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Background: Sarcomatoid carcinoma is a poorly differentiated non-small-cell lung carcinoma that comprises 3 subtypes i)the pleomorphic including different components such as squamous cell carcinoma, adenocarcinoma, or undifferentiated non-small-cell carcinoma and at least 10% spindle and/or giant cells; ii)the spindle cell consisting only of spindle cells and iii)the giant cell. The study aimed to assess the presence of immune cells in tumoral environment and the survival of patients (pt) with these tumors **Method:** Formalin-fixed paraffin-embedded tissues of pt treated with surgery for sarcomatoid carcinoma from 2009-2014 were retrieved and centrally revised and restaged. PAS diastase staining and immunohistochemistry with CK7, p63 and vimentin were performed to identify epithelial and mesenchymal components. The presence of tertiary lymphoid structures, plasma cells and necrosis were assessed. Clinical data were collected from patients' files regarding adjuvant treatment (chemotherapy, radiotherapy) and survival. Institutional Review Board, Ethical Approval and patient's signed informed consent were obtained. **Result:** Ten pt of median age 74 (59-80) years, were treated with pneumonectomy (1 pt) upper (4pt) or lower (5pt) lobectomy for pleomorphic (8pt) or giant cell (2pt) sarcomatoid carcinoma. Squamous or adenocarcinoma components were each present in 4 pt. Visceral pleural involvement was present in 5pt and parietal in 1 pt. TNM staging and the composition of tumor microenvironment are shown in Table 1. Tumor spread through airspace was present in 3 pt and lymphovascular invasion in 5 pt. At the time of the analysis, only 2 pt were alive, the median time to recurrence was 11.5 months and the median survival was 1.8 years

Patient number	Staging WHO 8TH Edition	Plasma Cells	Tertiary Lymphoid Structures	Pattern of Necrosis
1	pT3N0 (IIB)	Absent	Focal Aggregates	Diffuse
2	pT4N1 (IIIA)	Small	Primary Follicles	Focal
3	pT2N1 (IIB)	Absent	Focal Aggregates	Diffuse
4	pT2N0 (IIA)	Small	Primary Follicles	Diffuse
5	pT2aN2 (IIIA)	Absent	Focal Aggregates	Focal
6	pT1cN0 (IA3)	Small	Focal Aggregates	Diffuse
7	pT2aN2 (IIIA)	Absent	Primary Follicles	Focal
8	pT1cN0 (IA3)	Absent	Focal Aggregates	Diffuse
9	pT1cN0 (IA3)	Intermediate	Primary Follicles	Diffuse
10	pT4N0 (IIIA)	Absent	Focal Aggregates	Diffuse

Conclusion: Sarcomatoid carcinoma represents a rare disease with an aggressive clinical course and a poor prognosis even in stage IA3 treated with combination therapies. The exact mechanisms whereby the formation of tertiary lymphoid structures occurs and their function remain elusive. Studying these changes could reveal new ways for modulating immune responses to prolong the survival of these pt.

EP1.10 PREVENTION AND TOBACCO CONTROL

EP1.10-01 SOCIODEMOGRAPHIC CHARACTERISTICS AND PERCEPTIONS OF TOBACCO WORK AND HAZARDS IN A RURAL COMMUNITY OF NIGERIA

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Background: Introduction One of the major preventable causes of death is tobacco use and tobacco workers are exposed to a lot of hazards including physical, chemical, psychosocial and biological hazards but unfortunately many are unaware of these hazards. The aim of this study was to determine the Socio-demographic characteristics and perception of tobacco work and hazards in a rural community of Nigeria. **Method:** Methodology A cross-sectional descriptive study was carried out among 326 tobacco workers selected using a two-stage sampling method. Data was collected using anonymous pre-tested interviewer-administered questionnaires adapted from the Global Adult Tobacco Survey. Odd ratios and 95% confidence intervals were computed and P values of < 0.05 were considered statistically significant. **Result:** s Of the 326 respondents ,4(1.2%) were between 11-20 years, 52 (16.0%) between 21-30 years, 70 (21.5%) between 31-40 years, 88 (27%) between 41-50 years, 61 (18.7%) between 51-60 years, 28 (8.5%) between 61-70 years ,13 (4.0%) between 71-80 while 10 (3.1%)between 81-90.The age range of respondents was 20-70 years with a mean of 42.18 ± 15.412 years. Also, 264(81.0%) were males and 62(19.0%) were females. For marital status, 83 (25.5%) were single, 183(56.1%1.5%) married, 5 (1.5%) divorced, 51(15.6%) widowed while 4 (1.2%) were separated. Also, 113 (34.7%) had only primary education, 135(41.4%) had secondary education, 28 (8.5%) had tertiary education while 50 (15.3%) had no formal education. Only about half, 175 (49.9%) knew that tobacco is dangerous to health, 250 people (76.7 %%) were aware that tobacco is associated with tooth decay while 65 (19.8 %) were aware that it is associated with lung cancer. Age (p<0.0001), male gender (p<0.0001), and lower educational attainment (p<0.0001) were associated with a poor perception of the relationship between tobacco and lung cancer. **Conclusion:** Efforts targeted at raising

tobacco workers' awareness of the health effects of tobacco especial lung cancers are needed in rural communities. Programs should be directed at young males with lower levels of education.

Keywords: Perception, Tobacco work, Hazards

EP1.10-02 RISK FOR OCCURRENCE OF LUNG CANCER AMONG EXPOSED TO PROFESSIONAL AGENTS: A CASE-CONTROL STUDY

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Background: Lung cancer (LC) is the most frequent disease worldwide, but, with great differences among different regions. About 5% of the lethal cases, caused by cancer, are determined by the exposure to some substances, present at the working place. The most important cancerogenes for occurrence of professional cancer are ionizing radiation and various chemical and physical agents. For purposes of this study was used classification of the professional cancerogenes according to the International Agency for Research on Cancer (IARC). The exposure to carginogenes from group I (established) and 2A (probable) is taken into account.The aim of this investigation is to observe the eventual causal accociations among the professional exposure and the occurence and distribution of the lung cancer. **Method:** This was a case-control study. It comprised 185 patients with LC and matched controls with no malignant diseases. By calculating the odds-ratios, the risk factors that play a role in the disease onset, have been estimated. Statistical significance of the examined variables as risk factors has been defined with confidence intervals. **Result:** Professional exposure was present in 127 (68,6%), individuals with LC. Most of them were exposed on established (77,2%), and the others (22,8%) on probable cancer agents.The greatest part from the exposed was with more than 20 years at the same working place (established-72,4%;probable-69%). In the diseased group there was total of 124 actual smokers. Out of them, professionally exposed were 89 (71,8). Exposed to established cancer agents had 1,12% (95%CI, 0,70<OR<1,75), times greater risk to become ill from LC, compared to the non-exposed ones. Various are professions in individuals with LC. Greater frequency of the disease was registered in: constructors (present in 18,9% from the total exposed of the professional cancer agents), farmers (17,3%), transport workers (drivers, tractor drivers) (15,0%), mechanicals (8,7%).The most exposed were the farmers, in whom the average timeduration of the exposure was 36,36±9,04 years. The greatest part of the diseased farmers, transport workers and mechanicians had more than 30-year period of working. Transport workers had 2,50 (95%CI, 1,01<OR<6,15), while the mechanicians had 2,31 (95%CI, 0,76<OR<7,07), times non-significantly greater risk to become ill from LC in relation to non-exposed individuals. **Conclusion:** In order to the determined role of some professional cancer agents in occurrence of LC, prevention of this disease means several activities, among which are:complete elimination of the agents present at the working place, decrease of its concentration as well as the decrease of the exposition to the agent.

Keywords: professional exposition, Lung cancer, Occupation

EP1.10-03 LEVEL OF AWARENESS OF VARIOUS ASPECTS OF LUNG CANCER AMONG COLLEGE STUDENTS IN INDIA: DO WE NEED TO MAKE YOUTH AWARENESS AN IMPORTANT AGENDA?

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Background: Lung cancer is one of the most common causes of cancer mortality among men in India and incidence is increasing, but actually, they are largely preventable diseases. In India, advanced stage at the time of presentation is responsible for high mortality and morbidity and early detection is the only way to reduce it. The purpose of this study is to know the level of awareness of various aspects of lung cancer among college students to ensure prevention and early detection. **Method:** This assessment was part of Pink Chain Campaign—a campaign on cancer awareness. During the cancer awareness events in 2017–2018 at various colleges in Delhi, pre-test related to lung cancer was followed by awareness programme. Post-test using the same questionnaire was conducted at the end of interactive session, at 6 months and 1 year. **Result:** A total of 2571 out of 3200 students participated in the study (overall response rate was 80.3 %). Mean age of the study population was 19 years (range 17-21 years). There was a significant increase in the level of knowledge regarding lung cancer at 6 months, and this was sustained at 1 year. Among students who were just asked yes or no question, 229 students (8.9 %) were smokers and 423 students (16.4 %) were alcoholics. Internet and Newspapers were sources for knowledge in 72 % of students, whereas approximately 29 % of students were educated by TV and Magazines regarding various aspects of lung cancer. Post awareness at 6 months and 1 year, Pink Chain Campaign was the major source of knowledge related to lung cancer in more than 90 % of students by continuous and timely update on subject. Post awareness at 6 months and 1 year, there was a significant change in alcohol and smoking habits. Major reasons for not going for check-up were ignorance (52.9 %), fear (24.2 %) and lethargic attitude (29.4 %) initially, but over time, lack of time, lethargic attitude and hesitation became important factors after knowing various aspects of lung cancer. **Conclusion:** Knowledge of lung cancer due to smoking was known to most of the students but students were not well aware about environmental determinants of lung cancer. Overall awareness of risk factors, sign and symptoms, screening modalities of lung cancer has improved in a year along with practices related to smoking and alcohol, but there was not much improvement in people undergoing regular check-ups. To inculcate safe practices in the lifestyle of people, awareness programmes Such as the Pink Chain Campaign should be conducted more widely and frequently.

Keywords: Lung cancer. Awareness campaign. College students

EP1.10-04 CHARACTERISTICS OF SMOKER PATIENTS WITH LUNG CANCER IN THE LUNG CANCER

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Background: It is already known that tobacco has hamrful effects, however in Spain there is a significant population of smokers. Our aim is to study the characteristics of a sample of smokers and former smokers with lung cancer, evaluated in the Lung Cancer Unit (LCU). **Method:** Retrospective study with prospective data. All patients were included according to their smoking history in the LCU between 2010-2017. Variables, such as age, sex, histopathology, pack-year index (PYI), COPD, pulmonary emphysema, Charlson index, TNM, death and survival in months were included. Statistical analysis by statistical program SPSS 20.0. **Result:** We studied 108 smoker patients with an average age of 69.78 ± 10.738, 81.5% men and 18.5% women, 24.1% with COPD, and 42.6% with emphysema. The most frequent histopathologic finding was of adenocarcinoma (ADC) with 34.3%, followed by squamous carcinoma (SC) with 21.3%. 56.8% of men died with a PYI average of 44.26 ± 26.137, and a median survival of 9.00 months (95% CI 4.77-13.22) compared to 52.4% of women who died with a PYI average of 17.67 ± 16,889 and a median survival of 13.00 months (95% CI 0-34.60). The most common histopathology among smokers was ADC followed by SC. The distribution in smokers with PYI <20 was as follows: ADC 42.9% and SC 28.6%; with a PYI between 21 and 40 was ADC 36.7% and SC 23.3%; and in those with PYI> 40, ADC 25.0% and SC 22.7%. Similarly, those with a PYI less than 21, (57.1%) died with a median survival of 13.00 months (95% CI 0-30,531), most of them with a Charlson index lower than 3 (84.7%) and a TNM stage 3 or 4 (61.6%); with a PYI between 21-40, 50% died with a median survival of 8.00 months (95% CI 4.11-11.88), most with a Charlson index less than 3 (81.4%) and a TNM stage 4 (37.5%); and with a PYI greater than 40, 56.8% died with a median survival of 13.00 months (95% CI 7.17-18.72), most of them with a Charlson index less than 3 (80.7%) and a TNM stage 3 (38.4%). **Conclusion:** The most common lung cancer is ADC in all cases. The male population is the most affected with a higher mortality and a lower median survival. Mortality is similar in the PYI sections studied, where most had TNM stage ≥ 3, while the survival in these same groups was variable.

Keywords: Lung cancer, smokers, Tobacco

EP1.11-01 SCREENING AND EARLY DETECTION

EP1.11-01 LUNG CANCER SCREENING AND CANADA'S INUIT: A MISSED OPPORTUNITY

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Background: Inuit peoples account for 0.2% of Canada's population. Lung cancer rates in this population are disproportionately high for both genders with Canada's Inuit having the highest incidence of lung cancer in the world. Outcomes are also poor with median survival for all stages combined in Nunavut being approximately 10 months. Lung cancer screening with low dose CT scan is being implemented in many countries, and a pilot program exists in Ontario, Canada. However, the screening model may not be appropriate for the Inuit. **Method:** A literature review was performed regarding lung cancer screening, specifically with reference to the Inuit. **Result:** Several challenges must be considered for implementation of lung cancer screening with the Inuit population. The Prostate, Lung, Colorectal and Ovarian Screening Trial model (PLCO[M2012]) is the risk prediction model used in the Ontario Lung Cancer Screening Pilot for People at High Risk. This requires individuals to be between ages 55-74 and to have smoked daily for at least 20 years during their life. The average life expectancy among Inuit is 72 years, compared to 82 years for Canadians overall. Using this model where the average life expectancy is lower than the upper limit of eligibility restricts its applicability. Smoking rates among this indigenous group are approximately 3 times higher than the rest of Canada, which indicates a clear need for screening where a higher proportion of the population would be eligible. Nunavut is a vast land area of around 2 million square kilometres, with a population of approximately 35,000. The logistics of providing screening in remote communities only connected by air travel is therefore daunting. Other dominant health issues among the Inuit of Nunavut are high rates of tuberculosis, therefore screening CT scans may be further complicated by higher false positive scans requiring established algorithms for management of all abnormal scans. With the Inuit population growing faster than the rest of Canada, yet experiencing a reduced lifespan as compared to other Canadians, there is an opportunity to address the inequity that may be created with the current eligibility model used for screening in Ontario. Furthermore, current recruitment strategies and eligibility assessments are not well suited to this group's unique background. **Conclusion:** The current PLCO risk prediction model used in Ontario may not offer the best benefit for screening in this population while careful thought about how this group is recruited is also required to minimize barriers experienced by this vulnerable population.

Keywords: Screening, Indigenous

EP1.11-02 IMPLEMENTATION PLANNING OF LUNG CANCER SCREENING IN CHINA

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Background: Lung cancer is the leading cause of cancer-related deaths in China, with approximately 690,000 lung cancer deaths estimated in 2018; this has increased about fivefold from the mid-1970s. Lung cancer low-dose CT (LDCT) screening in smokers was shown to improve the survival in the US National Lung Screening Trial and more recently in the European NELSON trial. However, the predominant risk factor smoking contributes to a lower fraction of lung cancers in China than in Europe and the US. Therefore, it is necessary to establish Chinese-specific screening strategies. **Method:** To curate data on Chinese lung cancer screening programmes, we searched four Chinese and four English databases, and other sources including references in papers, policies or news from government websites and personal communications with principal investigators. We reviewed the current evidence for the implementation of lung cancer screening in China to generate Chinese-targeted recommendations. **Result:** There are 23 associated programmes completed or ongoing in China since the 1980s, mainly after 2000; and one has recently been planned. Municipal or city-level screening programmes are increasing, particularly after two central government-supported feasibility programmes: the Rural Cancer Screening Programme in 2009 and the Cancer Screening Programmes in Urban China in 2012. Some institutes have established collaborations with international lung cancer screening research groups, i.e. I-ELCAP and NELSON. Most of the programmes targeted community-based high-risk urban residents. Generally, their entry criteria are not smoking-stringent but involve other risk factors, e.g. second-hand smoking, family history of cancer, occupational exposures and air pollution. Some programmes have reported their preliminary results, which demonstrated a different high-risk subpopulation of lung cancer in China and the potential importance of risk-based selection. Evidence concerning LDCT screening implementation is mainly based on randomised controlled trials outside China, which indicates population recruitment, screening protocol and nodule management need more delicate considerations. In addition, LDCT screening programmes combining tobacco control would produce more benefits. Targeting populations to support cost-effectiveness will be important, especially in China where almost half of the lung cancer sufferers are non-smokers. **Conclusion:** In China, the high-risk subpopulation eligible for lung cancer screening has not as yet been confirmed, as all the risk parameters have not yet been determined. Though evidence on best practice for implementation of lung cancer screening has been accumulating in other countries, further research in China is urgently required, as China is now facing a lung cancer epidemic.

Keywords: Screening, China, Lung cancer

EP1.11-03 DIAGNOSTIC EVALUATION OF PATIENTS WITH SOLITARY PULMONARY NODULES IN A TERTIARY REFERRAL CENTER

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Background: Management of patients with Solitary Pulmonary Nodules (SPN) is primarily targeted at achieving an early diagnosis and treatment of all malignant nodules. We herein aimed to assess the adherence of pulmonologists to current clinical practice guidelines for SPN evaluation in a tertiary referral center for thoracic diseases. **Method:** The medical records of 64 patients with SPN, diagnosed and treated at Sotiria Hospital for Chest Diseases from January 2017 to September 2018 were retrospectively reviewed. Following analysis of the clinical features and imaging characteristics of all cases, the probability of malignancy was evaluated, and the management approach followed by pulmonologists was compared to the approach suggested by issued guidelines. **Result:** We observed a tendency by pulmonologists to monitor all SPN irrespective of size, density and likelihood of malignancy and reassess them at an earlier time than recommended by guidelines. Use of PET/CT in solid nodules > 8 mm of very low (50%) and high (80%) probability of malignancy was also observed, despite lack of a clear indication of PET/CT in the above patients' groups. Conventional bronchoscopy was performed in 81% of patients with a SPN of > 8 mm with intermediate and high probability of malignancy, even though this is not typically recommended. A low-dose protocol was applied in the majority of SPN cases monitored by computed tomography, in accordance with guidelines. Malignancy was diagnosed in 42/64 patients. **Conclusion:** Pulmonologists in real-world practice may adopt a more "aggressive" management approach towards patients with SPN, so as to exclude the possibility of an underlying malignancy.

Keywords: solitary pulmonary nodule, early diagnosis, guidelines

EP1.11-04 LOW DOSE LUNG CT SCREENING IN FIRST RESPONDERS IN THE PHOENIX METRO AREA: A FEASABILITY STUDY

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Background: United States Preventative Task Force recommends annual lung cancer screening with low dose computed tomography (CT) in adults ages 55-80, who have a thirty pack year history of smoking and are currently smoking or quit within the past 15 years. Thirty percent of all lung cancers diagnosed in United States are due to occupational exposure, with a vast majority diagnosed in first responders. No occupational specific guidelines exist for lung cancer screening with low dose CT for first responders. **Method:** November 1, 2018-March 21, 2019 low dose lung CTs were performed on a 144 first responders. Age ranges from 40-76, Gender: 116 Males and 28 Females. The average years of exposure was 23 yrs. Patients were screened at various Simon Med Radiology locations in Arizona with various CT scanners. The CT dose index ranged (CTDI vol) ranged from 1.6-2.6mGy. No contrast was used. **Result:** 40 lung nodules identified: 1 anterior mediastinal mass, 2.1x1.5cm which was removed in a 42 year-old and found to be an epithelioid thymoma. Lung-RADS screening follow-up was used even though a lot of the patients did not meet age criteria. The remainder of the lung lesions classified as follows: Lung-RADS (LR) 1:4, LR2:28, LR2s:1, LR3:4, LR4A:2 **Conclusion:** This study demonstrates value for LDCT as a screening modality for first responders. First responders are often diagnosed with lung cancer earlier than smoker for various reasons and therefore screened earlier in this study. The very early results are promising and ongoing follow-up will likely lead to further diagnoses of early lung cancer. This is a small study and warrants further investigation on a larger scale.

Keywords: lung, Screening, Firefighter

EP1.11-05 INTEGRATION OF LOW DOSE COMPUTED TOMOGRAPHY (LDCT) FOR LUNG CANCER SCREENING IN THE NATIONAL CANCER PROGRAM IN INDIA: A FEASIBILITY STUDY

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Background: Lung cancer is the commonest cause of cancer-specific mortality in India. It is difficult to screen and often misdiagnosed due to non-specific symptoms. However, improvement is likely with the advent of low-dose computed tomography (LDCT) screening recommendations by U.S. Preventive Services Task Force and American Cancer Society. Notably, specialists are concerned due to false-positive rate (up to 25%), radiation exposure and unnecessary invasive procedure, etc. Therefore it's pertinent to study the feasibility of LDCT integration in the national cancer program. **Method:** A descriptive online survey was developed for medical and surgical specialists using Google survey tool. Google platform was selected for its wide outreach and use by specialists in northern India. The survey period was 1 month and included items for lung cancer screening, LDCT awareness, the feasibility of its integration in the National cancer program, etc. The survey adopted a stratified sampling strategy for representation, and data collected were completely anonymous. **Result:** A total of 530 completed responses were collected. Majority specialists (60.37%) were from the private sector, employed at academic institutions (64.15%). The mean work experience was 7.83±5.64 years with an average of 34.47±8.73 lung cancer patients attended. Most had specialized in internal medicine (26.41%), pulmonology (20.75%) and general surgery (18.86%). Although 71.69% practiced smoking cessation counselling and 25.47% counted it as a potential benefit of LDCT screening, only a few (6.98%) were formally trained in it. Most cited early detection (78.67%) and false positive results (50.94%) as potential benefit and harm of LDCT, respectively. Almost half (52.83%) erroneously suggested LDCT screening in the smoking history of 20 to 30 pack-years & age 40 to 55 years. Poor patient knowledge (55.28%) and denial of cancer risk (36.03%) were quoted as primary causes of refusal for screening. Only a few (24.33%) specialists were aware of the National cancer program, but many (80.75%) favored integration of LDCT screening for reducing lung cancer-related mortality. Poor finances and logistics (67.92%), and human resource (38.11%) were identified as potential barriers. Provision from health budget (39.62%) and social insurance (22.64%) were the preferred funding options. **Conclusion:** In the present study a favorable attitude towards the inclusion of LDCT in national cancer program was observed among specialist doctors. However, the study also highlights potential barriers including financial and human resources to its integration warranting operational research. At the same time study also illustrate poor awareness of lung cancer screening protocols and inept smoking cessation counselling for which training should be formalized.

Keywords: ldct, Screening, Lung cancer

EP1.11-06 DESIGN AND IMPLEMENTATION OF AN INTEGRATED LUNG CANCER PREVENTION AND SCREENING PROGRAM USING A MOBILE CT IN BRAZIL

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Background: Lung cancer is a high-ranking cause of cancer deaths in Brazil. Low dose computerized tomography screening national guidelines has not yet been established, and public primary prevention and tobacco control programs have an inconsistent coverture, especially among the most deprived. The Cancer Prevention Department of Barretos Cancer Hospital has a large tradition in the use of mobile units to reach out and conduct cancer screening in underserved Brazilian populations. This study aims to design an integrated lung cancer prevention and early detection program using a mobile CT unit to reach high-risk lung cancer population. **Method:** The study is placed in Barretos, Brazil, with an estimated population of 120,000 inhabitants. Tobacco cessation intervention and LDCT screening will be offered in partnership between the municipal health system and Barretos Cancer Hospital. Every smoker seeking health assistance and those identified in active surveys in the community would be offered tobacco cessation support. High-risk individuals matching USPTF criteria will be offered LDCT using a mobile CT unit. **Result:** Nineteen tobacco cessation teams were formed in different public primary health unities throughout the city. Patient information are stored in a web-based databank (RedCap) and shared between teams. Screening flow was coordinated by municipal health office and Barretos Cancer Hospital. The CT mobile unit is intended to be placed near primary health care centers. It was estimated 3,376 eligible participants. A comprehensive epidemiological questionnaire will be asked, in addition with blood and sputum samples collection for further cancer biomarker studies. Those with symptoms of suspected lung malignancy or poor clinical condition would be excluded from screening. Nodules detected in LDCT screening will be managed under ACR Lung-Rads criteria. A multidisciplinary team will be available to discuss doubtful cases, diagnosis and treatment strategies. Two reports are generated for each LDCT screening exam and sent back to primary care teams, one with educational purposes and another with technical information. Primary care teams were trained, being responsible to manage non-cancer conditions eventually detected on screening. A direct line of communication was set between primary care teams, radiologists and multidisciplinary team. **Conclusion:** Tobacco cessation and lung cancer screening in high-risk individuals have to be integrated. Since Brazilian health assistance in public system is fragmented, it is imperative to design a coordinated flow and establish communication channels between primary care teams, radiologists and multidisciplinary team. There was good feedback by primary care teams and patients about the impact of screening in the tobacco cessation process.

Keywords: Mobile CT, Tobacco Cessation, lung cancer screening

EP1.11-07 DEVELOPMENT OF A CHROMOSOME INSTABILITIES IN PLASMA CELL-FREE DNA ASSAY FOR EARLY LUNG CANCER DETECTION AND TREATMENT RESPONSE MONITORING

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Background: Chromosomal instability (CIN) is one of the hallmarks of cancer. Tumor cells keep shedding DNA into blood stream which provides an opportunity for CIN analysis. Here we present a retrospective study to investigate the potential of CIN in plasma cell-free DNA (cfDNA) as a minimal-invasive biomarker for early cancer detection and cancer treatment responses monitoring. **Method: Method:** To characterization the baseline data of CIN in cfDNA, 171 plasma samples were collected since June 2017. 35 was from non-cancer individuals. 136 was from cancer patients. cfDNA was extracted and sent to low-coverage genome sequencing on the Illumina X10 platform, followed by chromosomal instability (CIN) analyses by a customized workflow Ultrasensitive Chromosomal Instability Detector (UCAD). **Result:** Increased plasma cfDNA CIN was observed along with disease progression. In lung cancer, cfDNA CIN increased along with the development of lesions, from adenocarcinoma in-situ, minimal invasive adenocarcinoma, invasive adenocarcinoma (P=0.034) to relapsed cancer (P<0.01). The sensitivity of early lung cancer detection was 30.7%, 37.5%, 45.5%, 50.0% and 98.1% for AIS, MIA, IAC, SCC and relapsed lung cancer, at a specificity of 75%. In primary lung cancer, cfDNA CIN decreased after curative therapies. And cfDNA CIN significantly increased after disease relapsed (P<0.01). And cfDNA levels did not show statistical differences regarding metastases sites. **Conclusion:** Conclusions: cfDNA CIN can help early cancer detection and treatment response monitoring.

Keywords: CIN, UCAD, cfDNA

EP1.11-08 ULTRA-HIGH-RESOLUTION CT TO PROJECT THE DETAILED COMPONENTS IN NODULES; FAT COMPONENTS IN PULMONARY HAMARTOMAS

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Background: The purpose of this study was to evaluate the utility of the detailed matrix of ultra-high-resolution CT (UHRCT) to detect the detailed attenuation heterogeneity in pulmonary hamartoma which contains fat component. **Method:** Seven consecutive patients (three males, four females; 48-73 y.o.) with pulmonary hamartoma who underwent UHRCT were enrolled retrospectively. Each patient's hamartoma was diagnosed by using bronchoscope, surgical therapy or follow up study. All CT studies were performed by using ultra-high-resolution CT machine (Aquilion Precision; Canon Medical Systems, Otawara, Japan). All CT examinations were performed with 160-detector row CT scanner; 120kVp, auto-mAs, 1792 channels, collimation 0.25 mm x 160 rows, 1024 matrix. Conventional high-resolution CT (HRCT) images were reconstructed with 1mm slice, 1mm interval, 512 x 512 matrix. Ultra-high- resolution CT (UHRCT) images were reconstructed with 0.25 mm slice, 0.25 mm interval, 1024 x 1024 matrix. The CT densities of each hamartoma were measured by placing ROI at the longest diameter of the nodule on CT image. The lowest densities in the nodule were statistically compared between on HRCT and UHRCT by using paired t-test. P value less than 0.05 was considered to be significant. **Result:** The average minimum densities of hamartomas on HRCT and UHRCT were -39.1 and -65.0, respectively (p = 0.092). **Conclusion:** The lowest densities of hamartomas were lower on UHRCT than on HRCT, not significantly. The UHRCT's smaller voxel may reveal the detailed heterogeneity in the nodule to detect fat component of hamartoma.

Keywords: Ultra-high-resolution CT, pulmonary nodule, Hamartoma

EP1.11-09 EVALUATION OF SEVEN-AUTOANTIBODY PANEL TEST IN EARLY DETECTION OF LUNG CANCER IN ROUTINE CLINICAL PRACTICE

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Background: There is an increasing incidence of pulmonary nodules due to the promotion and popularization of low-dose computed tomography (LDCT) screening for potential populations with suspected lung cancer. However, high rate of false-positive and concern of radiation-related cancer risk of repeated CT scanning remains major obstacle to its wide application. Here, we aimed to investigate the clinical value of a non-invasive and simple test, named 7 autoantibodies (AABs) assay (P53, PGP9.5, SOX2, GAGE7, GUB4-5, MAGEA1 and CAGE), in distinguishing malignant pulmonary nodules from benign ones in routine clinical practice. **Method:** 152 patients with malignant lung diseases and 151 with benign pulmonary diseases were identified. The serum levels of the 7-AABs were tested by Enzyme-linked Immunosorbent Assay (ELISA). The primary goal was to assess the sensitivity, specificity, false positive rate (FPR) and positive predictive value (PPV) of the 7-AABs panel in detection of lung cancer. **Result:** The serum levels of AABs (including PGP9.5, GAGE7, GBU4-5 and MAGEA1) in malignant group were significantly higher than that in benign group. The sensitivity and specificity of the 7-AABs panel test were 46.1% and 82.9% in whole group, and 35.3% and 70.0% in cases with pulmonary nodules. Comparing to 7-AABs panel test or LDCT screening plus multiplane reformation (MPR) alone, the combination of 7-AABs panel and LDCT screening+MPR improve the PPV (70.6% vs 89.5%; P < 0.001) and reduce the FPR (21.1% vs 30.0%; P < 0.001) in patients with pulmonary nodules. **Conclusion:** The 7-AABs panel may be a promising method for early detection of lung cancer. It would be a valuable diagnostic tool to distinguish malignant pulmonary nodules from benign ones.

Keywords: lung cancer,screening,LDCT,seven-autoantibody panel

EP1.11-10 CREATING A COMPREHENSIVE LUNG CANCER SCREENING PROGRAM TO DIAGNOSE EARLY STAGE LUNG CANCERS

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Background: Objective: The goal was to create a comprehensive lung cancer screening program at our Cancer Center that integrates evidence-based results as a way to identify early stage lung cancers in the high risk population of our community. Literature review: Lung cancer is the third most common type of cancer diagnosed in the United States, but it is the leading cause of cancer deaths (U.S. Cancer Statistics Working Group, 2018). Lung cancer is most often diagnosed at late stages which have low survival rates. The National Lung Screening Trial (NLST) was an NCI funded trial which determined that screening with low dose CT as compared to chest radiograph would reduce mortality by 20% in high risk populations (Team, 2011). Screenings for breast and colorectal cancer has been associated with improved patient outcomes and sets a precedent for implementing responsible lung cancer screening in high risk populations (Mulshine & D'Amico, 2014). **Method:** A comprehensive screening program was designed with a nurse coordinator as the main point person to ensure all screenings had follow up tracking completed. The screening program was designed to function in cooperation with the Hospital Comprehensive Lung Cancer Program as needed based on screening results. Program protocol were set up to include timely result reports to referring physician with clear follow up recommendations and result letters to screening patients. A tracking system was put into place to ensure the necessity of follow up scans are communicated to the patients and completed. **Result:** Since the start of our program in October 2012, we have performed 933 initial scans, 647 annual scans and 172 short-term follow up scans. We have diagnosed 13 lung cancers, 3 renal cancers, 1 thyroid cancer, 1 melanoma, 2 thymoma, and 1 breast cancer recurrence. **Conclusion:** We have found lung cancer screening to be an effective method of diagnosing early stage lung cancers in high risk populations.

Keywords: screening program

EP1.11-11 FAMILIAL LUNG CANCER: A CALL FOR ACTION

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Background: Lung cancer (LC) is the most deadly of all cancers mostly due to the fact that the disease is often detected at an advanced stage with less effective treatment options. While 80% of lung cancers can be directly attributable to tobacco smoking, the disease has been increasing in non smokers raising awareness to other risk factors that could be screened for and controlled in order to achieve higher rates of early stage diagnosis. **Method:** A retrospective analysis of the electronic records of LC patients followed in our district hospital between May 2012 and December 2018 was conducted. Patients with family history of cancer were selected and their demographic characteristics, smoking status, co morbidities and LC characteristics were analyzed. **Result:** A total of 524 patients were followed, 33 of whom with a positive family history of cancer (20 men and 13 women, median age of 61.7years old at diagnosis +- 12.8 years). Only 9 were never smokers and 63.6% (21) were diagnosed following the investigation of symptoms. The majority (24) had an adenocarcinoma subtype (3 EGFR mutations, 1 ALK translocation and 2 HER2 amplification were identified). Twenty patients (60.6%) had a family history of LC and the most frequent family member affected were parents (father: 14; mother: 11) and siblings (11). Cancer affected at least 2 family members of 15 patients. At the time of diagnosis 19 of the 20 patients with LC family history had an ECOG Performance Status of 0-1 and 8 (40%) had advanced stage disease. We found no significant difference in stage at diagnosis, smoking status or symptoms at diagnosis between patients with and without a LC family history of malignancy (p=0,120, p=0,117 and p=0,814 respectively). **Conclusion:** Studies demonstrating evidence of familiar aggregation of LC suggest a possible genetic susceptibility to this malignancy. Identification of individuals at particularly high risk of lung cancer due to this type of susceptibility would contribute to early detection and possibly to prevention through targeted and intense anti-smoking efforts. Perhaps due to the small dimension of our study population, our patients were not diagnosed in early stages of the disease despite a positive family history of lung cancer. This raises the question whether this particular group of people should be selected for specific cancer screening to allow for the possibility of curative treatments.

Keywords: Lung cancer, familiar aggregation, early diagnosis

EP1.11-12 LUNG CANCER SCREENING: IMPLEMENTATION IN A MULTI-STATE, COMMUNITY-BASED SETTING

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Background: The benefits of lung cancer screening (LCS) was largely proven in academic centers, and while implementation in the Veterans Health Administration has been reported, little data has been published on the broader community experience. We aimed to describe the LCS implementation experience in a multi-state, community-based healthcare network. **Method:** We reviewed individuals who were referred for LCS between 01/01/2012-03/31/2017 within our community-based network of 12 LCS programs spanning 22 LCS sites in Alaska, Montana, Oregon and Washington. One of the programs is considered centralized (shared decision making, evaluation and management occur at a single site) and 11 are considered decentralized (shared decision making, evaluation and management occur in geographically diverse community care settings with support from a central LCSP coordinator). 2013 Rural-Urban Continuum Codes from the United States Department of Agriculture were used to determine metropolitan/non-metropolitan/rural status. **Result:** Data collection is complete for 4,820 of the total 6,451 individuals, of which 9% (450/4,820) were excluded for being outside the age and smoking history LCS criteria range. A further 908 were excluded for other reasons. Thus, the preliminary results of 3,462 individuals are included here. Characteristics of the individuals are shown in the table. Of the 22 LCS sites 82% (18) were located in metropolitan areas, 18% (4) in non-metropolitan areas and none in rural areas. The distribution of screened individuals and LCS centers within the healthcare network are shown in the figure.

FACTOR	% (Number)
DEMOGRAPHICS	
Median age, years (IQR)	64 (60-69)
Gender, male:female	56%:44% (1,930:1,532)
Race	
White	87% (3,018)
Non-white	13% (444)
Current smoker on program entry	57% (1,974)
Median tobacco pack year history (IQR)	41 (35-50)
Median income by county, USD (IQR)	$65,965 ($54,102-$75,302)
Residential location	
Metropolitan	92% (3,204)
Non-metropolitan	7% (231)
Rural	<1% (19)
Unknown	<1% (8)
Median distance to screening site, miles (IQR)	7 (4-14)
INITIAL LOW-DOSE CT SCAN	
Individuals with Lung RADS 4	7% (232)
Individuals with at least one nodule >6mm	26% (905)
Median size of largest nodule, mm (IQR)	8 (6-12)
PULMONARY NODULE INTERVENTIONS	
All individuals that underwent a procedure	4% (128/3,462)
Individuals with positive nodules that underwent a procedure	14% (128/905)
Pulmonary resections	55% (71/128)
Malignant	92% (65/71)
Benign	8% (6/71)
Major postoperative complications	13% (9/71)
ATTRITION*	
Individuals that underwent attrition	17% (588)
Median time to attrition, months (IQR)	15 (12-21)
Nodule on first scan	46% (273/588)
Median size of largest nodule, mm (IQR)	5 (4-7)
Smoking on program entry	61% (360/588)

IQR, 25th-75th interquartile range; *Attrition defined as declining further screening or lost to follow-up.

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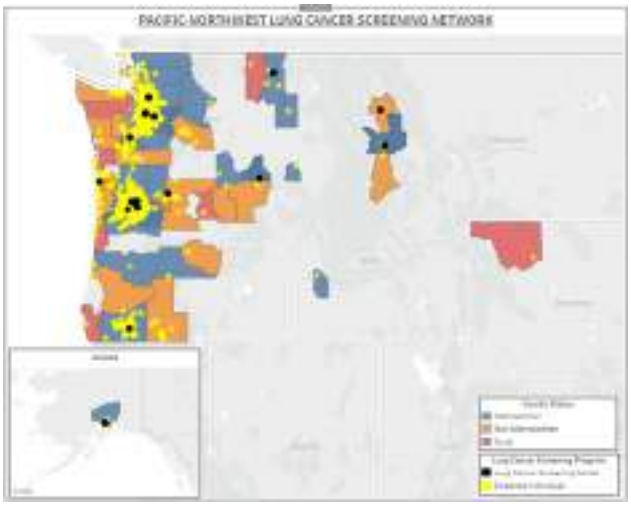

Conclusion: Screening in the community setting remains in metropolitan areas. Positive findings on the initial scan are common; however, intervention rates are low. Retention for screening also remains high.

Keywords: Lung cancer screening, Community-based lung cancer screening, Multi-state lung cancer screening

EP1.11-13 LUNG CANCER SCREENING PROTOCOL BY USING LOW DOSE COMPUTERIZED TOMOGRAPHY IN COMBINATION WITH DIGITAL TOMOSYNTHESIS: 4 YEARS FOLLOW UP RESULTS

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Background: Annual Low-dose computerized tomography (LDCT) screening for lung cancer is currently a standard protocol recommendation. However, LDCT has limitations in its high rate of false positive results, accumulation of radiation exposure, and relatively high cost. Using LDCT in combination with Digital Tomosynthesis (DT) may be an alternative screening protocol for lung cancer. **Method:** A lung cancer screening protocol using LDCT yearly alternate with DT in normal LDCT finding and abnormal finding that stable or decreased after annual LDCT for 2 years in solid and part-solid nodule has been performed in 634 former or current heavy smoker since July 2012 at Chulabhorn Hospital, Thailand. **Result:** At initial screening of LDCT, 196 (30.9%) had normal lung finding and 438 (69.1%) had abnormal finding. During annual follow up, 187 and 156 cases who had initial normal LDCT underwent DT screening on 1st and 3rd year of follow up, and no lung cancer was diagnosed within the 4 years follow up period. Meanwhile, among 271 participants who had stable or decreased lung lesions and underwent DT on 3rd year follow up, 3 lung cancers was diagnosed on 4th year follow up. Two lung cancers were early stage and one was stage 4, which represented as a new solid nodule, new solid component and new endobronchial lesion on LDCT finding, respectively, while DT could not detected the new solid component of part solid nodule. **Conclusion:** LDCT in combination with DT would be an alternative protocol for lung cancer screening particularly in normal lung lesion.

Keywords: Low-dose CT, Digital tomosynthesis, lung cancer screening

EP1.11-14 KNOWLEDGE AND PERSPECTIVES OF INDIAN MEDICAL PRACTITIONERS TO LUNG CANCER: A REGIONAL SAMPLE SURVEY

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Background: Lung cancer leads cancer-associated mortality figures in India. According to various cancer registries, It's a pervasive problem with incidence expected to rise to 67,000 new cases per year by 2020. Especially concerning are limited health resources to tackle this problem in terms of specialty centers and trained staff. Adding to woes are poor knowledge, and practices among general practitioners (GPs) pertaining to lung cancer screening and referral. Thereby putting an additional burden on the constrained Indian health care system as a majority of cases are diagnosed at advanced stages leading to poorer prognosis and high treatment costs. **Method:** A descriptive online survey was developed and pilot tested for GPs with Bachelor degree in Medicine & Surgery (MBBS) using Google survey forms. Google platform was selected for its wide outreach and use by GPs in northern India. The survey was done over 1 month period and included items related to etiopathology and diagnosis of Lung Cancer. The survey adopted a stratified sampling strategy for representation, and data collected were completely anonymous. **Result:** A total of 2674 complete responses were collected. Majority of GPs were in the private sector (67.68%) with a mean work experience of 8.93±6.70 years. An average of 10 (10.45±7.10) Lung cancer cases were attended by GPs with majority presenting with non-resolving cough and/or hemoptysis (66%). Most common risk factors reported were cigarette smoking (93.27%) and exposure to chemicals (74.49%). Only a quarter of GPs identified lung cancer mortality being the highest (29.09%) with attribution to smoking (23.60%). Only 69.10% GPs advocated Lung cancer screening for current and past smokers. Only 30.89% GPs affirmed that a substantial reduction in mortality (95%) can be achieved by timely and proper screening. Only a quarter (25.46%) GPs reported low dose CT Scan (LDCT) as best modality lung cancer screening. 1943 (72.66%) GPs reported tissue sample biopsy as a method of diagnosis followed by CT scan (58.18%). Histopathology (85.48%) and molecular markers (74.49%) were frequently reported to guide therapeutic decision making. **Conclusion:** Based on the survey, It can be concluded that knowledge of Indian GPs for Lung cancer is deficient in wake of high disease burden. Poor suspicion and detection of lung malignancy at early stages devoid patients of better prognosis and outcomes. Therefore it is recommended that sensitization workshops and training of GPs in opportunistic cancer screening and referral protocols be done.

Keywords: Survey, Lung cancer, physician

EP1.11-15 LUNG CANCER SCREENING PROGRAM WITH LOW-DOSE CT IN GREEK POPULATION

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Background: The majority of lung cancer patients are at an advanced stage at the time of diagnosis, when curative treatment is no longer feasible. On this basis, we performed screening with low-dose CT in patients with high risk of lung cancer development. **Method:** From Feb 2015 to Feb 2019, 500 patients were recruited in the study. Patients were screened for lung cancer with low-dose CT according to European Union position statement expert group. **Result:** Group A consisted of patients <55 years old (25%) including 80% of current smokers (30 ± 5 pack years) and 15% of overweight subjects. Group B consisted of patients >55 years old (75%) including 65% of current smokers (40 ± 8 pack years) and 9% of overweight subjects. Former smokers were divided into three groups, those who quit a) 15 years ago (48%), b) 10 years ago (29%) and c) 5 years ago (23%). Concomitant diseases of the whole population included hypertension (27%), diabetes mellitus (19%), COPD (24%), coronary disease (12%) and prior cancer (1%). Hypertension, diabetes mellitus and COPD were correlated with smoking in the population studied ($p<0.05$). Findings (nodules > 10mm) were observed in 13% of patients in Group A and in 8% of Group B. One patient in Group

A and one patient in Group B were diagnosed with squamous cell carcinoma and adenocarcinoma respectively. After screening, 13% of the whole population started low fat diet whereas 20% of the whole population refused follow up. Interestingly, 80% of the whole screened population agreed for an annual low-dose CT and 21% of this population quit smoking through screening period (p<0.05). **Conclusion:** Screening with low-dose CT offers a tool for the early detection of lung cancer that can save lives for those at high risk and might significantly improve the low survival rates for this disease. European countries should take into consideration the implementation of lung cancer screening programs as a preventive care strategy. The value of the screening test in lung cancer patients remains to be further elucidated.

Keywords: screening, lung cancer, low-dose CT

EP1.11-16 COMPARISON OF THREE DIAGNOSTIC MODALITIES FOR LUNG NODULES

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Background: Lung cancer screening and computed tomography (CT) have increased the detection of lung nodules. However, the diagnosis and selection of diagnostic modality are difficult for small nodules. The objective of this study was to determine the appropriate modality for lung nodule diagnosis. **Method:** We reviewed 446 consecutive cases that underwent radial endobronchial ultrasound (EBUS), percutaneous needle aspiration (PCNA), or surgical resection for the diagnosis of lung nodules (≤3cm) from February 2017 to January 2019. The patients underwent contrast-enhanced chest CT in our hospital before each examination. We performed retrospective data collection and analysis. **Result:** Radial EBUS was performed in 120 (27%) cases, of which 73 had a proper diagnosis; PCNA was performed in 151 (34%) cases, of which 131 had a proper diagnosis; surgical resection was performed in 175 (39%) cases, of which 172 had a proper diagnosis. We detected malignancy, benign nodules, and atypical cells in 290 (65%), 139 (31%), and 17 (4%) cases, respectively. The mean sizes measured on CT were 20, 19.7, and 12.1 mm in PCNA, radial EBUS, and surgical resection, respectively (p<0.001). The lung lobe with nodules (p=0.762) was not statistically different among the modalities. Radial EBUS was preferred for centrally located nodules (55/120; 45.8%; p<0.001). Surgical resection showed many portions of ground-glass opacity nodules (p<0.001). PCNA was attempted in peripherally located or solid lung nodules (p <0.001). The failure of diagnosis with PCNA, radial EBUS, and surgical resection occurred in 20 (13.2%), 47 (39.2%), and 3 (1.7%) cases, respectively (p <0.001). **Conclusion:** Surgical resection is preferable for small lung nodules and ground-glass opacity nodules; PCNA is preferable for peripherally located and solid nodules; radial EBUS is preferable for centrally located nodules. It is important to select the diagnostic modality based on the characteristics of each nodule.

Keywords: percutaneous needle aspiration, lung nodule, radial endobronchial ultrasound

EP1.11-17 THE IMPACT OF OCCUPATIONAL EXPOSURE ON DETECTION OF EXTRA-NODULAR AND EXTRAPULMONARY LESIONS IN LDCT FROM A PILOT SILESIAN STUDY

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Background: Smoking and additional exposure to occupational factors such as coal dust, can cause changes in the lungs and also in other organs. **Method:** We did the comparative analysis of the prevalence and nature of extra-nodular lesions and extra-pulmonary findings seen in low-dose computed tomographies (LDCT) done in 533 participants of the Pilot Silesian Study of Early Lung Cancer Detection. The study cohort consisted of miners (n=59) and people without occupational exposure (n=474). Statistical analysis was performed using Statistica 13.0 PL. Statistical significance was set at a p value below 0.05. Distribution of variables was evaluated by the Shapiro-Wilk test. The two groups were compared with the U Mann-Whitney test in case of non-normal data distribution. Chi-square test was used. **Result:** The value of 'pack-years' for miners was statistically higher than for people without occupational exposure (M: 37 v 30, p=0.01). Emphysema was more often found in the group of miners (44,07 % v 31,50 %, p = 0.05). COPD was also diagnosed more often in people exposed to coal dust than without occupational risk (45,76 % v 32,07 %, p=0.035). Extrapulmonary findings were reported in 86,44 % of miners and 62,45 % of people without occupational exposure (p=0.00027). Degenerative changes in the skeleton, osteoporosis, calcification in vessels were found statistically more frequently in miners. **Conclusion:** Long-term smoking, exposure to coal dust, physical work could contribute to a faster development of COPD and osteoarticular diseases.

Keywords: occupational exposure, LDCT (low dose computed tomography), lung cancer screening

EP1.11-18 FOLLOW-UP AND RECURRENCE AFTER SURGERY IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Background: Lung cancer is one of most common cause of cancer death in the world. Surgery is a potentially curative intervention in early stages of non-small-cell lung cancer (NSCLC), although some patients develop recurrence. Identification of factors related to recurrence is essential to reduce it. **Method:** The objectives of this study were to evaluate the follow-up of patients with early stage NSCLC who undergoing surgical resection, as well as, the factors related to recurrence. We retrospectively evaluated patients with early-stage NSCLC (stage 0-II) who underwent surgical resections between January 2015 and December 2017 at Hospital da Luz – Lisboa. Patients were evaluated at a multidisciplinary lung cancer tumour board team meeting and followed according to international guidelines. We characterised demographic, clinical and radiological features, surgical procedure, histology and follow-up. The mean and standard deviation were shown; the T-student and Fisher tests were used; P value ≤0.05 was considered significant. **Result:** There were included 46 resected NSCLC: 41 (89.1%) adenocarcinoma (ADC) – 25 invasive ADC, 11 ADC in situ (Tis) and 5 minimally invasive ADC; 4 (8.7%) epidermoid and 1 (4.2%) pleomorphic carcinoma. Twenty-seven (58.7%) were female and 29(63.0%) were current or former smokers; mean age was 63.1±9.3 years old (37-82). We underwent 30 (65.2%) lobectomies, 13 (28.3%) anatomic segmentectomies, 2 (4.3%) wedge resections and 1 (2.2%) bilobectomy, all with mediastinal lymph node dissection. No major complications were reported. Regarding surgical stage, 11 (23.9%) were stage 0, 26 (56.5%) Ia, 7 (15.2%) Ib, and 2 (4.3%) IIa. Thirty-nine (84.8%) patients were in follow-up or died due to non-lung cancer cause (1 case). The follow-up was 28.7±8.5 (12-47) months. Recurrence was documented in 4 (8.7%) patients; the time of recurrence development was 14.8±9.2 (4-26) months; Second primary lung cancer occurred in 3 6.5%) patients. Comparing recurrence and follow-up groups, there was only difference regarding age (73.0±7.8 vs 62.4±9.1; p=0.032) - gender (p=1.0), smoking history (p=0.621), nodule characteristics (solid vs sub solid) (p=0.140), lung resection (lobar vs sublobar) (p=0.297) and stage (stage 0/I vs stage II) (p=1.0). All Tis lesions were in follow-up. **Conclusion:** In this group with resected early-stage NSCLC, most of the patients were in follow-up and the age was the only factor associated to NSCLC recurrence. Although low recurrence documented, it is essential to perform more accurate patient selection ensuring a radical cure. Probably other variables, as molecular/genetic parameters, can help to identify those with high-risk recurrence and the liquid biopsy can be useful in the detection of lung cancer recurrence.

Keywords: non-small-cell lung cancer, Follow-up, Recurrence

EP1.11-19 SURVEILLANCE WITH PET/CT AND CTDNA OF LUNG CANCER PATIENTS AFTER COMPLETION OF DEFINITIVE THERAPY; A RANDOMIZED TRIAL

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Background: Even after treatment with curative intent lung cancer patients have a high risk of relapse. Patients are currently followed with CT. However, after surgery and especially radiotherapy CT has limited accuracy potentially delaying the diagnosis of a relapse. There is a scarcity in evidence regarding the most efficient follow-up interval as well as maging method. Together with CT the use of PET/CT for follow-up has been increasing and there is a need for improved understanding and perhaps questioning of the role of imaging in surveillance. Relapse of tumour activity can also be reflected by shedding of tumour DNA (ctDNA) into the blood stream. Studies have shown increase in circulating ctDNA months before standard radiologic assessment. Blood sampling and subsequent analysis of ctDNA therefore represent a promising minimally-invasive strategy to assess genomic tumour material and follow its changes. The purpose of this on-going clinical trial is to improve early detection of lung cancer relapse enabling more patients to receive definitive treatment of their relapse, ultimately leading to improved survival. **Method:** This national, randomized trial compares two strategies for surveillance of patients with non-small cell lung cancer treated with curative intent (figure 1): standard follow-up +/- imaging with FDG PET/CT. Primary endpoint is frequency of treatable relapse and secondary endpoints includes survival and quality of life, number and type of invasive procedures, adverse events and type of treatment after verification of relapse, as well as use of healthcare resources. Based on samples collected during this randomized trial we will evaluate if monitoring patients with ctDNA enable us to track cancer evolution and detect early signs of relapse, as well as exploring potential new stratification of patient cohort with focus on high-risk and low-risk groups. Hereby, designing an optimal surveillance strategy for individual patients.

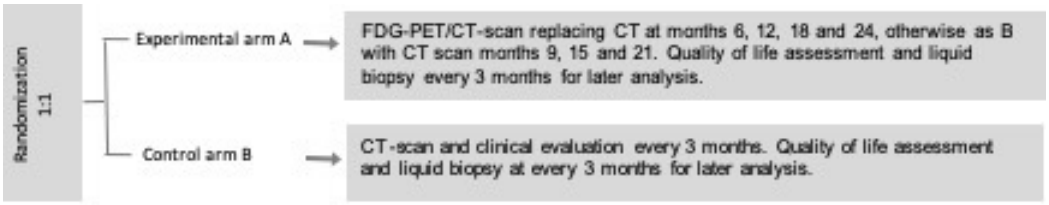

Figure 1: Overview of the SUPE_R trial

Result: The trial has been starting gradually since end-2018 and is now including patients in 4/5 Danish regions. The study aims to include 750 patients by 2021. In order to obtain baseline blood sample for ctDNA patients are included both prior to treatment (by April 2019 n=61) and 3 months after treatment (only patients in complete remission, n=25). **Conclusion:** SUPE_R will provide the scientific basis for implementing new ways for surveillance of patients with lung cancer as well as provide knowledge transferable to other groups of cancer patients. This is the first study considering bioinformatics and methodological aspects of liquid biopsies and relating them directly to imaging and clinical benefits for the patients.

Keywords: Surveillance, PET/CT, ctDNA

EP1.11-20 A PANEL OF LIQUID BIOMARKERS FOR EARLY RESPONSE CAPTURING OF NSCLC THERAPIES IN ADVANCED STAGES

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Background: CT scans are the gold standard to measure treatment success of Non-Small Cell Lung Cancer (NSCLC) therapies. In recent years, liquid biopsies became an adequate diagnostic tool especially in advanced disease stages. **Method:** Here, we investigated very early tumor response of patients receiving chemotherapy or targeted therapies using a panel of already established and explorative liquid biomarkers. Blood samples from patients were taken at baseline and day + 1 for the chemotherapy cohort (n = 25) and at baseline, day +7 and +14 for the targeted therapy cohort (n = 25). DNA mutational load, a panel of 17 microRNAs, glycodelin, glutathione disulfide, glutathione, soluble caspase-cleaved keratin 18 (M30 antigen) and soluble keratin 18 (M65 antigen) were measured using serum and plasma from patients. Baseline and first follow-up CT scan were evaluated by an experienced radiologist and correlated with biomarker data. **Result:** In the majority of patients a decrease in glycodelin abundance as well as mutational load coincided with clinical response as assessed by CT scan. Consequently, an increase of these biomarkers implicated progressive disease. Among the measured miRNAs, miR-103, miR-628-3p, and let-7e showed largely similar behavior within individual patients upon treatment initiation. The abundance of these miRNAs increased in responding patients and in a subset of patients experiencing tumor progression. Similar observations were seen for the apoptosis markers while the best results were obtained with the detection of M65. **Conclusion:** Taken together, several investigated biomarkers showed high potential for an early response capturing in defined NSCLC cohorts.

Keywords: NSCLC, Biomarker, Early Response Capturing

EP1.11-21 LUNG CANCER SCREENING PILOT IN ISRAEL

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Background: Lung cancer kills more people than any other cancer, both in Israel and worldwide. In israel 2000 die from the disease each year where the prevalence of smoking is 22.5% above age 21. There is not yet a national lung cancer screening program in Israel, therefore the Israeli Lung Cancer foundation (ILCF) initiated and funded in cooperation with Assuta Medical centers, a pilot program, ILCF-A, calling participants at risk to come and get checked. The activity took place during the international Lung Cancer awareness month, November 2018. **Method:** A call for free lung cancer screening was published and promoted on Facebook. People who enlisted filled a questionnaire to evaluate eligibility for screening, which was age 55–74 years, 30 pack-year of smoking history and current smokers or ones who quited within 15 years. There was only a screening arm and LDCT was performed for all subjects. CT reporting and management was performed using LUNGRADS. **Result:** Overall 90 subjects were eligible and underwent screening of which, 45% were women and 55% men. The average age of subjects was 63 and the average pack years was 45. Most of the subjects were current smokers. In one third of the subjects, nodules were not detected., when detected, average size of nodules was 3.25 mm. Of all subjects, eight were classified with positive results. Four with LUNGRAD score of 3 are under LDCT follow-up. Of the four who had LUNGRAD score of 4, One subject was diagnosed with stage 1 Lung Cancer and had a successful surgery, two subjects were found to be healthy by PET-CT and Bronchoscopy and 1 is still under investigation. Lung Cancer detection rate was 1.11% and FP rate was 7.7%. **Conclusion:** The ILCF-A trial provided evidence that Lung Cancer Screening in Israel is beneficial. In addition, raising awareness and calling the public to come get screened via digital media has an impact. Despite the limitation of this small study, results of cancer detection rate and FP rates were comparable with NLST and NELSON trials. Although the smoking rate of women in Israel is more then half then that of men (12% compared with 27%), their responsiveness for undergoing screening was as high. Based on this promising evidence, Lung Cancer National Screening program in Israel is recommended and feasible.

Keywords: Screening, Awareness, Pilot study

EP1.11-22 INCORPORATING GENETIC COUNSELING INTO THE THORACIC ONCOLOGY UNIT: A PILOT PROJECT IN THE REAL WORLD

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Background: Lung Cancer (LC) is the 6th cause of cancer death in Mexican population. Genetic counseling (GC) in LC is not often offered in the Oncology departments in Mexico. CG is a process including education, genetic cancer risk evaluation, guidance about Genetic Testing (GT), and psychosocial support. Germline mutations in *ATM, TP53, BRCA2, EGFR*, and *PARK2* cause a small percentage of LC; those patients (pts) could have benefits such as identify the genetic etiology, adjust surveillance, direct therapy, calculate transmission risk and even struggle with stigma. There are no clear criteria to refer LC pts to CG/GT. We started a GC service to identify which pts would benefit of GT. Herein, we describe our pilot project **Method:** We reviewed medical records (MR) and offered GC to the new LC pts from Sept2018-Feb2019. The main objectives were: identify patterns of hereditary cancer syndromes, and analyse pedigrees of pts carrying the *EGFR* T790M mutation prior to treatment. We collected clinical, familial and demographic variables through the CG session. We reviewed the liquid biopsy results for *EGFR, ALK* and *ROS*. CG also included supportive measures and recommendations for GT according to the personal and family history (FH). No germline testing was available. **Result:** 79 cases were reviewed (66 MR and 13 CG sessions) Mean age was 61.54y (range 26-88). 45(57%) were females. 57% (45) were smokers. 40(50.6%) had positive FH. 8 had at least 1 member with LC, notably 1 had 3 relatives with LC. 21(26.58%) had at least 2 relatives with Cancer. Two pts had 7 and 10 relatives with CA. *EGFR* was mutated in 16 (20.25%), but T790M prior to therapy was found on 2 pts; they had no FH of LC. 3 tested positive for *ALK*, none tested positive for *ROS*. Pts with FH tended to be younger (p=0.046). 10 (12.65%) pts meet criteria for GT according to FH for breast, ovarian, prostate and colon cancer; 1 of those relatives tested negative for *BRCA1&2* for Ovarian CA. **Conclusion:** We think that implementing this service could increase the awareness of the potential use of GC in LC. Our sample is small, nonetheless we could identify at least 10 pts who would benefit of GT: multigene testing would be needed at least for these pts. Recognise the cases with hereditary background could bring many advantages to pts and their families. We expect to offer GT to LC pts and eventually, measure the potential advantages against stigma.

Keywords: Genetic Counseling, Real World, GCRA

EP1.11-23 PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL OF FDG-PET-CT IN FOLLOW UP OF STAGE II-IIIA NSCLC POST TREATMENT

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Background: Early stage Non-Small Cell Lung Cancer (NSCLC) accounts for some 70% of all lung cancer and, although curative treatment may be an option, the 5 year survival remains poor at just over 50%. If cancer recurrence or new disease following initial treatment could be detected earlier, especially whilst still asymptomatic, overall survival may be improved by enabling the earlier use of modern effective salvage therapies. Currently, there is limited evidence, and no consensus in Australia or internationally, on the most effective surveillance strategy following curative treatment. Hence, there is a critical need for a prospective study to examine whether a modern approach to surveillance imaging with PET-CT to detect NSCLC recurrence or new disease earlier and whilst still asymptomatic will not only improve survival but is cost effective. **Method:** We propose a randomised controlled trial of systematic PET-CT for follow up of patients treated with curative intent for stage II-IIIA NSCLC at hospitals across Australia. Patients will be randomised to either usual care or systematic PET-CT 6 monthly over 3 years and followed for 5 years. Patients with new or recurrent disease will be referred for treatment to their usual clinical team and treatment details collected. The primary outcome of this study will be overall survival. Secondary outcomes include, 1. Detection rate for new tumours and a/symptomatic recurrence 2. Number/type of investigations used in the control arm. 3. Number/type of investigations used in the evaluation of new problems. 4. False positive/negative detection rate. 5. Cost effectiveness analysis. 6. Patient experience. Study design is a 2 arm trial with 1:1 randomisation to routine PET-CT surveillance added to usual care (or usual care alone), commencing 6 months after surgery or curative radiotherapy. The study will be stratified by centre, stage, curative therapy and ongoing smoking status. **Result:** Section not applicable **Conclusion:** The study results will define for each stage of disease, whether active surveillance with PET-CT added to usual care prolongs survival compared to usual care. It will also allow for collection of real-word data to understand of what constitutes usual care such that the mortality from the commonest cause of cancer death in our community.

Keywords: Follow up, PET-CT, NSCLC

EP1.11-24 THE TREAT MODEL 2.0: PREDICTING LUNG CANCER IN PATIENTS SEEKING CARE IN HIGH-RISK CLINICS

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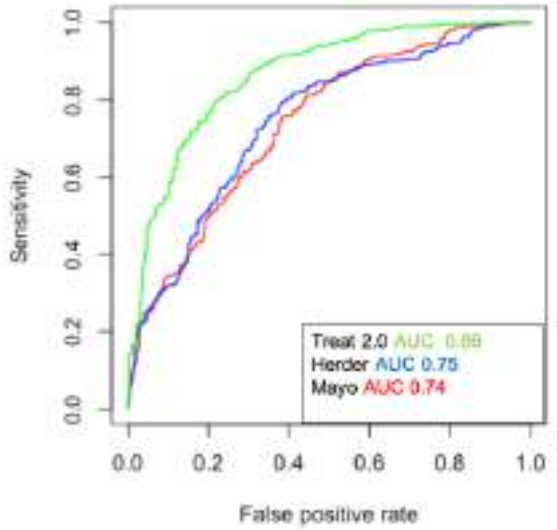
Background: Appropriate risk-stratification of indeterminate pulmonary nodules (IPNs) is necessary to estimate the best diagnostic strategy. Validated models for patients with high-risk IPNs are poorly calibrated. We sought to expand our previous Thoracic Research Evaluation And Treatment (TREAT) model into a more generalized, robust model for lung cancer prediction, the TREAT 2.0. **Method:** A total of 1402 patients with known or suspected lung cancer were used to recalibrate the TREAT 1.0 model. Clinical data and patient demographics were retrospectively collected from six clinics located in four U.S. states. Six datasets were divided into 3 clinical groups: patients who presented to a pulmonary nodule clinic (n=375), patients who presented to an outpatient thoracic surgery clinic (n=553) and patients who presented for surgical resection (n=474). A logistic regression model using multiple imputation was developed and validated. Model variables included age, body mass index, gender, smoking pack-years, size of nodule, spiculation, growth over time, location in upper lobe, prior cancer history, pre-operative FEV1, pre-operative symptoms, FDG-PET positivity, and clinical group. The discrimination and calibration of the TREAT 2.0 model was estimated and compared to two other common models for lung nodules, the Mayo Clinic and Herder models. **Result:** Lung cancer prevalence was as follows: pulmonary nodule clinic 42%, thoracic surgery clinic 73%, and surgical resection cohort 90%. The strongest predictors of cancer were clinical group, age, nodule growth, PET positivity, and smoking pack-years. The median TREAT 2.0 area under the receiver operating curve (AUC) for the imputed dataset was 0.86 (95% confidence interval (CI), 0.86-0.87) and the Brier score was 0.13. The TREAT 2.0 model had better accuracy ($p < 0.001$) (Figure 1) and calibration than the Mayo Clinic (AUC =0.74 95% CI: 0.74-0.75; Brier score=0.21) or Herder models (AUC=0.75; 95%CI: 0.74-0.75 and Brier score=0.19).



Conclusion: The TREAT 2.0 model is more accurate and better calibrated than the Mayo Clinic or Herder models in patients presenting with nodules at high risk for lung cancer. Nodule calculators such as the TREAT 2.0 that account for variation in lung cancer prevalence with a variable for clinical group may improve generalizability and increase use in clinical practice.

Keywords: Lung cancer, prediction model, lung nodule

EP1.12 SMALL CELL LUNG CANCER/NET

EP1.12-01 DOES PCI STILL HAVE A ROLE IN LIMITED SCLC?

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Background: Prophylactic cranial irradiation (PCI) has long been an integral part of treatment protocols for limited stage small cell lung cancer (SCLC). PCI stands for "prophylactic" while it may be not really prophylactic, rather therapeutic for un-detectable brain disease. **Method:** A survey of 39 questions was conducted on the online platform "Survey Monkey" for practicing oncologists, radiotherapists, pulmonologists and thoracic surgeons. The aim of this survey is to establish a practice baseline for a future multicenter study of overall survival (OS) benefits of PCI versus MRI follow-up in limited SCLC. **Result:** 41 respondents participated from 14 European countries (26 oncology centers) and from 4 US radiotherapy centers: medical oncologists (31%), radiation oncologist (25%), pulmonologists (34%). Brain imaging at diagnosis of SCLC is performed by MRI in 83% and CT with contrast in 49%. Brain follow up after chemotherapy is performed by MRI in 49%, CT with contract in 41%, and no imaging in asymptomatic patients in 20%. PCI is recommended to 67% of patients and performed immediately after the last chemotherapy in 37%, or 2 months after chemotherapy in 49%. The most important criteria whether patient needs PCI are performance status and response to chemotherapy. The most common schedule of PCI is 25Gy in 10 fractions, 41% of respondents. In case of a single brain metastasis after PCI the 1st choice of treatment is SRS, in 93%. Regarding the role of PCI 46% of respondents think that PCI prevents brain metastases from occurring, and 54% think that PCI treats occult brain metastases. **Conclusion:** The lack of clinical trials about PCI for limited SCLC patients is undisputed. Our survey shows practice patterns to PCI for patients with limited SCLS depends on Institution and/or specialty. These results establish a practice baseline for a multicentral trial of PCI versus MRI observation, and 93% of our respondents agreed to take part in this trial.

EP1.12-02 SCLC TREATMENT UPTAKE AND SURVIVAL OUTCOMES: A 2-YEAR COMPARISON BETWEEN 2 TERTIARY REFERRAL CENTERS IN ALBERTA, CANADA

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Background: Although the guideline recommend treatment for small cell lung cancer (SCLC) has not changed for several decades, real world evidence on patterns of practice and outcome are scarce. We compared two similar sized cancer care centers in the province of Alberta over a two-year period for experiences with both extensive stage (ES) and limited stage (LS) SCLC diagnoses, treatment and survival outcomes **Method:** Retrospective analyses were conducted on the clinical data of SCLC patients retrieved from the Glans-Look Lung Cancer database. All SCLC patients diagnosed between 2015 and 2016 at the Tom Baker Cancer Centre (TBCC), Calgary and Cross Cancer Institute (CCI), Edmonton were included. The characteristics of patients seen at the two institutions were compared using the Fisher Exact test. The overall survival (OS) outcome based on guideline recommended 1st and 2nd line SCLC treatments as well as treatment location was estimated with Kaplan Meier survival analysis and multivariate Cox Proportional Hazard model. **Result:** Between 2015 and 2016, 105 SCLC patients were diagnosed at the TBCC, Calgary and 243 at CCI, Edmonton, Alberta. Patient characteristics were similar for both centers. 66% (69/105) of SCLC were ES at TBCC as opposed to 78% (189/243) in CCI ($p = 0.024$). Overall, treatment uptake rates in TBCC compared to CCI were as follows: 1st SCLC treatment (chemotherapy, surgery, radiotherapy) rate 88% (92/105) versus 86% (208/243), prophylactic cranial irradiation (PCI) 27% (28/105) vs. 37% (89/243) and 2nd line chemo- and or radio-therapy 33% (35/105) vs. 30% (74/243). 6% (2/36) of LS patients at TBCC compared to 28% (15/54) at CCI had surgery ± adjuvant as their 1st treatment. More ES patients at CCI received chemo & thoracic RT (32 vs.19%, 61/189 and 13/69) as well as PCI (31 vs.16%, 58/189 and 11/69) than those at TBCC. OS at CCI versus TBCC was not statistically different for all SCLC patients (11 vs. 10 months, $p = 0.217$; HR = 1.278, 95% CI: 0.978 -1.671, $p = 0.072$) nor when we stratified patients by LS or ES. **Conclusion:**

Despite subtle variation in the uptake of PCI, surgical resection of peripheral LS, management patterns for SCLC patient, including the uptake of second line treatment were consistent between the two geographically separate centers. It is reassuring that similar survival outcomes can be achieved in the real world setting by the adoption of standard practices across a single health administered jurisdiction.

Keywords: Chemoradiotherapy Uptake, Prophylactic Cranial Irradiation, Small Cell Lung Cancer Survival

EP1.12-03 THE SIGNIFICANCE OF INSM1 EXPRESSION IN SMALL CELL LUNG CANCER

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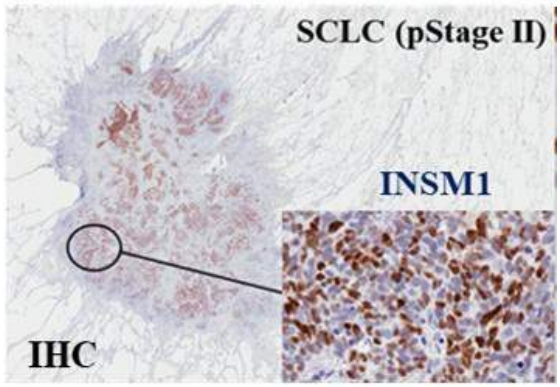
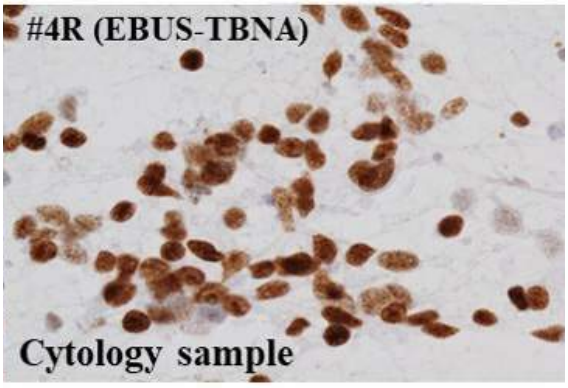
Background: We previously demonstrated that INSM1 expressed in NE tumors (NETs) exclusively and INSM1 is a highly sensitive and specific immunohistochemical (IHC) marker in NETs, such as small cell lung cancer (SCLC). In the present study, we investigated 1) diagnostic performance of INSM1 in the diagnosis of SCLC in various types of samples 2) the association of INSM1 with clinical course. **Method:** We evaluated INSM1 as an IHC marker in 384 formalin-fixed paraffin-embedded lung cancer samples (291 surgically resected samples (90 SCLCs and 201 NSCLCs) and 55 CT-guided biopsy samples (25 SCLCs and 30 NSCLCs)), in 50 cytology samples (25 SCLC metastatic lymph nodes and 25 NSCLCs) obtained by endobronchial ultrasound-guided transbronchial needle aspiration. The mRNA expression levels of INSM1 was examined using qRT-PCR in 37 SCLCs and 40 NSCLCs. We evaluated the association of INSM1 expression (IHC and qRT-PCR data) with clinical course. **Result:** INSM1 was expressed in 94% of formalin-fixed paraffin-embedded SCLC samples (109/115) and in 92% of cytology SCLC samples (23/25). Whereas, 4 out of 231 formalin-fixed paraffin-embedded NSCLC cases (1.7%) had weak expression of INSM1 and none of the cytology NSCLC samples were positive. The mRNA level of INSM1 was significantly higher in SCLCs including in two cases who were INSM1 negative with IHC. No association between IHC positivity and mRNA expression level of INSM1 with evaluated clinical features including overall survival was observed. **Conclusion:** Our study suggests INSM1 is a reliable IHC marker for SCLC in various types of clinical samples. There was no association between INSM1 and clinical courses in the present study.





Keywords: Lung cancer, SCLC, INSM1

EP1.12-04 CAN PROPHYLACTIC CRANIAL IRRADIATION REDUCE NEUROLOGICAL SYMPTOMS IN PATIENTS WITH SMALL CELL LUNG CANCER?

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Background: The central nervous system is the usual site of metastasis in patients with small cell lung carcinoma (SCLC). Despite advances in combined treatment modalities, it's the main cause of morbidity in these patients. High prevalence of brain metastases, combined with the poor intracranial penetration of most chemiotherapy regimens used, led to development of prophylactic cranial irradiation (PCI), a preventive radiotherapeutic treatment, which has been shown to be effective in reducing the incidence of brain metastases. Earlier studies showed that patients who had PCI, had reduced rate of symptomatic brain metastasis at one year (14.6% vs 40.4%) and had slightly better overall survival. In Institute for pulmonary diseases of Vojvodina, there are around 1200 newly diagnosed patients with lung cancer in each year, of which around 200 patients (14%) have SCLC. PCI is now routinely administered to patients with SCLC, after a complete/partial response to initial treatment. **Method:** This was a retrospective study conducted at the Institute for Pulmonary Diseases of Vojvodina, Serbia, which included patients diagnosed with SCLC in this institution, between October 2015 - October 2017. The patients were divided into two groups, one who received PCI after complete/partial answer to systemic therapy and chest irradiation, total of 34 patients. The control group consisted of 30 patients, who also had good answer to systemic therapy and chest radiation therapy, but didnt receive PCI. **Result:** In this study, significantly higher percentage of patients in the PCI group (84.8% vs 40.0%) didn't develop neurological symptoms (p= 0.000). In the group of patients who received PCI, only 5 out of 34 (14.7%) developed CNS symptoms, an average of 10 months after completing the PCI. In the control group, 60% (18/30) of patients experienced neurological symptoms, on average 11 months after diagnosis. Data analysis found that patients in PCI group were 8.4 times less likely to develop neurological symptoms. Also, it was confirmed that overallsurvival was better for patients who received PCI after systemic and irradiation treatment, the mean OS of patients in the PCI group was 19.0 months, compared to the control group where it was 15.4 months. **Conclusion:** The authors strongly believe that PCI should remain a standard of care for patients with SCLC, after response to initial treatment. If not only for prolonging the overall survival, but also because it improves the quality of life in these patients by reducing the neurological symptoms.

Keywords: SCLC, brain, irradiation

EP1.12-05 IS THERE A ROLE FOR MEDIASTINAL LYMPH NODE DISSECTION IN PULMONARY CARCINOIDS?

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Background: Pulmonary carcinoids are slow growing tumours with surgery being the mainstay of treatment. Histology(typical/atypical) and nodal status are known prognostic markers. In light of the results of the ACOSOG Z0030 trial, the role of mediastinal lymphnode dissection in surgery for NSCLC is being questioned. This question becomes more pertinent in pulmonary carcinoids, where nodal positivity is known to adversely impact survival and surgery is the only curative treatment option. **Method:** We performed a retrospective analysis of a prospectively maintained database of surgery in pulmonary carcinoids. Data regarding histology, type of surgery, imaging, nodal status, margin status and follow up were captured from the database and where missing, from the electronic medical records. Statistical analysis was performed using SPSS version 20 for Mac. **Result:** 141 patients with pulmonary carcinoid tumours treated with curative intent in a single center from August 2004 to February 2017 were included. 108 (76.6%) were typical carcinoids and 29 (20.6%) were atypical carcinoids. 4 patients were not classified. 120 (86.42%) patients underwent mediastinal nodal sampling or systematic clearance. The median survival in patients undergoing lymphnode dissection was 66 months, where as it was 53.5 months in those who did not(p = 0.43). Twenty (16.66%) patients were node positive. Node positivity rate in typical carcinoids was 11.11%, while that in atypical carcinoids was 27.58% After a median follow up of 57 months, 115 (81.6%) patients are alive and

disease free, 10 (7.1%) are alive with disease, 6 (4.3%) have died due to disease, 6 (4.3%) have died due to other causes. Estimated 5 yr survival in patients with typical carcinoids is 96.9% while that of patients with atypical histology is 67.8%. (p<0.001) Patients with positive nodes had an estimated 5 yr survival of 80.5% while that in node negative patients was 95.37%. (p=0.12). **Conclusion:** In our series, the node positivity rate was higher than reported in literature and this could be seen in both patients with typical and atypical histology. Nodal positivity also showed a trend towards decreased survival showing that it is an important prognostic factor. Lymphnode dissection showed a trend towards improved survival, though not statistically significant. The lack of statistical significance could be attributed to the fewer number of cases in the study and the lower number of events. In view of the relatively low morbidity of the procedure and the lack of any other curative treatment option we suggest that systematic lymph node dissection be performed for all cases of pulmonary carcinoids. A randomized study to answer this question appears unlikely.

Keywords: pulmonary, carcinoid, atypical

EP1.12-06 NEW TREATMENT OPTION FOR ES-SCLC: PATIENT CHARACTERISTICS AND USE OF AN ATEZOLIZUMAB REGIMEN IN THE REAL-WORLD SETTING

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Background: Results from the Phase III IMpower133 study (NCT02763579) were previously made public. Based on improvements in overall survival in patients with extensive-stage small cell lung cancer (ES-SCLC) who received atezolizumab plus carboplatin and etoposide (IMpower133 regimen) vs chemotherapy administered in the 1L setting, the NCCN added this regimen to its guidelines (category 1, preferred) on October 10, 2018. Accordingly, some providers began implementing this regimen in their clinical practice, creating a unique opportunity to characterise its early and broad use in a real-world setting. **Method:** Patients with ES-SCLC who started treatment within 90 days of initial diagnosis and had a confirmed administration of atezolizumab with carboplatin or cisplatin and etoposide (atezo regimen) on or after September 25, 2018, were included from the de-identified Flatiron Health electronic health records–derived database, representing > 280 US cancer clinics (≈ 800 sites of care). Treatment data were analysed through April 30, 2019. Broad use was defined as treatment with the atezo regimen outside of several main clinical trial restrictions (ECOG PS ≥ 2, abnormal laboratory values, cisplatin use or as 2L treatment). Frequencies and percentages are reported. Monthly uptake was defined as the percentage of ES-SCLC patients starting 1L therapy each month who were treated with the atezo regimen. **Result:** Uptake of the atezo regimen increased from 10% in October 2018 to 46% in February 2019 (before FDA approval on March 18, 2019) and 66% in April 2019 (after FDA approval); 143 patients were identified, 92% of whom had ES-SCLC at initial diagnosis (Table). The atezo regimen was used broadly among 46% of patients (18% with ECOG PS ≥ 2, 18% with an abnormal laboratory value, 1% on cisplatin, 17% as 2L ES-SCLC treatment). The median time from ES-SCLC diagnosis to start of the atezo regimen was 16 days for 1L patients and 78 days for 2L patients. Patients treated with the atezo regimen in the 1L were administered atezolizumab at a median of 8 days after start of chemotherapy; those treated in the 2L were typically administered atezolizumab immediately at the start of the line. **Conclusion:** This real-world analysis demonstrates the broad use of the atezo regimen, with nearly half of patients treated outside of several main IMpower133 trial restrictions. Further, a rapid uptake of the regimen even before FDA approval underscores its impact on changing clinical practice and the high unmet need of this patient population.

Table. Characteristics of Patients Treated With the Atezolizumab Plus Carboplatin/Cisplatin and Etoposide Regimen in Routine Clinical Care

Patients, n	143
Treated prior to FDA approval (March 18, 2019), n (%)	101 (71)
Median age at ES-SCLC diagnosis (IQR), years	67 (61, 73)
Aged ≥ 65 years at ES-SCLC diagnosis, n (%)	90 (63)
Female, n (%)	71 (50)
White, n (%)	100 (70)
Smoking history, n (%)	137 (96)
Stage at initial diagnosis, n (%)	
LS	7 (5)
ES	132 (92)
Unknown	4 (3)
ECOG PS, n (%)a	
0 or 1	76 (53)
2+	26 (18)
Unknown	41 (29)
Radiation therapy, n (%)b	14 (10)
LS setting, n	7
ES setting, n	7
Regimen, n (%)	
Atezolizumab, carboplatin, etoposide	141 (99)
Atezolizumab, cisplatin, etoposide	2 (1)
Line of therapy of atezo regimen in ES setting, n (%)	
1L	119 (83)
2L	24 (17)
Median time from ES-SCLC diagnosis to start of line of therapy containing atezo regimen (IQR), days	
1L	16 (11, 26)
2L	78 (59, 98)
Median time from ES-SCLC diagnosis to first administration of atezo within line (IQR), days	
1L	24 (14, 27)
2L	78 (59, 98)
Abnormal baseline laboratory value, n (%)c	26 (18)

1L, first line; 2L, second line; atezo, atezolizumab; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration; IQR, interquartile range; LS, limited stage; PS, performance status. a ECOG PS value closest to within −30 to +7 days of treatment start. b Includes radiation therapy to chest following initial diagnosis of SCLC, including concurrent radiation therapy with systemic chemotherapy, chemotherapy followed by radiation therapy, up-front palliative radiation therapy to the chest or for superior vena cava syndrome. c Abnormal values defined as those not meeting the following definitions: absolute lymphocyte count ≥ 500/μL, lymphocyte count ≥500/μL, absolute neutrophil count ≥ 1500 cells/μL, platelet count ≥100,000/μL, hemoglobin ≥ 9.0 g/dL, aspartate aminotransferase ≤ 5 × upper limit of normal (ULN), alanine aminotransferase ≤ 5 × ULN, alkaline phosphatase ≤ 5 × ULN, serum bilirubin ≤ 1.25 × ULN, serum creatinine ≤ 1.5 × ULN, serum calcium ≤ 12 mg/dL.

Keywords: first line, Atezolizumab, real-world

EP1.12-07 HIGH DISCREPANCY OF CHEMOTHERAPY OUTCOMES BETWEEN PATIENTS WITH PERIPHERAL AND CENTRAL SMALL CELL LUNG CANCER

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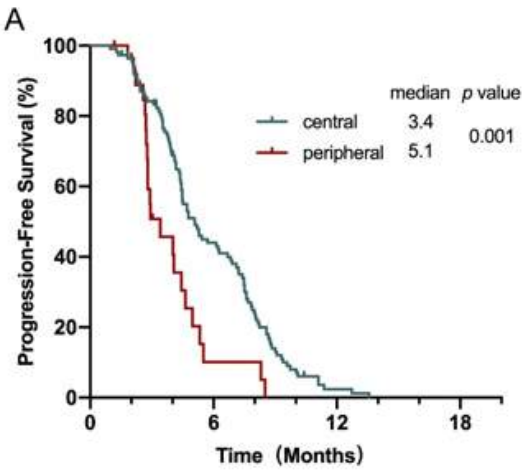
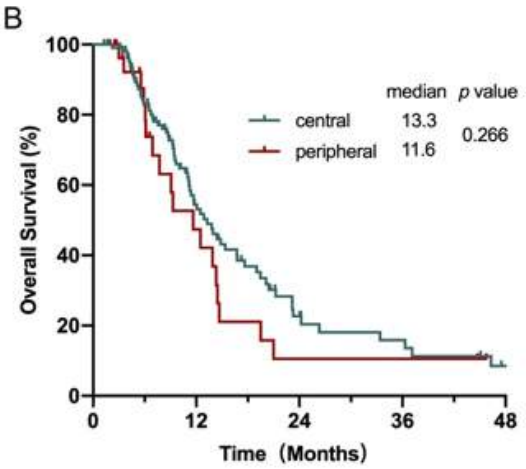
Background: Previously we found that imaging central and peripheral LCNEC has distinct clinicopathologic features and survival. As LCNEC and SCLC are all neuroendocrine tumor, this study further investigated whether imaging tumor location impact the outcome of first line chemotherapy in patients with small cell lung cancer extensive disease. **Method:** Patients with ES-SCLC diagnosis between May 2014 and September 2015 in Shanghai Pulmonary Hospital, Tongji University were included. Contrast enhanced CT scans were reviewed retrospectively for tumor location (central or peripheral) and imaging features. The clinical characteristics and outcomes of chemotherapy were collected and compared. **Result:** 140 patients were identified with a median age of 64, 89.3%, 76.4% and 98.6% were male, smokers and ECOG PS 1 respectively. Among them, 135 received etopside based chemotherapy and 5 received irinotecan based chemotherapy.111 (79.3%) had central-type and 29 (20.7%) had peripheral-type SCLC. The patients characteristics were similar between the central and peripheral subgroups. Peripheral subgroup showed less marginal GGO (65.5% vs 84.7%, p=0.02), obstructive pneumonia (48.3% vs 80.2%, p=0.001), obstructive atelectasis (3.4% vs 40.5%, p<0.001) and effusion (37.9% vs 61.3%, p=0.011) than central tumors. Peripheral subgroup had lower ORR (44.8% vs 73%, p=0.004) and DCR (79.3% vs 92.8%, p=0.042). The median PFS was 4.6 months in the entire cohort and peripheral subgroup had significantly short PFS than central one (median PFS: 3.4 vs 5.1 months, p=0.001, figure A). The median OS was 12.9 months and peripheral subgroup had numerally short OS (median 11.6 vs 13.3 months, p=0.266, figure B).





Conclusion: Central type tumors account for most of SCLC, while patients with peripheral tumors had a significantly lower ORR, shorter PFS and OS after the first line chemotherapy than central type.

Keywords: SCLC, imaging features, Chemotherapy

EP1.12-08 PROGRAMMED DEATH-LIGAND 1 AND HUMAN LEUKOCYTE ANTIGEN CLASS I EXPRESSION IN VARIOUS NEUROENDOCRINE TUMORS OF THE LUNG

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Background: Pulmonary neuroendocrine tumors (PNETs) encompass a broad spectrum of tumors including typical carcinoid (TC) and atypical carcinoid (AC) tumors, small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) with important pathological, biological and clinical differences. Recently, FDA grants Atezolizumab regimen for use in combination with carboplatin and etoposide for the frontline treatment of patients with extensive stage SCLC. The aim of this study was to investigate Programmed death-ligand 1(PD-L1) and Human leukocyte antigen (HLA) class I expression patterns in PNETs. **Method:** PD-L1 and HLA class I expression was evaluated by immunohistochemistry in a total of 37 resected lung neuroendocrine tumors using tissue microarray. Correlations between the expression of HLA class I/PD-L1 and clinicopathologic features and prognostic significance were analyzed. **Result:** Of the 37 patients enrolled in this study, 32 patients (86.5%) were male and the median age was 66 years (range, 35–81 years), and 28 patients (75.6%) were current or ex-smokers. The pathologic stage (AJCC 8th) in the patients at presentation was IA(including IA1, IA2, IA3) in 11 patients (24.3%), IB in 4 patients (10.8%), IIA in 1 patients (2.7%), IIB in 4 patients (10.8%), IIIA in 10 patients (27.0%), IIIB in 4 patients (10.8%), and IVA in 1 patients (2.7%). Histologically, 6 patients (16.2%) were diagnosed TC, 5 patients (13.5%) with AC, 9 patients (24.3%) with SCLC, and 17 patients (45.9%) with LCNEC. Positive PD-L1 expression in tumor cells was 29.7% (11/37, 1% cut-off), and the numbers (proportions) of positive PD-L1 expression according to histologic subtypes were as follows; TC/AC/SCLC/LCNEC, 2(33.3%)/2(40.0%)/1(11.1%)/6(35.2%). HLA class I expression was reduced in 86.5% (32/37). The numbers (proportions) of reduced HLA class I expression according to histologic subtypes were as follows; TC/AC/SCLC/LCNEC, 5(83.3%)/5(100%)/8(88.9%)/14(82.4%). In survival analysis, (median overall survival (OS); 56 months) there was no significant difference in OS according to PD-L1 and HLA class I expression status. However, two cases with HLA(+)/PD-L1(+) showed more unfavorable survival curves and three cases with HLA(+)/PD-L1(-) showed a tendency of more favorable clinical course. **Conclusion:** Lung NETs shows frequent HLA class I reduction and variable PD-L1 expression. Although this is a preliminary study including small number of NETs, the finding that NETs with HLA(+)/PD-L1(-) showed favorable clinical course suggests immune microenvironment might be one of the important biomarker for NETs of the lung.

Keywords: Pulmonary neuroendocrine tumors, Programmed death-ligand 1, Human leukocyte antigen class I

EP1.12-09 EGFR-MUTANT ADENOCARCINOMA TRANSFORM INTO SMALL-CELL LUNG CANCER: REAL OR NOT

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Background: Small-cell transformation is well known as one of the acquired resistance mechanism to EGFR-tyrosine kinase inhibitors (TKIs), nevertheless we recently found an interesting phenomenon that most small-cell transformations actually are combined small-cell lung cancer before TKI treatments rather than pure adenocarcinoma. **Method:** We retrieved 13 patients with former pathological diagnosis of adenocarcinoma before TKI therapies from 1,082 cases with SCLC component and compared the previous biopsy results of the these cases. All the previous adenocarcinomas slides were gathered and were reviewed one by one carefully again by an advanced pathologist. **Result:** All patients were stage IV EGFR-mutant adenocarcinomas and treated with EGFR-TKIs before SCLC transformation diagnosed.

After their disease progress, re-biopsy were performed to identify resistance mechanism. Previous pathology showed only one patient was diagnosed with combined SCLC mixed with adenocarcinoma before TKI, the rest 12 cases were pathologically diagnosed of pure adenocarcinoma and identified as small-cell transformation. We amazingly found that 9 of 12 patients actually contained very few SCLC component when we reviewed these cases, varying from less than 1% to 5%. Dubious SCLC components were found in two patients. Only one patient was a real small-cell transformation and we didn't find any SCLC mixture on previous adenocarcinoma sections. In conclude about 75% (9/12) of cases originally diagnosed with small-cell transformation were actually pseudo-small-cell transformation. Combined SCLC with very few SCLC components were prone to be misdiagnosed into pure adenocarcinoma. **Conclusion:** Most metastatic lung cancers were diagnosed with small biopsy, in which the potential mixture of SCLC was much more easily to miss, so the pseudo-small-cell transformation may be more common than estimate in real world. It's worth noting that careful review again of the previous adenocarcinoma sections is essential before diagnosis of small-cell transformation.

Keywords: SCLC transformation, EGFR mutation, NSCLC

EP1.12-10 MOLECULAR CHARACTERIZATION OF NSCLC-LIKE AND SCLC-LIKE SUBSETS IN CHINESE PULMONARY LARGE-CELL NEUROENDOCRINE CARCINOMA (LCNEC)

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Background: LCNEC is an aggressive, biologically heterogenous carcinoma which can be molecularly characterized as SCLC-like and NSCLC-like. Accurate distinction of molecular subset is of major clinical relevance since it may guide treatment choices in LCNEC. Here we determined the genomic characteristics of the two LCNEC subsets in a Chinese cohort to clarify their correlations with traditional lung cancer histologies. **Method:** FFPE samples from 31 LCNECs were sequenced using a 520-cancer-related gene panel, with an average sequencing depth of 1385X. Comparative mutational analysis was conducted between NSCLC-like LCNECs from our cohort and adenocarcinomas from TCGA dataset **Result:** Despite similar clinical features in terms of stage and age at diagnosis, NSCLC-like (42%, 13/31) and SCLC-like (32%, 10/31) subsets from LCNEC displayed distinct molecular characteristics. NSCLC-like subset harbored significant higher mutation frequencies of *STK11, KEAP1* and *FAT3* (53.8%, 38.5% and 38.5%, p=.007, .046 and .046), while SCLC-like subset was characterized by highly mutated *RB1* (100%, p<.001) and *PTEN* (50%, p=.007). Compared with TCGA adenocarcinomas, NSCLC-like LCNEC displayed more frequent mutations in *TP53*, *STK11*, *APC*, *KMT2D* and *SMARCA4* (76.9%, 53.8%, 30.8%, 30.8% and 23.1%; p=.043, .004, .045, .005 and .049). In addition, potential targetable alterations were present in 46.2% (6/13) pts of NSCLC-like subset. For those advanced stage pts, 2/5 NSCLC-like and 5/5 SCLC-like pts received relevant chemotherapy according to their molecular characteristics. The clinical outcomes of these pts are still under follow-up. **Conclusion:** This study demonstrates the distinct molecular features between NSCLC-like and SCLC-like subsets, and highlights the predominant genomic similarity and separate entities between NSCLC-like LCNEC with adenocarcinoma. Given the evidence that genomic profiling may aid in informing treatment decisions for pts with LCNEC, our study indicates that, based on accurate molecular typing, 46.2% NSCLC-like pts may benefit from potential targeted therapy and the rest of them may be more suitable to receive NSCLC-chemotherapy

Keywords: large-cell neuroendocrine carcinoma(LCNEC), next-generation sequencing (NGS), driver gene

EP1.12-11 EFFECT OF TREATMENT MODE ON PROGNOSIS OF RESECTABLE LIMITED-STAGE SMALL CELL LUNG CANCER

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Background: The optimal choice of post-operative treatment mode for resectable limited-stage small cell lung cancer (SCLC) is controversial in clinical practice. Different treatment modes may have different effects on prognosis of small cell lung cancer after resection. **Method:** Data from a total of 122 patients with limited-stage SCLC undergoing operation were collected at our Cancer Hospital from 2012 to 2016. Clinical and pathological features, and treatment modes (including surgical methods, postoperative adjuvant radiotherapy and chemotherapy, prophylactic brain radiotherapy, etc.) were compared in small cell lung cancer after resection .The survival outcomes among different factors were analyzed by Kaplan-Meier method, and the survival differences among different factors were compared by log-rank method. Multivariate cox regression analysis was used to explore independent prognostic factors. **Result:** The median follow-up time was 54.23 months. Among 122 patients, the 1-, 3- and 5-year overall survival (OS) rates were 95.08%, 75.14% and 63.79%, respectivly. The 1-, 3- and 5-year recurrence-free survival (RFS) rates were 80.99%, 66.62% and 61.86%, respectively. Recurrences were diagnosed in 56 (45%) patients, including 22 (39%) with brain metastasis, 15 (27%) with intrapulmonary recurrence, 7 (13%) with bone metastasis, 6 (11%) with hepatic metastasis, and 6 (11%) with other metastasis. Operation patterns affected OS. 116 patients received lobectomy and 6 patients received pneumonectomy. Median OS of these two groups were 68.37 and 35.37 months, respectively (p = 0.028). The T stage affected the postoperative OS. The median OS of T1,T2,T3 were 65.87, 71.29 and 29.92 months, respectively (p = 0.021). The disease-free survival (PFS) and OS of patients receiving adjuvant chemotherapy or combined with radiotherapy were longer than those receiving surgery only. The median PFS of adjuvant chemotherapy group, chemotherapy and radiotherapy combination group, and simple surgery group were 69.01,53.87 and 19.37 months, respectively (p=0.002). Accordingly, the median OS were 70.6, 65.56 and 30.8 months (p=0.002). Patients with postoperative prophylactic cranial irradiation (PCI) had a longer OS than those without PCI (62.28 vs. 78.84 months, p=0.028). **Conclusion:** As for patients with resectable limited-stage SCLC,the 5-year survival rate of patients with surgery is higher than those without. Lobectomy is the optimal surgery mode, and adjuvant chemotherapy combined with prophylactic cranial irradiation after operation can significantly prolong the OS.

Keywords: small cell lung cancer, surgery, Chemotherapy

EP1.12-12 FACTORS ASSOCIATED WITH SURVIVAL OUTCOMES AMONG RELAPSED SCLC DIAGNOSED AT A CANADIAN CANCER CENTRE

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Background: The 5-year survival rate for small cell lung cancer (SCLC) is only 7%. This poor survival is partly accounted for by sparse management options for the high proportion of patients developing disease progression or recurrence after their initial treatment (Koinis et al. 2017). Clinical guidelines recommend 2nd line chemotherapy only for SCLC patients who relapse ≥90 days after their 1st line treatments. This study examined factors predicting favorable survival outcomes among relapsed SCLC patients seen at the Tom Taker Cancer Centre, Alberta Canada. **Method:** Retrospective analyses were conducted on clinical data of SCLC patients retrieved from the Glans-Look Lung Cancer database. All SCLC patients diagnosed between 2010 and 2016 who completed ≥ 4 cycles of 1st line platin doublets or single-agent etoposide and then relapsed during or after their initial treatments were included. The characteristics of patients relapsing ≥90 versus <90 days were compared using the Fisher Exact test. The overall survival (OS) was estimated using the Kaplan Meier survival and multivariate Cox Proportional Hazard model. **Result:** 190 SCLC patients were identified, of which 68% were extensive stage (ES), 57% were female, and 98% were smokers (Ex or current), with a median age of 67 at diagnosis. Most patients relapsed in ≥90 days:

57/60 (95%) for Limited stage (LS) and 102/130 (79%) for ES (p = 0.003). 48% of LS and 45% of ES received 2nd line systemic treatment (2L). In ES, receiving 2L cisplatin/etoposide was associated with better survival compared to not receiving 2L (HR=0.426, p=0.016) and having a longer relapse interval (≥90 days) was also associated with better survival (HR=0.539, p=0.015). Stratifying by relapse intervals, receiving 2L was associated with better survival in both the ≥90 (445 vs 286 days, p = 0.049) and <90 days (301 vs 219 days, p = 0.059) strata. In LS, favorable OS was associated with initial thoracic radiation (RT) receipt (HR=0.237, p=0.024) and no distant metastases (DM) at relapse (HR=0.257, p=0.005). Also of note, 83% LS and 21% ES had RT (p < 0.001) and at relapse, 52% LS and 92% ES had distant metastases. **Conclusion:** The median OS in relapsed SCLC is low but is at least improved with 2L receipt in relapsed ES patients irrespective of the time to relapse (≥90 or <90 days). Hence, more effective therapy is required for these patients.

Keywords: Small Cell Lung Cancer, 2nd Line Chemotherapy, Overall Survival

EP1.12-13 CONSOLIDATION RADIOTHERAPY IN EXTENDED DISEASE SMALL CELL LUNG CANCER: SINGLE CENTER EXPERIENCE

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Background: Consolidation radiotherapy in extended disease small cell lung cancer (ED-SCLC) showed improved 2 year overall survival (OS) in patients who responded to chemotherapy according to the results of CREST trial and many centers included this treatment in local guidelines. **Method:** We retrospectively reviewed medical records of patients with small cell lung cancer (SCLC) treated at the Institute of Oncology Ljubljana from January 2010 to December 2014. Median follow up was 65 months. We compared median overall survival (mOS) of patients with ED-SCLC treated with chemotherapy (ChT) only and those treated with ChT and consolidation radiotherapy (RT). We also compared mOS of patients treated with different consolidation doses. **Result:** Out of 703 patients 411 (58.5%) had ED-SCLC and were included in our analysis. Of those 59 patients received only best supportive care (BSC), 66 patients had RT only, 113 had ChT only and 173 patients had combination of ChT and RT. Median OS of patients who had either BSC or RT only was poor, 1.86 and 2.42 months, respectively. Patients who had any form of additional chest irradiation had significantly better mOS than patients with ChT only (9.9m vs 7.6m, p=0.002). Consolidation radiotherapy was delivered to 76 patients. Patients with consolidation RT had significantly longer mOS compared to patients with ChT only, 11.1 months (CI 10.1-12.0) vs 7.6 months (CI 6.9 - 8.5), p<0.001. They also had longer 1-year OS (44% vs 23%) as well as 2-year OS (10% vs 5%). Different fractionation schemes were used for consolidation RT. Patients with 45 Gy (in 18 fractions) had better mOS compared to lower doses 30-36Gy (in 10-12 fractions), 17.2 months vs 10.3 months, p=0.03. Patients with higher dose of consolidation RT had better 1-year OS (68%) than those with lower dose (30%) and also better 2-year OS (18% vs 5%). **Conclusion:** Consolidation RT improved mOS in ED-SCLC as compared to ChT only. Higher dose of consolidation RT (45Gy) had greater impact on survival than lower doses (30-36Gy).

Keywords: SCLC, consolidation radiotherapy, chemoradiotherapy

EP1.12-14 MULTIPLE PRIMARY MALIGNANT NEOPLASMS IN PATIENTS WITH SMALL CELL LUNG CANCER. THE EXPERIENCE OF OUR CENTER

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Background: Treatment and, mainly, modern diagnostic tools during the first diagnosis of the disease and follow-up, seem to improve survival in patients with small cell lung cancer (SCLC) and thus increase the number of patients diagnosed with multiple primary malignant neoplasms. **Method:** The aim of this retrospective study was to estimate and report the incidence of multiple primary malignant neoplasms and discuss the clinical characteristics of this subgroup of patients with SCLC. The study includes all patients consecutively admitted between 1/1983 -3/2019 at the Department of Medical Oncology, Evangelismos General Hospital, Athens, Hellas. **Result:** Five hundred fifty eight patients [386(69%) men, 172(31%) women, 285(51%) with limited and 273(49%) with extended disease] were included in the study. Median age was 63 (33-87)years, median ECOG was 2 (0-4) and median time of follow-up was 18+ (1+ - 696+) months. Three hundred ninety six (71%) had a short period of follow-up ≤24 months (group A), while 162 had a period of follow-up >24 months (group B). Multiple primary malignant neoplasms were detected in 23(4%) patients, 20(5%) men and 3 (2%) women (p<0.05), synchronous in 11(48%) and metachronous in 12(52%) patients, p=NS. The second malignant neoplasms were lung adenocarcinoma, squamous cell lung carcinoma, colon adenocarcinoma, bladder transitional cell carcinoma, head and neck squamous cell carcinoma, prostate adenocarcinoma, NHL, and thyroid follicular carcinoma in 7, 5, 4, 3, 2, 1 and 1 cases respectively. In the group of the 285 patients with limited disease 16(6%) multiple primary malignant neoplasms were observed in relation to 7/273(2.5%) of the patients with extensive disease (0.01< p<0.05). The multiple primary neoplasms were 12/396(3%) and 11/162(7%), p <0.05 in patients of the groups A and B respectively. **Conclusion:** 1. Development of multiple primary malignant carcinomas in patients with SCLC, does not seem to be a rare phenomenon. 2. The great majority of the multiple primary carcinomas (lung adenocarcinomas, squamous cell lung carcinomas, bladder transitional cell carcinomas, head / neck carcinomas) is smoking dependent. 3. The risk was higher in males, in patients with limited disease and in those surviving more than 24 months.

Keywords: Multiple Primary Malignant Neoplasms, SCLC, Second Primary Neoplasms

EP1.12-15 ONCOLOGIC TREATMENTS AND OUTCOMES FOR SMALL-CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES

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Background: Brain metastases (BM) are common in patients with small-cell lung cancer (SCLC), and are associated with short survival. Few data are available on this specific population of patients with SCLC and BM, as they are usually excluded from prospective randomized clinical trials. **Method:** We present data on all patients diagnosed with BM from SCLC from the Cancer Register of the Hospital Universitari Dr. Josep Trueta during 2013–2017. Age, gender, and treatment in patients were recorded. Data cut-off for survival analysis was 28th March 2019. **Result:** We identified 50 patients with SCLC and BM. Median age: 66 y (range: 48–82 y); male: 39 (78%). Synchronous BM were observed at the diagnosis of primary lung cancer in 33 (66%) patients. Impact of treatments on median overall survival (mOS) is summarized in Table 1. Only 1 patient received brain surgery (with an OS of 6.5 months). One-third of patients (34%) received best supportive treatment as unique treatment. The 1-year OS was 18% in our study.

Table 1

Treatment	%	mOS (without treatment)	mOS (with treatment)	p-value
Brain radiotherapy	52 %	1.4 m	9.1 m	< 0.000001
Chemotherapy	50 %	1.5 m	6.9 m	=0.003
Brain radiotherapy and chemotherapy	34 %	1.6 m	10.7 m	=0.000331

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Conclusion: Our real-world data reinforce the need for better therapies to improve the prognosis of patients with SCLC and BM.

Keywords: SCLC, brain metastasis, brain radiotherapy

EP1.12-16 CD47 EXPRESSION AND PROGNOSIS IN PATIENTS WITH SMALL CELL LUNG CANCERCD47 EXPRESSION AND PROGNOSIS IN PATIENTS WITH SMALL CELL LUNG CANCER

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Background: CD47 is an integral membrane protein expressed in all cells. CD47 present two opposing roles in cell survival. CD47 can interact with signal-regulatory protein-α (SIRP-a) on macrophages, prevents phagocytic clearance. Besides, CD47 signaling through the thrombospondin-1 limits self-renewal and suppresses expression of the stem cell transcription factors cMyc, Sox2, Oct4, and Klf4 in non-transformed cells. Data on the clinical significance of CD47 expression in patients with small cell lung cancer remain limited. **Method:** Forty-five naive patients with small cell lung cancer diagnosis were evaluated. Tumor samples obtained by biopsy or surgical resection, were collected for CD47 evaluation. Tumor samples were scored according to the fraction of stained cells at each intensity. The staining intensity of the cell membrane was scored within a scale ranging from 0-3. To determine the prognostic and predictive biomarkers of CD47, patients were stratified according to a cutoff point. This cutoff was optimized as a function of overall survival (OS) using the X-tile and Cutoff Finder software **Result:** Preliminary results showed that CD47 was present in 26.7% of population. We stratified the CD47 in two cohorts: CD47 positive-negative and a score of CD47>80. The CD47>80 was present mainly in patient with more than 60 years old (35% vs. 8.0%, p=0.024). Longer overall survival was associated with ECOG-PS 0-1 (20.2 vs. 6.9 p=0.001), disease stage IIIB (49.4 vs. 8.0, p=0.020), absent of CNS metastases (14.1-6.8, p=0.016) and absent of pleural effusion (16.2 vs. 6.99, p=0.002). Interestingly, patient with CD47 positive present better OS (10.8 vs. 6.99, p=0.485) but not reaching significance and patient with a score of CD47>80 have better OS (14.0 vs 9.2, p=0.296). **Conclusion:** Immune checkpoint CD47 expressed on the surface of tumor cells allows them to escape immunosurveillance. We previously reported that high CD47 expression was associated with the presence of somatic EGFR mutations in patients with NSCLC. In these patients, high CD47 expression was an independent prognostic factor of worse progression-free survival. Recent studies have indicated that the signal-regulatory protein (SIRP)α–CD47 pathway regulate a phagocytosis checkpoint in macrophages and other innate immune cells. In contrast, in this report we found that high CD47 expression was associated with <60 years old patient and better overall survival. Previously, studies in small cells lug cancer express high levels of CD47 and the blocking of CD47 enhances phagocytosis inhibits tumor growth. CD47 have a dual role, when interact with SIRPα avoid clearance of cells, but it interacts with thrombospondin 1 inhibits cell cycle progression and induces senescence in endothelial cells. Previous studies have shown that the protein TSP1 is as potent inhibitor of angiogenesis and its antiangiogenic activity is mediated by its receptors, CD36 and CD47. In conclusion CD47 have different function according to the ligand, and is a potential biomarker in cancer

Keywords: CD47, immune checkpoints, small-cell lung cancer

EP1.12-17 NEUROENDOCRINE MARKER STAINING PATTERN CATEGORIZATION OF SMALL-SIZED PULMONARY LARGE CELL NEUROENDOCRINE CARCINOMA

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Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is categorized as high-grade neuroendocrine carcinoma and is known to be associated with shorter survival than that of other non-small cell lung cancers. Radical therapies for these tumors are considered to have limited applicability to small-sized cases because of their rapid growth and early metastasis. The study aim was to identify subgroups with good or bad prognosis in patients with small-sized LCNEC (sLCNEC) that were based on immunostaining patterns with neuroendocrine markers. **Method:** From January 2001 to December 2017, of all patients with surgically resected LCNEC, we selected patients whose pathological tumor sizes were ≤30 mm in diameter (defined as small-sized tumors) and who underwent complete anatomical resection with hilar and mediastinal lymphadenectomy. We classified patients with sLCNEC into 2 subgroups based on immunostaining patterns with 3 neuroendocrine makers (chromogranin A, synaptophysin, and neural-cell adhesion molecule). **Result:** Forty-eight patients with sLCNEC were enrolled in this study. Of 48 patients with sLCNEC, 21 were categorized as the small-sized triple-positive group (sTP), whose patients were positive for the 3 neuroendocrine markers, and 27 patients were categorized as the small-sized non-triple-positive group (sNTP), whose patients were not positive for all 3 neuroendocrine markers. Table 1 shows cliniopathological characteristics among sNTP and sTP. The percentage of lymph node metastasis was significantly lower in sNTP than in sTP (11% and 48%, respectively, $P< 0.01$). There was no significant difference in overall survival, but recurrence-free survival (RFS) and tumor-specific survival (TSS) were significantly poorer in sTP than in sNTP (Fig 1). Multivariate analysis using 6 clinical factors (age, sex, surgical procedure, pN status, histology, and adjuvant chemotherapy) revealed that sTP were independent prognostic factors for poorer RFS and TSS than those of sNTP.

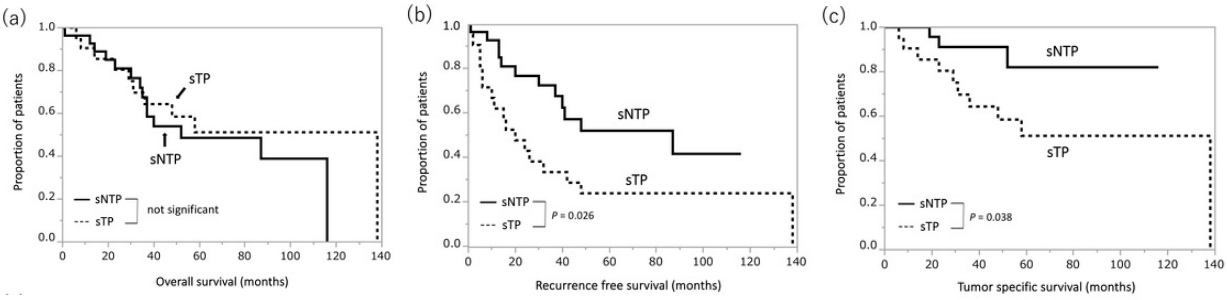
Table 1

Cliniopathological characteristics among sNTP and sTP.

Charasteristics	sLCNEC			*P* value
	All patients (n = 48)	sNTP (n = 27)	sTP (n = 21)	
Age (years)				0.08
Mean	67.7	68.6	66.5	
Range	30-81	51-81	30-78	
Gender				0.27
Male	40 (83)	24 (89)	16 (76)	
Female	8 (17)	3 (11)	5 (24)	
Smoking history				*
Current or former	44 (92)	27 (100)	17 (81)	
Never smoked	4 (8)	0 (0)	4 (19)	
Tumor diameter(mm)				0.84
Mean	22.1	22.2	21.9	
Range	8-30	8-30	12-30	
Pathological stage				*
I	35 (73)	24 (89)	11 (52)	
II	6 (12)	2 (7)	4 (19)	
III	7 (15)	1 (4)	6 (29)	
Lymphatic invasion (ly)				*
Positive	34 (71)	16 (59)	18 (86)	
Negative	14 (29)	11 (41)	3 (14)	
Surgical procedure				0.68
Lobectomy	42 (87)	23 (85)	19 (90)	
Segmentectomy	6 (13)	4 (15)	2 (10)	
Adjuvant chemotherapy				0.17
Chemotherapy	11 (23)	4 (15)	7 (33)	
None	37 (77)	23 (85)	14 (67)	

Values are presented as n (%) or mean.
sLCNEC: small-sized LCNEC patients,
sTP: small-sized LCNEC patients who were positive for all 3 neuroendocrine markers (synaptophysin,chromogranin A and NCAM),
sNTP: small-sized LCNEC patients who were positive for 1 or 2 of 3 neuroendocrine markers.
*: $P < 0.05$, **: $P < 0.01$.

Fig 1



Conclusion: The sNTP subgroup had good prognosis and the sTP subgroup had poor prognosis.

Keywords: Large cell neuroendocrine carcinoma, Small-sized tumor, Neuroendocrine marker

EPOSTERS

EP1.12-18 NET-001: A PHASE II STUDY OF ABI-009 IN METASTATIC NEUROENDOCRINE TUMORS OF THE LUNG OR GASTROENTEROPANCREATIC SYSTEM

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Background: Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies with limited systemic treatment options. Preclinical evidence has shown that the PI3K/AKT/mTOR signaling pathway plays a central role in the pathogenesis and progression of NETs. Clinical studies with the mTOR inhibitor, everolimus, demonstrated its safety and efficacy in the treatment of NET, however, patients will ultimately progress. A novel mTOR inhibitor, ABI-009 (albumin-bound rapamycin nanoparticles, *nab*-rapamycin), has a favorable safety profile and evidence of efficacy in patients with solid tumors and offers promise for NETs. A preclinical study showed significantly greater antitumor activity and prolonged survival with ABI-009 compared with equal weekly dosing of oral rapamycin and oral everolimus. This preclinical study demonstrated superior efficacy of ABI-009 to oral mTOR inhibitors and suggest that ABI-009 may result in disease control after everolimus failure. The goal of this phase II pilot study is to evaluate the utility of ABI-009 in NETs to warrant a full phase II clinical study. **Method:** This pilot phase II trial is a prospective, open-label, single arm, single center trial evaluating the efficacy and safety of ABI-009 in patients with gastroenteropancreatic or lung NETs who have undergone prior treatment with everolimus. Patients with unresectable, metastatic grade 1 and 2 NETs of the gastroenteropancreatic system or lung who have progressed or have been intolerant to everolimus will be eligible for inclusion in this study. The study will enroll 10 patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. ABI-009 will be administered intravenously at 100 mg/m^2 on days 1 and 8 of a 21-day cycle. Patients will be treated until disease progression. Tumor response will be assessed by computerized tomography scan at baseline then every 9 weeks for 1 year, then every 12 weeks thereafter until progression. The primary endpoint is disease control rate at 6 months measured by RECIST 1.1. Currently, 3 of the planned 10 patients have been enrolled. ClinicalTrials.gov Identifier: NCT03670030. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: neuroendocrine tumors, mTOR inhibitor, ABI-009

EP1.12-19 CHARACTERISTICS OF PATIENTS WITH SMALL-CELL LUNG CANCER IN THE REAL-WORLD: A SYSTEMATIC REVIEW

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Background: Patients with poor performance status (PS) ≥2 are generally underrepresented in clinical trials. Describing patients' characteristics outside clinical trials setting would help better characterize unmet needs. This study aimed to assess the characteristics of SCLC patients, overall and according to sub-types; extensive-stage (ES) and limited-stage (LS). **Method:** A systematic review of observational studies was conducted using MEDLINE and Embase databases between January 1998 and October 2018. Pragmatic searches of the grey literature were conducted to identify additional sources. Studies reporting epidemiological data on SCLC were independently screened, adjudicated and data were abstracted by two assessors, with conflicts resolved by a third. **Result:** Of the 2,418 sources identified, 394 were reviewed in depth and 140 were retained. An additional 28 sources were identified through pragmatic searches yielding a total of 168. Median age at diagnosis (reported in 32 studies) ranged from 54 to 74 years. Sex distribution was reported in 86 studies, with a male predominance irrespective of stage. Eastern Cooperative Oncology Group PS was reported in 30 studies. The majority of studies were hospital-based (n=28, 93%) and data mainly originated from medical records or chart review (22, 73%). PS was assessed at baseline or at the time of diagnosis in 26 studies. Twenty-three (77%) studies reported poor PS status for ≥25% of the SCLC population, with six reporting poor PS in ≥50% of the SCLC population. The proportion of SCLC patients with poor PS ranged from 14% to 88%. Findings were heterogeneous across studies due to the variability in thresholds used to define the categories, study setting and inclusion of both LS- and ES-SCLC patients for reporting. For studies reporting PS by stage (n=4), the proportion of patients with poor PS ranged from 13% to 53% in ES-SCLC and 11% to 12% in LS-SCLC. **Conclusion:** A significant percentage of patients with SCLC outside clinical trials present with a poor PS. LS-SCLC patients have a better PS. Prevalence of poor PS was higher for ES-SCLC and the reported figures are higher compared to non-small cell lung cancer.

Keywords: SCLC, systematic review, clinical characteristics

EP1.12-20 RETROSPECTIVE STUDY ABOUT THE IMPACT OF METASTATIC SITE IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a very aggressive type of lung cancer. It is characterized by a high cellular proliferation and an early development of widespread metastases (nearly 70% of patients presents macroscopic metastases at diagnosis). SCLC spread mainly to bone, brain and liver. In extensive disease, metastatic involvement of the liver, bone and central nervous system seems to have a worse prognosis comparing with other sites, though the studies are quite inconclusive. **Method:** We conducted a descriptive and retrospective study including all patients diagnosed with metastatic SCLC between January 2012 and December 2018. A Kaplan Meier survival analysis (log-rank analysis) was carried out to study the impact of the metastatic involvement (depending on the localization) at diagnosis and at recurrence. **Result:** Of the 58 patients included, 58.6% presents liver involvement at diagnosis. These patients present a worse overall survival (OS), with a mean of 1.9 months, and a clear trend to worse progression-free survival (PFS, with a mean of 5.6 months (P=0.56). Bone involvement was presented in 41.4% of the patients. No difference was observed neither in OS (with a median of 6 vs 7.9 months) nor PFS (3.9 vs 3.3 months). Lastly, only the 19% present brain metastases at diagnosis, and it didn't show significant differences in OS (8.3 vs 6.7 months) but it did in SLP (2.6 vs 5 months). When the tumor relapses, it usually does in multiple localizations (51.3%) and the main organ involved is the lung (78.3%). It didn´t show any difference in prognostic between sites. **Conclusion:** SCLC is a very aggressive tumor. Due to its biological behavior, a large proportion of the patients presents an advanced staged at diagnosis. In extensive disease, the number of organ sites involved is related to prognosis, but it´s not clear which localizations have a greater impact on survival rates. In our studies, liver and bone metastases are related to worse prognosis and short survival. Surprising, in our series, brain metastases don´t seem to impact in patient's prognosis. When the tumor relapses, tumor extent (limited vs extensive) is a factor that affects the prognosis. However, in our experience, there are not clear differences between one or another, all of them related to poor prognosis. More studies will be needed to be able to clarify the prognostic impact of the metastases site, both at diagnosis and relapse.

Keywords: SCLC, metastases, prognostic

EP1.12-21 TREATMENT PATTERNS AND PROGNOSTIC FACTORS IN SMALL-CELL LUNG CANCER PATIENTS IN ISRAEL – REAL WORLD ANALYSIS OF A HEALTH SERVICES DATABASE

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Background: Small-Cell Lung Cancer (SCLC) is an aggressive smoking-associated malignancy, with rapid growth and early metastatic dissemination that accounts for 10-15% of all lung cancers. Data on current epidemiology and clinical aspects of the disease in Israel are lacking. In this observational study, we analyzed treatment patterns and prognostic factors in patients with SCLC in Maccabi Healthcare Services (MHS), a public integrated care organization in Israel. **Method:** Patients with newly diagnosed, histologically confirmed SCLC who initiated systemic anti-cancer treatment between 2011 to 2017 were identified from the MHS cancer registry. Their demographic, clinical and treatment data were retrospectively analyzed. **Result:** 235 SCLC patients were identified; 61% male, median age 64 years (IQR: 58, 70), 95% ever smokers, 62% had extensive stage disease (ES), 11% had brain metastases and 60% had 0-1 ECOG performance status (PS), all at treatment initiation. First-line treatment was platinum-etoposide regimen for the whole cohort. 107 of 235 patients (46%) continued to 2nd-line therapy and 29 patients (12%) received 3rd-line regimen. Median overall survival (OS) for the study population was 11.8 months. Patients with limited stage disease (LS) had a significant longer survival than those with ES (23.5 vs 9.1 months, P<0.001). In a multivariable model for all-cause mortality, males had a HR of 1.59 (95% CI 1.14-2.21, P=0.006) compared to females, and patients with ES had a HR of 4.76 (95% CI 1.37-16.49, P=0.014) compared to LS. Additionally, risk of death increased significantly with ECOG PS at presentation (ECOG PS 2 vs 0-1, HR=1.49 (95% CI 0.93, 2.40), ECOG PS 3-4 vs 0-1, HR=3.29 (95% CI 1.10, 9.84)). For LS disease, female sex and concurrent chemo-radiation were associated with significantly longer survival. Median survival after initiation of 2nd line was significantly longer for those re-challenged with platinum-based regimen compared with those switched to topotecan: 9.1(95% CI 6.1-12.1) vs. 4.5 months (95% CI 3.3-5.7), P=0.001. Results were not affected by platinum sensitivity (i.e. interval from end of first-line to beginning of second line ≥3 months). A multivariable model considering 2nd line patients and incorporating age, sex, stage, PS and brain metastasis at diagnosis confirmed these results. **Conclusion:** Overall survival for SCLC patients in a real world setting was found to be similar to those reported in clinical trials. Extent of disease, sex and PS were significantly associated with prognosis. Re-challenge of platinum-based doublet was associated with longer OS compared to switching to topotecan treatment.

Keywords: SCLC, First line treatment

EP1.12-22 THE EXPRESSION AND PROGNOSTIC ROLES OF PD-L1, PAPR1 AND DLL3 IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is an aggressive high-grade neuroendocrine tumor with limited treatment. Recently chemotherapy combined with anti-PD-L1 therapy was approved for SCLC. PARP1and DLL3 inhibitor are under clinical trials but the data revealed that these agents benefit a proportion of SCLC patients. Which patient can benefit from anti-PD-L1, PARP1 and DLL3 inhibitor therapy and whether combination of these agents can improve the survival of SCLC are unknown. We aim to examine the expression and prognostic roles of PD-L1, PARP1 and DLL3 and to analyze the correlation between them and clinicalpathological factors. **Method:** All protocols were approved by the Ethics Committee of Xi'an Jiaotong University and informed consent was signed. FFPE samples were obtained from Department of Pathology at The First Affiliated Hospital of Xi'an Jiaotong University from 2011 to 2018. SCLC was confirmed in all patients by surgical pathology and graded by AJCC TNM staging system. The expression of PD-L1, PARP1 and DLL3 were detected by immunohistochemistry as previously described. The association between PD-L1, PARP1, DLL3 and clinicalpathological characteristics was performed by $\chi 2$ test. The survival curves were analyzed by the log-rank test and Cox proportional hazards model. **Result:** Except for CYFRA21-1 and DLL3, no correlation between PD-L1, PARP1 and DLL3 and clinicalpathological factors were noticed (Table 1).

Table 1. Correaltion between PD-L1, PARP1, DLL3 and clinialpathological factors in SCLC patients												
	PD-L1 negative	**PD-L1 positive**	**χ^2**	*P*	**PARP1 negative**	**PARP1 positive**	**χ^2**	*P*	**DLL3 negative**	**DLL3 positive**	**χ^2**	*P*
Age												
<60	11	12			17	6			8	15		
>=60	8	13	0.42	0.56	17	3	0.80	0.74	7	11	0.07	0.79
Gender												
Male	14	21			28	7			15	28		
Female	4	4	0.27	0.70	6	2	0.10	1.00	3	5	0.10	1.00
Smoking status												
Smoker (including previous smoker)	12	15			23	4			10	17		
Never-smoker	6	10	0.20	0.76	11	5	1.64	0.26	5	11	0.15	0.70
Central or Peripheral												
Central	11	16			21	6			10	17		
Peripheral	7	9	0.04	1.00	13	3	0.07	1.00	5	11	0.15	0.70
CEA level												
CEA normal	9	12			16	5			7	14		
CEA high4	4	7			9	2			4	7		
Unknown	9	2	5.68	0.06	9	2	0.13	0.90	4	7	0.04	0.98
CYFRA21-1 level												
CYFRA21-1 normal	7	11			14	4			5	13		
CYFRA21-1 high	5	7			9	3			9	3		
Unknown	6	7	0.16	0.92	11	2	0.03	0.83	4	9	7.54	0.02
NSE level												
NSE normal	2	0			1	1			0	2		
NSE high	10	17			21	6			11	16		
Unknown	6	8	3.04	0.22	12	2	0.79	0.49	4	10	1.73	0.42
TNM stage												
TNM stage 1-2	10	13			13	10			6	17		
TNM stage 3-4	7	12	0.19	0.66	16	3	3.73	0.05	9	11	1.69	0.19

We also demonstrated that PD-L1 predicts poor prognosis (HR=0.26, *P*=0.01), while either PARP1 or DLL3 has no correaltion with prognosis in SCLC patients (HR=0.40, *P*=1.39 and HR=0.07, *P*=1.29 respectively). Interestingly, we found SCLC patients with negative PD-L1 and PARP1, negative PD-L1 and DLL3 performed the best survival (Figure 1).

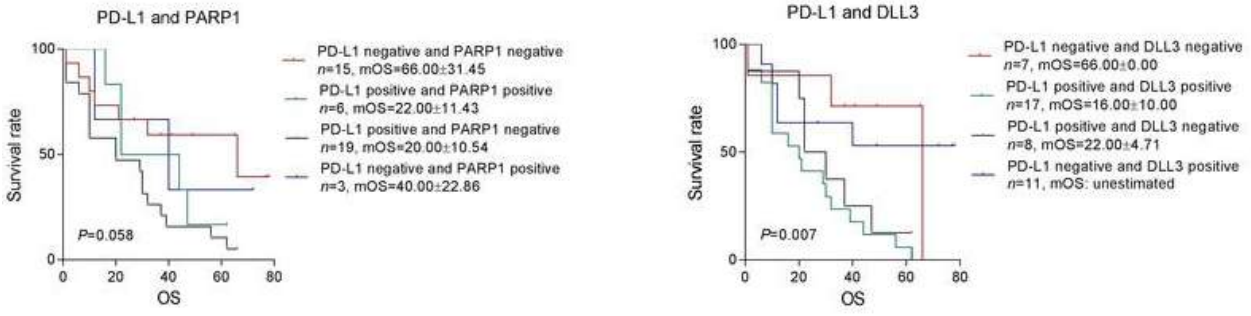

Figure 1. Overall survival of SCLC patients with different expression patterns of PD-L1 and PARP1, PD-L1 and DLL3.

Conclusion: PD-L1 is a negative prognositc factor in SCLC. Different expression pattern of PD-L1 and PARP1, PD-L1 and DLL3 lead to significantly different prognosis in SCLC.

Keywords: PD-L1, PARP1, DLL3

EPOSTERS

EP1.12-23 SURGERY IS ASSOCIATED WITH FAVORABLE OUTCOME IN PATIENTS WITH EARLY STAGE SCLC – RETROSPECTIVE INSTITUTIONAL EXPERIENCE

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Background: Small-cell lung cancer (SCLC) is characterized by rapid growth, early metastases and dismal outcome. Only few patients are diagnosed in early stages and thus might be candidates for potentially curative treatment. However, the value of surgery within multimodal treatment of early stage SCLC remains under debate. The aim of this study was to evaluate long-term outcome in patients with early stage SCLC undergoing curative intent surgery. **Method:** Eligible patients with SCLC who underwent curative intent surgery at the Medical University of Vienna between 2006 and 2016 were retrospectively analyzed focusing on treatment modalities and long-term outcome. **Result:** A total of 31 patients were included (male, n=20 (65%); median age 63.9 years). Clinical TNM-8 staging at diagnosis was stage I in 20 (65%), stage II in 5 (16%) and stage IIIA in 6 (19%) patients. 4 patients (13%) received induction chemotherapy. Sublobar resection was performed in 14 (45%) patients whereas 9 (29%) underwent lobectomy, 4 (13%) bilobectomy and 4 (13%) pneumonectomy. 24 (77%) patients received adjuvant treatment (chemotherapy, n=17 (55%); radiotherapy, n=1 (3%), chemoradiotherapy, n=5 (16%); PCI: n=8 (26%)). Median overall survival (OS) of all patients was 43.5 months, 3-years OS 58% and 5-years OS 42%, retrospectively. Patients undergoing sublobar resection had decreased median OS compared to patients undergoing lobectomy/bilobectomy/pneumonectomy (25.5 vs. 89 months, p=ns). Importantly, patients with TNM-8 stage I undergoing adjuvant chemotherapy had significantly improved OS compared to patients without adjuvant treatment (median OS 44 vs. 12 months, p=0.01). **Conclusion:** This institutional experience shows good long-term outcome after adequate surgical resection followed by adjuvant treatment in selected patients with early stage SCLC. Our data indicate that sublobar resection should be avoided, however, well designed prospective trials are required to define the optimal treatment modalities in these patients.

Keywords: SCLC, surgery, multimodality treatment

EP1.12-24 EFFICACY OF CHEMOTHERAPY IN SMALL CELL LUNG CANCER: SECOND LINE AND BEYOND

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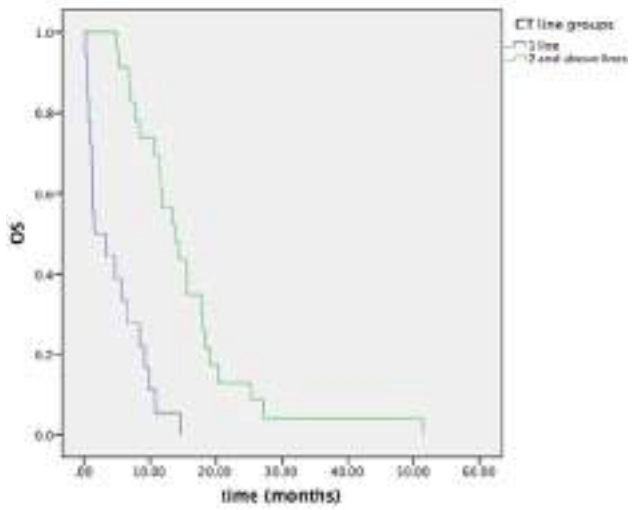
Background: Small cell lung cancer (SCLC) is aggressive neuroendocrine carcinoma; despite of chemo sensitivity at first line, almost all cases will be relapsed in 10-12 months. In the absence of checkpoint inhibitors, chemotherapy (CT) is single choice for refractory pts. **Method:** A single center, retrospective analysis was performed to assess the survival data of 2nd line and beyond CT in the pts with SCLC. The patients' characteristics were recorded. Kaplan meier survival rates were calculated. **Result:**



A total of 52 (Female/Male:14/38) pts were evaluated. Median age was 64±7(range:47-77) years. Median follow-up was 9 (range:0-51) months. ECOG PS were 0,1 and 2 (9,34 and 9 pts), respectively. At the time of diagnosis, 15 (28.8%) pts were limited, 37 (71.2%) pts were extensive stage. Brain metastases were observed in 8 (15.4%) pts. 14 pts with limited stage disease were received chemoradiotherapy. Profilactic cranial radiation was administered all responders. Platinum and etoposid (PE) combination was the first line CT regimen. ORR was 61.6% (CR:46.2%, PR:15.4%). 31 pts were received 2nd line CT. Irınotekan (16 pts), topotecan (6 pts), PE (6 pts), platin-paclitaxel (5 pts) were 2nd line CT regimens. 5 pts were received 3rd, 2 pts were received 4th line CT. Median OS was 8.5±1.9 (95%CI:4.8-12.2) months for all pts. Median OS 14±3.8 (95%CI:6.4-21.5) and 6.9±1.9(95%CI: 3-17) months, for limited and extensive stage, respectively. Median PFS (for first line therapy) were 8.8, 7.7 and 8.1 months for limited, extensive and all pts. For second line treatment, median PFS was 5 months. For pts who had received 2 and above line CT, median OS was 14±2 (95%CI:10-17.8) months (Fig1). 5 pts were received 3rd line CT, 2 of 5 pts were survived 25 and 51 months. 14 (34%) pts had achieved 1 year and longer survival. Most of these 14 pts were limited stage and platinum-sensitive and had received at least 2 lines CT (13/14 pts). **Conclusion:** Despite of high response rates, prognosis is still poor in SCLC. Because of high tumor mutation burden, adding immunotherapy to CT had improved survival. However, some pts cannot be reached immunotherapy in the worldwide. In the absence of checkpoint inhibitor for some countries, with 2-3 line CT regimens (platin based, irinotecan/topotecan and paclitaxel agents), the pts could be survived ≥12 months. Irinotecan and topotecan seems most effective agents for refractory pts. Median PFS for the pts received 2nd line CT was 5 months and it was similar to literature.

Keywords: small cell lung cancer, chemotherapy

EP1.12-25 COMPARISON IN THERAPEUTIC OF OPERATION COMBINED WITH CHEMOTHERAPY AND WITH PD-1 AND PD-L1 INHIBITORS FOR STAGE 2 SMALL CELL LUNG CANCER

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Background: The treatment of small cell lung cancer has always been a comprehensive treatment based on chemotherapy. In recent years, the surgical treatment has certain positive effects on the OS and PFS of early small cell lung cancer. Studies on the treatment of small cell lung cancer by surgical treatment combined with chemotherapy have reported positive effects. As the application of pd-1 and pd-l1 inhibitors in non-small cell lung cancer has been approved by FDA, the treatment of pd-1 and pd-l1 inhibitors in small cell lung cancer still needs to be studied. In particular, the study of surgical treatment combined with pd-1 and pd-l1 inhibitors in the treatment of small-cell lung cancer is still a new field, and there is no authoritative report at present. **Method:** 115 cases patients with IIA-IIC small cell lung cancer were divided into three groups. Group B: lobectomy + lymph node dissection combined with EP; Group C: lobectomy + lymph node dissection combined with pd-1 / pd-l1 inhibitors. The length of hospital stay, blood routine, blood biochemistry, complications, bone marrow suppression, OS, PFS and DFS were observed in the three groups. **Result:** Group A: the average hospitalization time of 53 patients was 2-3 days, including 3 patients with fever, 21 patients with fatigue, 4 patients with diarrhea and 2 patients with skin rash, 1 patient died, and 30 patients with abnormal blood routine examination. Average DFS4.2-5.8 months, PFS 2.1-2.7 months, OS 6.4-9.3 months; Group B: the average hospitalization time of 46 patients was 10-21 days, including 10 patients with fever, 27 patients with fatigue, 2 patients with diarrhea and 3 patients with rash, and 41 patients with abnormal blood routine examination. Mean DFS7.7-8.3 months, PFS3.4-6.7 months, OS9.4-12.3 months; Group C: the mean hospitalization time of 16 patients was 10-27 days, including 12 patients with fever, 9 patients with fatigue, 1 patient with diarrhea and 2 patients with rash, and 14 patients with abnormal blood routine examination. Average DFS7.1-8.9 months, PFS 3.7-6.1 months, OS 10.1-11.1 months. **Conclusion:** Chemotherapy alone is an effective treatment for small cell lung cancer, especially for advanced small cell lung cancer. Surgical treatment combined with chemotherapy can prolong OS and DFS in early small cell lung cancer. Surgical treatment combined with PD-1/PD-L1 inhibitors also has certain effect, which is one of the possible treatments.

Keywords: small cell lung cancer Lobectomy of lung chemotherapy, pd-1/pd-l1

EP1.12-26 RETROSPECTIVE STUDY ABOUT THE IMPACT OF BRAIN METASTASES AND CRANIAL IRRADIATION IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a very aggressive type of lung cancer. Due to this behavior, it presents early development of metastases. Brain metastases (BM) are very common and are related with a great impact on both survival and quality of life. Prophylactic cranial irradiation (PCI) is used for patients without detectable brain metastases, improving survival and decreasing the incidence of brain relapses (BR). Cranial irradiation (CI) for affected patients are usually used in patients with clinical BM, but its benefits are less clear. **Method:** We conducted a descriptive and retrospective study including all patients diagnosed with SCLC tumor between January 2012 and December 2018 (both localized and metastatic). We study the impact of PCI and CI in both patients with/without BM at diagnosis. A Kaplan Meier survival analysis (log-rank analysis) was carried out to study the overall survival and the impact of the radiotherapy treatment. **Result:** Of the 98 patients included, 60.2% presents extensive-stage, while 39% were locally advanced. Of the advanced stages, only 18.4% presented brain involvement at the diagnosis. 34.7% of the patients received RT at the diagnosis (37.5% PCI and 50% of the patients with BM received CI). Over the course of the disease, 35.1% of the patients present BR. 67.6% of the patients treated with RT at diagnosis (both PCI and CI) relapsed in the brain, meanwhile, the 54.8% in the group without RT (no significant differences). However, in the RT group, 69.5% of patients relapse outside the brain (mainly the lung). Chemosensitive didn´t show any relation with the incidence of BR (30.4% RT group vs. 35.7% in no-RT group). Overall, there were no significant differences in survival (p 0.19) between the group treated with RT (both PCI and CI) and the group which didn´t. **Conclusion:** SCLC presents early dissemination. Brain is one of the main organs involved. PCI for patients without detectable BM decrease the incidence of brain relapses and improve survival. The impact of CI is less clear in patients that already have BM. Surprisingly, in our series, we didn´t find any difference with PCI or CI in overall survival and BR. A high proportion of the patients in both groups (with/without BM at diagnosis) didn´t receive radiotherapy, due to a very poor clinical status (which can may lead to bias). More studies will be needed to be able to clarify the prognostic impact of these metastases and the effectiveness of this treatment nowadays.

Keywords: SCLC, brain, radiotherapy

EP1.12-27 PROPHYLACTIC CRANIAL IRRADIATION IN SMALL CELL LUNG CANCER - IS IT STILL AN ENIGMA?

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Background: Small cell lung cancer accounts for 15% of lung cancer burden and is characterized by widespread metastases. Brain is a susceptible site of relapse hence prophylactic Cranial Irradiation (PCI) has been used. Patients of Small cell lung cancer (SCLC) are more prone to develop brain metastasis. However the efficacy of PCI in treating SCLC has not been clear and various randomized studies demonstrated conflicting results. There exists a controversy regarding the benefit from PCI in SCLC with time to develop brain metastases (BM) and progression free survival (PFS). In the current study we studied the benefit of PCI in time to develop BM and PFS. **Method:** Medical records of patients of SCLC treated between June 2016 – June 2018 were evaluated. Clinical presentation, evaluation, treatment details and outcome were recorded. Case records of incomplete workup or treatment, not eligible for radical treatment were excluded. Eligible patients received a median of 3 cycles of EP chemotherapy followed by thoracic radiation therapy (TRT) and PCI. **Result:** Fifty patients of SCLC were registered during the study period. The distribution as per histology and stage include, Limited stage 22, Extensive stage 28, 20 were metastatic and 30 were non metastatic .Eight patients received best supportive care ,15 patients received thoracic RT and PCI and 9 patients received PCI alone . The median follow-up was 10.8 months (6 – 26 months). 7 out of 15 patients had progression and 6 (40%) of them developed BM. The median time to develop BM was 10.2 months (6.7 -27.5 months). The median PFS was 11.2 months (6- 28 months). **Conclusion:** This study shows the contemporary line of management in SCLC. The time to develop BM and median PFS was comparable with existing literature. PCI benefits all stages of SCLC in terms of time to develop BM and PFS benefit.

Keyword: Small cell lung cancer, prophylactic cranial irradiation, brain mets

EP1.12-28 ANTICANCER EFFECTS OF IMIPRAMINE, REPOSITIONED DRUG, FOR SMALL CELL LUNG CANCER

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Background: Drug reposition is one of the blue oceans on discovery of new drugs. Anticancer new drugs by reposition are also vigorous mining area by *in vivo*, *in vitro* and *in silico*. Treatment of small cell lung cancer (SCLC) is restricted due to lack of chemotherapeutic agents. Imipramine, a challenging drug for SCLC was discovered by *in silico* reposition recently. We tried imipramine to the patients who diagnosed SCLC after 1st line chemotherapy **Method:** From July of 2013 to December of 2015, patients who diagnosed SCLC were enrolled. All of them were treated 1st line combination chemotherapy, platinum and etoposide and some of them were done radiotherapy to main lesion. After chemotherapy or combined radiation therapy, imipramine was prescribed 25-75mg according to patient's tolerance alternately. **Result:** Fifteen patients were participated, 6 (40%) of them were limited, 9 (60%) of them were extensive stage, but more limited stage in imipramine group compare to not prescribed group (4 to 2). All of them were smokers, 12 were man (80%), mean age was 64.6. Classified by TNM stage, stage 3 was 8, stage 4 was 7. There were no differences of age, performance status, cancer stage, chemotherapy and radiation. Amount and duration of imipramine, the prescribed group, was mean 55 mg, and 9 month. Survival of two groups was imipramine prescribed group, 22 ± 6.3 month, and not prescribed group 13.0 ± 2.8 month. (P=0.105) **Conclusion:** Trial of imipramine is one of the promising agent to control or maintenance of neuroendocrine tumor, especially SCLC.

Keywords: small cell lung cancer, Drug reposition, Antidepressant

EP1.12-29 RETROSPECTIVE STUDY ABOUT SMALL CELL LUNG CANCER: OUR EXPERIENCE IN A SPANISH HOSPITAL

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Background: Incidence of small cell lung cancer (SCLC) has been decreased during the last decades. This neoplasm appears almost exclusively in smokers and it is characterized by aggressive biology and early development of metastases. Due to this aggressiveness, a large proportion of patients present a poor performance status at the time of diagnosis. Though the tumor is initially highly responsive to therapies, most of the patients will relapse after treatment. The prognosis is generally poor, even in limited stage disease. **Method:** We conducted a descriptive and retrospective study including all patients diagnosed with SCLC tumor between January 2012 and December 2018 (both localized and metastatic forms were included). A Kaplan Meier survival analysis (log-rank analysis) was carried out to study the overall survival. **Result:** diagnosed in advanced stages (60.2%), while 29.6% were locally advanced and only 8.2%, localized. In metastatic stage, the main organ affected was the liver (35.7%), followed by the bone (24.5%). Only 12% presented brain metastases at the diagnosis. The vast majority were smokers (68.4%) or ex-smokers (27.6%), with only one patient that had never smoked. The 78.4% of the patients received chemotherapy (36.7% with concomitant radiotherapy). After the initial treatment, up to 55.4% of the patients recurred, mainly involving various localizations (50%). Only 39% received a second line of chemotherapy, and 24% a third line. At the end of the study, 84.6% of the patients had died (median of 19.7 months since diagnosis). Log-rank analysis (Kaplan-Meier estimates) showed significant differences (p<0.05) between tumor

stages and platinum-sensitive status. On the contrary, there wasn´t significant difference related to sex, smoke status, type of recurrence or type of chemotherapy chosen in second line. **Conclusion:** SCLC is heavily related with smoke. Most of them exhibit an aggressive behavior, with an advanced stage at diagnosis (in our study, up to 60.2%, and 29.6% locally advanced). Thought usually presents high chemosensitivity, most of the patients recur. At this point, the prognosis is poor, with a low benefit with the treatment, in our series regardless of the drug. Unlike the previous series, we haven´t seen a worse outcome related to sex or smoke status. More studies will be needed to be able to clarify the prognostic impact of factors such as the smoke status, sex, type of relapse or second line treatment.

EP1.12-30 CLINICOPATHOLOGICAL FEATURES AND SURVIVAL OF LUNG NEUROENDOCRINE TUMORS

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Background: Lung neuroendocrine tumors (NETs) are a heterogenous group of malignances classified into four histological types, being small cell lung cancer (SCLC) the most frequent and mortal. Due to the rarity of the disease, limited clinical data is available for NTEs. Herein we aim to describe the epidemiology, clinical features and survival of this group of neoplasms. **Method:** This is a retrospective analysis of patients diagnosed with lung NETs between 2010 and 2014 at Instituto Nacional de Enfermedades Neoplasicas (INEN) in Lima, Peru. Demographic characteristics, possible predisposing factors, histological type and stage were collected from clinical files. Survival analysis was calculated with Kaplan-Meier method. Prognostic factors were analyzed with Cox regression method. **Result:** We identified 69 patients with lung NETs, which corresponds to the 2.8% of lung cancers diagnosed in the same time period. Median age at diagnosis was 62 years and 59.4% of patients were male. Possible risk factors described were smoking history (50%) and familiar history of cancer (23.2%). Mean time from onset of symptoms to diagnosis was 3 months. Frequent symptoms at diagnosis were cough (75%), chest pain (59%), dyspnea (50%), weight loss (49%), hemoptysis (28%), hyponatremia (19.6%) and superior vena cava syndrome (13.8%). Between NETs, SCLC was the most common histological type (82.8%), followed by typical carcinoid (12.1%) and large cell neuroendocrine carcinoma (5.2%). Almost all patients (91.8%) had unresectable disease at diagnosis (21.3%, stage III; 70.5% stage IV) according TNM classification. Among SCLC, 60.4% had an extensive disease according to the IASLC classification, with extra thoracic compromise in bone (25.6%), brain (23.1%), suprarenal gland (21.1%) and liver (15.8%). The preferred systemic treatment was cisplatin/etoposide (93%) in the metastatic setting. The median overall survival for all histological types was 6.7 months (range 4.1 – 9.2) (Differences by histological grade in Table 1). Among clinical factors, weight loss at diagnosis emerged as a prognostic factor associated with survival of high-grade NETs (HR 3, 95% CI 1.6 – 5.5).

	I	II	III	IV	mOS
Carcinoids	40%	0%	30%	30%	87m (40.4 – 133.6)
High-grade NETs	8.8%	0%	21.1%	70.2%	4.5m (2.6 – 6.4)

Conclusion: Lung NETs have a heterogenous clinical presentation with unresectable disease at diagnosis in almost all cases. SCLC is the most frequent histology, however, this proportion regarding of the total cases of primary lung neoplasms is markedly lower than what is reported in the literature, probably to our lower frequency of smokers. The survival of this group of patients is poor in comparison to other series being weight loss at diagnosis an important prognostic factor in this series.

Keywords: Neuroendocrine, small cell lung cancer, epidemiology

EP1.12-31 RESPONSE RATES AND OVERALL SURVIVAL IN BRAZILIAN PATIENTS DIAGNOSED WITH SMALL CELL LUNG CARCINOMA

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Background: Despite its relative low incidence when compared to other lung tumors, small cell lung carcinoma (SCLC) is the most aggressive lung cancer subtype. About 30% of patients diagnosed with SCLC do not respond to first line chemotherapy and disease relapse usually occurs within 6 months. **Method:** Here, we evaluate clinical and treatment-related data of patients diagnosed with SCLC that attended the Clinical Oncology service at A.C.Camargo Cancer Center (ACCC - IRB approval 2445/17). **Result:** Between the year 2000 to 2017, 92 individuals were diagnosed with SCLC in the ACCC. The median age at diagnosis was 65, (varying from 32-86), with a slightly higher frequency in males (55.4%). Complete clinical and demographic information was available for 57 cases (62%), which encompassed patients from 2005 to 2017. The median age at diagnosis and male/female ratios were the same for this subset. Most patients were smokers (87.7%), presented co-morbidities (68.4), were diagnosed with extensive disease (78.9%) while 22.8% had brain mets at diagnosis, a common metastatic site of SCLC. Familial history of cancer was identified in 29 cases (50.9%). The overall survival (OS) of this cohort was 26.75 months, ranging from 1.3 month to 309 months. All but one patient underwent first line chemotherapy, and the most commonly used regimen was the combination of Cisplatin (CDDP) and Etoposide (VP-16) (73.7%), followed by the combination of Carboplatin and Etoposide (14%). Complete response was observed for 8.7% of patients and partial response in 38.6%. Stable disease and disease progression were respectively observed in 5.2% and 17.5% (33% were not classified) of patients. Second and third line treatments were respectively given to 45% and 22.8% of patients. Additionally, along with chemotherapy, 43.8% of the patients received radiotherapy; overall survival was similar for patients treated with chemotherapy alone (477 days) versus chemotherapy plus radiotherapy (386 days) (p=0.57, one-way ANOVA). No differences in OS were seen for patients receiving distinct chemotherapy regimens (p=0.38, Kruskall Wallis test) and response to first-line therapies was not capable to predict overall survival (p=0.15). As expected, patients with limited stage disease presented a trend towards better OS as compared to extensive disease (70.7 x 27.3 months) (p=0.08). **Conclusion:** We intend to evaluate genetic variants in these patients' tumor samples to investigate mechanisms that could influence outcomes and predict response.

Keyword: Small Cell Lung Carcinoma, Epidemiology, Chemotherapy Response

EP1.12-32 CLINICO-PATHOLOGICAL FEATURES OF SMALL CELL LUNG CANCER IN ALBANIAN PATIENTS

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Background: Lung cancer is the leading cause of cancer-related death in the world. Small cell lung cancer (SCLC) is an aggressive type of lung cancer and accounts for 15% of all lung cancer cases. Progress in the survival rate of SCLC is poor with a 5-year survival rate of only 5-10%, depending on tumour stage at presentation. **Method:** Purpose of this study was to describe.1- the main characteristics of small cell lung cancer and overall survival of these patients. All patients with SCLC were evaluated in the main university hospital for lung diseases. Demographic, clinical, histological characteristics were reviewed. **Result:** 153 patients diagnosed with sclc between 2015 and 2018 were included. this counts 5.8 % of all lung cancer patients (n=2598) .The mean age was 62,2 +/- 4,0 years, with the majority being men (93%). 88.2 % of patients had a smoking history. 12% of them were presented with liver metastasis. The median overall survival was 6,1 months after the diagnosis. Twelve patients had a previous familiar cancer history. At diagnostic, the most frequent symptoms were cough (65%) and dyspnea (51,3%). The mean time between the first symptoms and diagnosis was 123 +/- 89 days. **Conclusion:** Small cell lung cancer is an agressive tumor with low overall survival because albanian patients come later to the health

care profesionists and are heavy smokers. Policies for smoking cessation should be strengthened and a lung cancer screening program should be initiated.

Keywords: lung, Small Cell, cancer

EP1.12-33 PROGNOSTIC ANALYSIS OF SURGERY VS. CONSERVATIVE THERAPY WITH CHEMOTHERAPY IN STAGE OF LIMITED DISEASE SMALL CELL LUNG CANCER

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Background: The current standard of care for limited disease small-cell lung cancer (SCLC) consists of combination chemotherapy and thoracic radiotherapy during the early cycles of chemotherapy. Unfortunately, the prognosis is poor and the long-term survival is limited. The 5-year overall survival rate of SCLC reaches 5%. Furthermore, the role of surgery as a part of multimodality treatment with curative intent remains controversial. Here we investigate the long-term survival benefit of patients with limited disease SCLC following surgery combined with chemotherapy compared to those without surgery. **Method:** In this retrospective analysis was analyzed all the patients with limited disease small-cell lung cancer from our hospital database. Between January 2010 and May 2015, all patients with limited disease small-cell lung cancer were retrospectively enrolled and data retrospectively analyzed. Patients were grouped for multimodality treatment with chemotherapy and surgery consisting of primary tumor resection and systematic lymph node dissection (Group 1) versus chemoradiotherapy alone (Group 2). Survival time was defined as the frame of the date of diagnosis to the time of death. Deaths from other causes are censored. The primary endpoint for this analysis was the survival time. **Result:** A total of 47 patients were included. About 16 Patients received treatment in the main focus with surgery (group 1), 31 patients had treatment without surgical treatment (group 2). In group 1 with surgical treatment 4 patients of 16 died within the first 16 months. The minimal survival time was 13 months and the maximum was detected at 48 months. The median survival time was discovered at 13 months, the arithmetic mean was 23 months. The standard deviation from the mean was 3,94. In the group without surgery 11 patients of 31 died. In this group the minimal survival time was 1 month and the maximum survival time was determined at 43 months. The median survival time was founded at 10 months, the arithmetic mean at 17 month. The standard deviation from the mean was detected at 16,08. **Conclusion:** One of the leading cause of death from cancer around the world is small cell lung cancer. The characteristics of rapid growth and early metastasis, is still an intractable problem for the treatment of small lung cancer. In addition only few patients are diagnosed in early stages, so that a surgical treatment can be considered. If we compare the patients who had surgical treatment with patients without surgery, we see that the group with surgical treatment seems to have a longer median survival time. The surgery seems to be safe and an important component of the multidisciplinary treatment.

EP1.12-34 SMALL CELL LUNG CANCER REVEALED BY CHOROIDAL METASTASIS: CASE REPORT

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Background: Ocular metastasis sit preferentially in the choroid, a vascularized membrane located between the sclera and the retina. Lung cancer is the second cancer provider of ocular metastasis after breast cancer. Choroidal metastasis are rarely indicative of primary neoplasia and are part of a generalized cancer. **Method:** We experienced a 70-year-old man, an ex-smoker (45 packs/year) which showed a decrease in visual acuity of the right eye. Physical examination was remarkable for just a exophtamia. The ophthalmological report revealed a retinal detachment and a choroidal tumor process of the right eyeball. The chest CT scan showed a central right pulmonary mass measured 80X50X47 mm and associated with three right superior lobar nodular formations and ipsilatetal mediastinal lymphadenopathy. Using a flexible bronchoscopy, we found a reduction of the superior right lobby caliber by an infiltrated mucous. **Result:** The bronchoscopic biopsy was performed, and the tumor was found to be small cell lung cancer, classified T4N3M1 according to The eight IASLC classification. The patient had benefit of chemiotherapy combining "Cisplatin and Etoposid" with radiotherapy of the right eyeball. After three curs of chemotherapy and radiotherapy we note a regression of the exophtamia, the radiological control was demand. **Conclusion:** The research primary cancer will be done quickly to allow for the therapeutic management. Chemotherapy and radiotherapy remain the treatment of choice for limited extension and improved patient survival.

EP1.12-35 COMPARISON OF LONG TERM RESULTS BETWEEN MATCHED CHEMORADIOTHERAPY AND SURGERY FOR LIMITED STAGE SMALL CELL LUNG CANCER

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Background: The role of surgery in patients with SCLC is undefined. Our study was conducted to compare the long term results of chemoradiotherapy with surgical treatment for limited stage SCLC. To compare the efficacy of chemoradiotherapy or surgery for limited-stage small cell lung cancer (SCLC). **Method:** A retrospective analysis was performed on 138 patients with limited-stage SCLC who received surgery (69 patients) or chemoradiotherapy (69 patients) between January 2000 and September 2016 in Zhejiang Cancer Hospital. Patients of the chemoradiotherapy group were selected by using 'pair-matched case-control' methodology from a cohort of 503 patients who received chemoradiotherapy. **Result:** The major prognostic factors including T, N stage, treatment duration, age, gender, and whether or not received prophylactic cranial irradiation were well balanced between two groups. The median overall survival (OS) time and 5-year OS rate were 37.1 months and 45.0% in surgical group versus 45.0 months and 45.0% in chemoradiotherapy group (P=0.846). The median progression-free survival (PFS) time and 5-year PFS rate were 27.1 months and 37.8% versus 36.2 months and 40.0% respectively in the two groups (P=0.610). The 5-year OS rate (62.3% vs. 40.1%, P=0.038) and 5-year PFS rate (80.1% vs. 40.1%, P=0.048) in surgical group were significantly higher than those of chemoradiotherapy group in patients with stage I disease. While the 5-year OS rate (41.2% vs. 50.6%, P=0.946), 5-year PFS rate (64.7% vs. 42.1%, P=0.280) of surgery for stage II SCLC were comparable to chemoradiotherapy. As for stage III SCLC, compared with the surgical group, the chemoradiotherapy group had a better 5-year OS trend (25.1% vs. 47.6%, P=0.220). **Conclusion:** Surgery could confer survival benefit in patients with p-stage I disease, but not in patients with p-stage II and III disease.

Keywords: surgery, chemoradiotherapy, small cell lung cancer

EP1.12-36 TREATMENT OUTCOMES AND RISK FACTORS OF LIMITED-STAGE SMALL CELL LUNG CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Background: The aim of this study was to report clinical outcomes and prognostic factors in limited- stage small cell lung cancer (LD-SCLC) patients treated with chemoradiotherapy (CRT). **Method:** Data on 107 LD-SCLC patients who received CRT between September 2000 and March 2017 were analyzed retrospectively. The median age of the patients was 66 years (range 42–85 years); 79 (73.8%) patients were male and 28 (26.2%) were female. Seventy-four (69.2%) patients received concurrent CRT (CCRT) with 45 Gy in 30 twice-daily fractions (n=52) or with 54–60 Gy in 27–30 once-daily fractions (n=22). The other 33 patients received sequential CRT (SCRT) with 54–60 Gy in 27–30 once-daily fractions. Prophylactic cranial irradiation was administered to 35 (32.7%) patients. Cisplatin/etoposide or carboplatin/etoposide were mainly selected as chemotherapy regimens. Survival rates were estimated using the Kaplan-Meier method, and univariate and multivariate analysis was performed using the log-rank test and Cox proportional hazard model, respectively. **Result:** Median follow-up duration

was for 28.6 months (range 1.6–147.2 months). Three-year overall survival, progression-free survival and cause-specific survival rates were 51.1%, 38.8% and 51.5%, respectively. On univariate analysis metastatic lymph node status (N0 vs N≥1) and timing of CRT (CCRT vs SCRT) were detected as significant prognostic factors for overall survival (3-year overall survival: 100% vs 48.2%, *p*=0.02; and 56.6% vs 37.7%, *p*=0.04, respectively). On multivariate analysis, however, these factors did not reach statistical significance. **Conclusion:** Treatment outcomes in LD-SCLC patients suggested metastatic lymph node status and timing of CRT as prognostic factors for overall survival.

Keywords: radiotherapy, small cell lung cancer, chemoradiotherapy

EP1.12-37 HIGHER CONSISTENCY OF MUTATIONS BETWEEN TUMOR DNA AND CTDNA IN SMALL-CELL LUNG CANCER COMPARED TO NON-SMALL CELL LUNG CANCER

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Background: Small-cell lung cancer (SCLC) is an aggressive neuroendocrine lung tumor representing 15% of lung cancers, patients with SCLC usually have a poor prognosis and limited treatment options. This is primarily due to the lack of adequate tumor tissues to assess and delaying therapy to repeat biopsies is often not possible. Circulating cell-free tumor DNA (ctDNA) based test for EGFR mutations in patients with Non-small cell lung cancer (NSCLC) has been approved by US Food and Drug Administration, however, whether it is feasible to perform genomic profiling of ctDNA from SCLC patients still have been lacking. SCLC is characterized by early hematogenous spread, we hypothesized that ctDNA sequencing in SCLC is more comprehensive as a promising biomarkers than that in NSCLC. **Method:** To analyze the consistency of gene mutation sites between tumor DNA and perepheral blood ctDNA in patients with lung cancer (SCLC and advanced NSCLC), and further explore the feasibility of ctDNA as a clinical tool in SCLC. Paired tumor and blood samples were obtained from systemic treatment naïve patients with SCLC and advanced NSCLC. DNA was sequenced by target-capture deep sequencing of 808 previously annotated genes related to solid tumors. **Result:** During February 2017 to April 2018, 8 SCLC and 119 advanced NSCLC patients were enrolled from 3 centers. A total of 256 somatic variations were detected in tumor DNA and ctDNA. TP53 and RB1 are the most frequently mutated genes in SCLC patients and mutations occurred most frequently in NSCLC were *EGFR*, *TP53*, *KRAS, ALK*. In matched tumor DNA and ctDNA, we observed significant higher concordance of mutations in SCLC (90%) compared to NSCLC (65%). Furthermore, the variant allele frequency (VAF) of shared mutations in SCLC highly correlated to each other (r=0.68). In addition, a subset of mutations was exclusively detected in ctDNA, indicating that the genomic landscape derived from ctDNA reflects that from SCLC to a certain degree. **Conclusion:** Taken together, our data showed the potential advantage of sequencing ctDNA in SCLC over than that in NSCLC to reveal the global genomic landscape. SCLC ctDNA analysis will be used as a powerful research tool that can shed light on this poorly understood disease and could also provide clinical information that benefits patients.

Keywords: tumor DNA and ctDNA, small-cell lung cancer, Non-Small Cell Lung Cancer

EP1.12-38 RETROSPECTIVE ANALYSIS OF IMMUNOTHERAPY UTILIZATION IN ADVANCED SMALL CELL CARCINOMA AT AN ACADEMIC CANCER CENTER

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Background: Small-cell carcinoma (SCC) is an aggressive neuroendocrine carcinoma which commonly originates in the lung (SCLC). In contrast to non-small cell lung cancer (NSCLC), immunotherapy (IO) utilization has been limited for SCLC. Nivolumab was approved as a single agent in 2018 for third-line therapy. In 2019, the IMpower133 trial led to approval of first-line chemo-IO (atezolizumab plus carboplatin and etoposide) for extensive-stage SCLC. Despite these approvals, there is limited data about experience utilizing IO in SCC outside of clinical trials, including patterns of care, survival, and incidence of brain metastases. We therefore conducted a retrospective review of IO utilization at an academic cancer center in the United States. **Method:** Institutional pharmacy database was used to perform an unstructured data collection of medical record numbers based on SCC diagnosis and IO treatment codes between January 1, 2008 and October 1, 2018 at The Ohio State University Medical Center. Patient data was then abstracted from the electronic medical record. Variables included demographics, co-morbidities, stage, metastatic sites (including brain), treatment history (including chemotherapy, IO and radiation), and treatment response. Survival from the start of IO to death and median overall survival (OS) from diagnosis to death were calculated. **Result:** Forty patients, 17 women and 23 men, were eligible for evaluation. The median age was 64 years (30-91 yo); 36 patients were current/former smokers. At diagnosis, most were extensive-stage (65%). Common metastatic sites at diagnosis included brain (20%), bone (35%) and liver (33%). Overall, 22 patients (55%) developed brain metastases over the course of disease. Median line of IO was 2nd line (range 2nd-5th line); nivolumab-ipilimumab was the most common regimen (43%), followed by nivolumab (38%), then pembrolizumab (20%). Patients received an average of 4 cycles of IO (range 1-35). Nine patients were treated on clinical trial. Median survival after IO was 4.2 months and median OS of 17.3 months. Median survival for patients with brain metastases was 2.2 months vs. 10.3 months without (P=.01). Most patients had no durable response to IO; however, responses were observed in 7 patients (1 CR, 6 PR) and 8 patients had stable disease.

Table 1: Treatment Summary	
Treatment	**Patients – no.**
Chemotherapy – any line	
Carboplatin	28
Cisplatin	15
Etoposide	40
Topotecan	19
Irinotecan	23
Paclitaxel	11
Gemcitabine	1
Immunotherapy	
Nivolumab-ipilimumab	17
Nivolumab	15
Pembrolizumab	9
Radiation Therapy	
Radiation (non-CNS site)	36
Radiation (CNS)	24
Type of CNS radiation	
Prophylactic Cranial Irradiation	8
Whole brain radiation (therapeutic)	16
Gamma knife/stereotactic radiation	6

Conclusion: This retrospective review describes our experience utilizing IO in advanced SCLC at our academic institution. Although treatment patterns are changing with first-line IO, this data reflects the variability of patient responses. Several patients had prolonged responses, indicating potential areas of further investigation. This data will also be used to evaluate IO activity in CNS disease.

EP1.12-39 SURVIVAL AND PROGNOSTIC FACTORS IN PATIENTS WITH SMALL-CELL LUNG CANCER: A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

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Background: With limited advances in the management of small-cell lung cancer (SCLC) within the past thirty years, SCLC still imposes a substantial burden. Identification of prognostic factors help optimize development of appropriate treatment strategies. As part of a larger systematic review, this study aimed to describe survival and prognostic factors in SCLC. **Method:** A systematic review of observational studies was conducted using MEDLINE and Embase over the period 01 January 1998-17 October 2018. Pragmatic searches of the grey literature, including conference abstracts and proceedings, were also conducted to identify additional sources. Search outputs were independently screened, adjudicated and abstracted by two assessors independently, with conflicts resolved by a third. **Result:** Of the 2,418 sources identified in the literature, 394 were retained for full text review, out of which 140 were included. In addition, 28 were identified through pragmatic searches yielding a total of 168 sources. Data mainly originated from Asia-Pacific (51; 42.2%), North America (30; 24.8%) and Europe (29; 24%). Eight different measures of survival were used across 121 studies (102 overall, 40 limited-stage [LS]-SCLC and 42 extensive-stage [ES]-SCLC): median overall survival (OS) was the most commonly reported, followed by 1- and 5-year survival rates. A total of 71/102 (69.6%) studies on SCLC, 19/40 (47.5%) on LS-, and 17/42 (40.5%) on ES-SCLC reported median OS. In SCLC, the median OS ranged from 4.6 to 29.1 months, while it ranged from 10 to 47 months in LS-SCLC and from 4 to 14.2 months in ES-SCLC. Survival trend was reported in three studies using data from SEER registries with a general trend towards an increase in survival rate when 2- and 5-year survival rates were reported. When reported (one source), no improvement in OS trend was noted. Chemotherapy, radiation therapy, prophylactic cranial irradiation, performance status, age and sex were among prognostic factors identified in both stages of SCLC. **Conclusion:** SCLC survival rate is low yet variable with significantly lower rates in ES-SCLC and minimal changes in survival trend. Significant variability exists in measurement and reporting SCLC survival and survival trend, thus hampering comparability of findings, syntheses of findings and clinical decision-making.

Keywords: prognostic, SCLC, systematic review

EP1.12-40 NEUROENDOCRINE TUMORS OF THE LUNG: CLINICO-PATHOLOGICAL CHARACTERIZATION AND FOLLOW-UP OF PATIENTS TREATED AT AN ARGENTINEAN UNIVERSITY HOSPITAL IN THE LAST 10 YEARS

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Background: Neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body, most commonly from the lungs and gastrointestinal tract. Histological characteristics and clinical behaviour define lung NETs, which are classified into four groups: typical (TC) and atypical carcinoids (AC), large-cell neuroendocrine carcinoma (LCNC) and small-cell lung cancer (SCLC). The identification and differentiation of TCs from ACs or LCNECs and SCLC is essential for treatment options and prognosis. **Method:** We performed a retrospective review of patients with lung NETs treated in our institution in the last decade. We analysed histological confirmed primary lung NETs cases. Demographics, clinical characteristics, imaging, treatment and outcome are described for this patient population. **Result:** A total of 91 patients with lung NETs were included; 28/91 (30.8%) were lung carcinoids (TC:14 and AT: 14) and 63/91 (69.2%) were high grade lung NETs (SCLC: 54 and LCNC: 9). Comparing low and high grade NETs groups of patients, we could identify differences in the following variables: mean age at diagnosis (51±14 vs 61 ±9 years, p=0.000), mean time from the beginning of symptoms to achievement of pathologic diagnosis (10.5±15.9 vs 3.9 ± 2.6 months, p=0.002), ECOG^{3}2 (14% vs 42%, p=0.001), smokers (57% vs 95%, p=0.000), median % of Ki67 expression (4%, (1-30%) vs 50%, (20-90), p=0.000), history of inflammatory lung disease (18% vs 32%, p=0.028) and presence extra-thoracic disease at diagnosis (47% vs 68%, p=0.000). No statistically differences between groups were observed in: sex, family history of lung cancer, second diagnosis of cancer and body mass index at diagnosis. Functioning carcinoid syndrome was observed in 10% (3/28) of patients with lung carcinoids. For the entire cohort, the median overall survival (OS) was 19 months (IC95%: 14-24 months). The five year OS for patients with lung carcinoids was 62% and 13% for high grade NETs. **Conclusion:** In our series of lung carcinoids we observed a high frequency of: atypical carcinoids, advanced disease at presentation and smoking history. However, the 5-year overall survival is the expected for this population. More knowledge is needed about this entity in South American countries.

Keywords: SCLC NET

EP1.13 STAGING

EP1.13-01 MULTIPLE LUNG NODULES: HISTOPATHOLOGIC, MOLECULAR AND CLINIC APPROACH OUTCOMES

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Background: Distinguishing multiple primary lung cancers from intrapulmonary metastases in patients with synchronous multifocal lung carcinomas can be challenging. Histologic and molecular features, in conjunction with clinical and radiological information, can all be tools to assist with staging of multiple nodules. **Method:** Retrospective descriptive study. Patients diagnosed with multiple lung nodules and underwent surgery between 07/2011 - 2/2018 were included Pathologists trained in lung cancer performed the histological diagnosis of each of the nodules according to WHO 2015 classification and comprehensive histologic assessment analysis and, subsequently, a molecular analysis by Oncomine Focus Assay panel in Ion PGM platform was made. We also carried out clinical and demographic analyzes. **Result:** A total of 22 patients were retrospectively studied Median Age: 67,5 years old (r 39-79). Non smokers: 6/22 (27,7%) patients. 13/22 (59%) pts men. 95,5% was staging with PET before surgery/mediastinoscopy, 6 of them reported mediastinal lymph node involvement by PET but only mediastinal involvement was evidenced in the biopsy in 1 case. 6 cases showed 2 nodules in same lobe, 12 cases showed 2 or more nodules in same lung but in different lobe, 2 cases bilateral nodules, (2 of 4 required sequential surgery). 21/22 mediastinoscopy before surgery, Segmentectomy, lobectomy or both were the most frequent surgeries. The lobe most frequently affected was the right upper lobe (alone or combined) followed by the left lower lobe. There were no cases of neoadjuvant treatment and 6 patients required adjuvant chemotherapy. The decision to perform adjuvant was evaluated in the tumor board. 4/22 relapses (sites of relapses: nodes, bones, lung). One of them had performed adjuvant treatment. Despite a high rate of sub-lobar surgeries, the incidence of local relapse was low (1 case lung and 3 mediastinal nodes). With a median follow-up of 19 months there was only one death and 4 relapses. The combination of WHO 2015 classification and CHA criteria improves the accuracy of synchronous or metastatic tumors. The addition of molecular testing is useful to define discrepancies in challenging cases. **Conclusion:** Decisions regarding post-surgery treatments were not defined by molecular biology. Both the TNM and the histological concordance between the nodules were the main determinants to make a therapeutic decision. Gene panels could help make decisions based on these finding. Being able to address and differentiate early stages vs. intrapulmonary metastatic disease can have a prognostic impact and help predict the outcome and guide the therapy.

EP1.13-02 NEGATIVE PREDICTIVE VALUE OF EBUS-TBNA FOR MEDIASTINAL STAGING OF NON-SMALL CELL LUNG CANCER

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Background: Mediastinal staging must precede surgery in patients with resectable non-small cell lung cancer (NSCLC). According to current guidelines, minimally invasive techniques, such as endobronchial ultrasound with transbronchial needle aspiration or/and biopsy (EBUS–TBNA/B), represent the preferred first-line approach for mediastinal staging, before performing mediastinoscopy. We herein aimed to evaluate the negative predictive value (NPV) of EBUS-TBNA in a tertiary referral center and correlate NPV with primary tumor features and other clinicopathological variables. **Method:** We retrospectively studied the medical records of 20 patients with resectable NSCLC, submitted, from January 2017 to January 2018, to EBUS-TBNA in the Department of Interventional Pulmonology of the first Pulmonology Clinic of Sotiria Athens General Hospital; EBUS-TBNA had been performed prior to surgical resection of the primary tumor and surgical lymph node staging in all patients. The EBUS-TBNA results were correlated with surgical staging. **Result:** Among all lumph node stations sampled, there were 46 with negative EBUS-TBNA results. Post-operatively, 6 EBUS-TBNA negative lymph nodes were re-staged as positive. The remaining 40 EBUS-TBNA negative nodes were true negative, as confirmed by surgical staging. NPV of EBUS-TBNA was 87%, and thus within the range of previously published results. Among cases with negative EBUS-TBNA results, a statistically significant correlation was observed between low NPV (false negative EBUS-TBNA) and T3 tumor size (> 7cm), pre-bronchoscopy N2 disease, presence of necrosis within the primary tumor, and microscopic vascular invasion (p-value <0.05 in all cases). **Conclusion:** Patients with T3 tumors (>7cm), N2 disease before the performance of EBUS-TBNA, and those with tumor necrosis or microscopic vascular invasion may be at greater risk for false negative EBUS-TBNA results. Given the small sample size of our study and its retrospective study design, it must be emphasized that these findings are highly preliminary and must be confirmed in larger prospective series.

Keywords: Non-Small Cell Lung Cancer, EBUS-TBNA, mediastinal staging

EP1.14 TARGETED THERAPY

EP1.14-01 MAJOR THERAPEUTIC RESPONSE TO T-DM1 IN METASTATIC LUNG ADENOCARCINOMA WITH HER2 MUTATION

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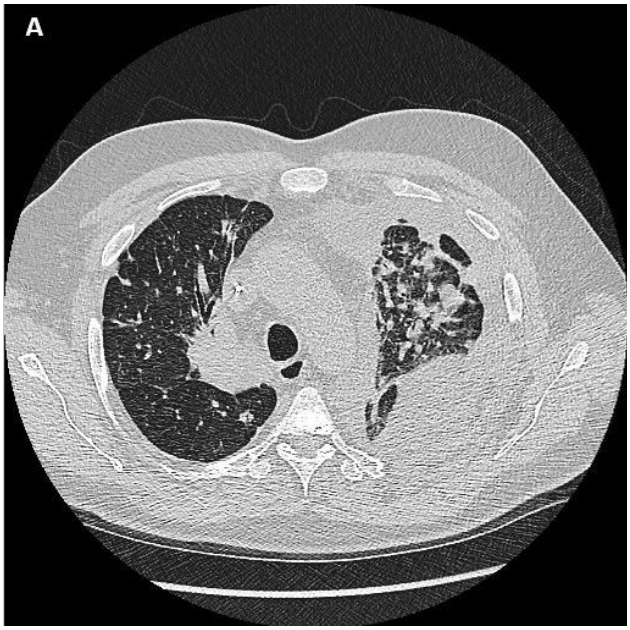
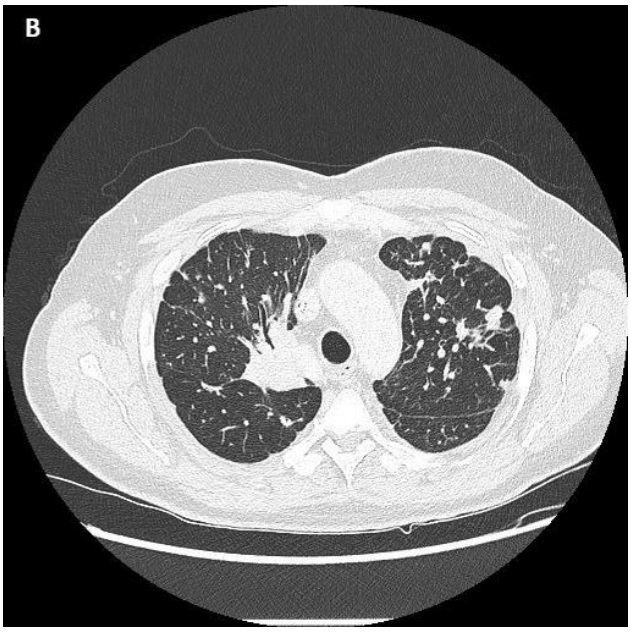
Background: The *HER2* exon 20 mutation is described in 1-5% of patients with Non-small cell Lung cancer, and at the moment no targeted agents are approved in Europe. However, the use of conjugated antibodies such as trastuzumab and ado-trastuzumab emtansine (T-DM1) has shown promising results. **Method:** We describe the case of a major response to T-DM1 in fourth line treatment in a patient with metastatic adenocarcinoma and *HER2* mutation. **Result:** A 60-year-old male, former smoker (3 packs/year), presented to the emergency room in 2016 for dyspnoea. A bilateral pleural and compressive pericardial effusion with tamponade requiring pericardial drainage were discovered. A lung adenocarcinoma with *HER2* mutations was diagnosed. He benefited from two successive treatment lines between September 2016 and September 2017 (carboplatin- paclitaxel and bevacizumab followed by bevacizumab maintenance until progression, then pemetrexed for two cycles). At this time, he developed a new disease progression as a recurrence of tamponade requiring surgical drainage and a third line with docetaxel and trastuzumab was started for twelve cycles. After eight months, he presented an acute respiratory failure due to the recurrence of pericardial and pleural effusions, requiring a pleural drainage (Fig.1A). After discussion at the multidisciplinary meeting, a fourth line of treatment with T-DM1 in compassionate has been proposed. After three cycles, we observed an excellent clinical response, with disappearance of dyspnoea, resumption of normal daily activity. The radiological evolution was also very favourable (Fig.1B). The patient benefited from other six months of treatment before getting a new progression. **Conclusion:**





In this case T-DM1 showed a major clinical and radiological benefit despite its use in fourth line. Other clinical reports and phase II trials confirmed promising results with targeted agents already used in breast cancer. Several studies are exploring the efficacy of these agents, opening up new hopes.

Keywords: NSCLC, HER2 mutation, T-DM1

EP1.14-02 COMPARATIVE EFFICACY OF FIRST-LINE CERITINIB AT A DOSE OF 450MG WITH FOOD AND ALECTINIB IN ADVANCED ALK+ NSCLC

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Background: Anaplastic lymphoma kinase (ALK) rearrangement occurs in approximately 3% to 7% of patients with non–small cell lung cancer (NSCLC), and the clinical data have demonstrated the success of therapeutic approaches targeting the ALK protein in this patient population. Ceritinib and alectinib were both second generation of ALK inhibitors that approved as first-treatment for

ALK+ NSCLC. Ceritinib is initially approved at the recommended dose of 750 mg/day fasted (ceritinib 750-mg fasted). Ceritinib at a dose of 450 mg with food (ceritinib 450-mg fed) compared to ceritinib 750-mg fasted showed consistent efficacy and less gastrointestinal toxicity in the Ascend 8 trial. Although a previous cross-study indirect study compared the efficacy of ceritinib 750-mg fasted with alectinib, the efficacy of ceritinib 450-mg fed compared with alectinib is unknown. **Method:** Progression-free survival of ceritinib 450-mg fed was indirectly compared with that of alectinib using a Bucher anchor-based indirect comparison approach using ceritinib 750-mg fasted as the common anchor. The comparative efficacy of alectinib vs ceritinib 750-mg fasted was obtained from matching-adjusted indirect comparison(MAIC) and the comparative efficacy of ceritinib 450-mg fed vs ceritinib 750-mg fasted was estimated using reconstructed individual patient-level data from Ascend-8 trial. The corresponding 95% CI of HR for ceritinib 450-mg fed vs alectinib was calculated using the standard errors of the HRs of alectinib vs ceritinib 750-mg fasted and ceritinib 450-mg fed vs ceritinib 750-mg fasted. **Result:** The HR of alectinib vs ceritinib 750-mg fasted in the MAIC was 0.78 (95% CI 0.50-1.23). The estimated HR of ceritinib 450-mg fed vs ceritinib 750-mg fasted was 0.71(95% CI 0.41-1.23). In the anchor-based indirect comparison, HR of ceritinib 450-mg fed vs alectinib was 0.91(0.45-1.85). **Conclusion:** In the cross-study indirect comparison, the efficacy of ceritinib 450-mg fed was comparable with alectinib with numerically lower hazard of progression or death. However, results from indirect comparison can be limited by unobserved or unmeasured confounding. Head-to-head randomized phase III trials are needed to formally compare the efficacy of ceritinib 450-mg fed vs alectinib

Keywords: ALK, Ceritinib, alectinib

EP1.14-03 DRIVER GENES AS PREDICTIVE INDICATORS OF BRAIN METASTASIS IN PATIENTS WITH ADVANCED NSCLC: EGFR AND ALK AS WELL AS RET GENE MUTATIONS

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Background: Brain metastasis is a cause of disease progression and death in lung cancer patients, and is also one of the most common metastatic sites of lung cancer. Non-small lung cancer (NSCLC) accounts for about 80% of all lung cancer patients, and adenocarcinoma has become the main subtype of NSCLC in recent years. A retrospective analysis verified the role of gene mutations in brain metastasis in patients with non-small lung cancer (NSCLC). **Method:** The clinicopathological data of 552 patients who received driver genes detection for lung cancer in the Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital from January 2015 to June 2017 were collected; NGS was used for gene detection. The driving genes for detection were EGFR, ALK, KRAS, ROS-1, BRAF, ERBB2, RET and c-MET, which were eight lung cancer driving genes recommended in NCCN guidelines. All the tests were carried out in the Center of Molecular Pathology in the Affiliated Tumor Hospital of Zhengzhou University. **Result:** Of the 552 patients with advanced NSCLC, 153 (27.7%) had brain metastases. Univariate analysis showed that age (*P* = 0.008), gender (*P* = 0.016), smoking history (*P* = 0.010), lymph node metastasis (*P* = 0.003), and three driver genes: positive EGFR mutation (*P* = 0.001), positive ALK gene fusion (*P* = 0.021) and positive RET gene fusion (*P* = 0.003) were factors influencing the incidence of brain metastasis. Logistic multivariate regression analysis revealed that only positive EGFR mutation (*P* = 0.012), positive ALK gene fusion (*P* = 0.015), positive RET gene fusion (*P* = 0.003), pathological type (*P* = 0.009), lymph node N2–3 metastasis (*P* = 0.000) and a younger age (*P* = 0.000) were independent risk factors for brain metastasis. In addition, a ROC curve was plotted with the above factors with AUC=0.705 (P=0.000). **Conclusion:** EGFR mutation, ALK gene fusion and RET gene fusion in advanced NSCLC patients play roles in brain metastasis as positive driver genes.

Keywords: non-small lung cancer, driver gene, Brain metastases

EP1.14-04 VALIDATION OF NEW TARGETS INTERFERING AT PHOSPHATIDYLETHANOLAMINE PRODUCTION AGAINST NSCLC

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Background: Besides all medicine advancements, lung cancer is still the leading cancer-related cause of death worldwide. In this scenario, our group validate new targets to drug development focusing in interfering at phosphatidylethanolamine (PE) production as a breakthrough strategy, once PE has been previously described as increased in Non-Small Cell Lung Cancer (NSCLC) tumors. Two critical points in PE production should be highlighted: ethanolamine cellular uptake and the enzyme responsible for the limiting step of the main route of PE synthesis, CTP:phosphoethanolamine cytidylyltransferase (Pcyt2). Therefore, this study aimed to evaluate *in vitro* modulation of Pcyt2 enzyme and ethanolamine cellular uptake in A549 cells to validate the therapeutic potential of these targets for NSCLC treatment. **Method:** Pcyt2 was silenced in A549 cell line by CRISPR-Cas9-Mediated technology using 4D-Nucleofector™ System, followed by sorting using FACSAria II and confirmation of Pcyt2 protein depletion by Western blotting. Cellular sensitivity to meclizine (a Pcyt2 inhibitor) and isopropanolamine (an ethanolamine uptake inhibitor) was assessed by MTT assay. The proliferation capacity was evaluated by plotting cell growth curves and Colony Forming Units (CFU) assay. Cells were fixed in ethanol overnight in freezer, stained with 7-Aminoactinomycin D and analyzed by flow cytometry using BD LSRFortessa. All statistical data are expressed as mean ± standard deviation (SD) and were analyzed by one-way ANOVA followed by the Tukey's test using GraphPad Prism software, version 7. **Result:** Initially, A549 cells Pcyt2 knockout (KO) cells were established and confirmation in three different passages by Western Blotting. KO cells were resistant to meclizine ($p<0.001$) and more sensitive to isopropanolamine ($p<0.05$) than wild-type (WT) cells. Only WT cells proliferate more when cultured in media with ethanolamine supplementation ($p<0.01$), which is related to the S-phase arrest ($p<0.05$). KO cells showed proliferation changes which were not affected by meclizine treatment both in clonogenic and cell cycle assays. This data is closely related to the reduction of pRb expression and the increase of p21 expression in KO cells. On the other hand, WT cells were arrested in G0/G1 phases and their proliferation capacity was reduced (34% less colonies, $p<0.01$) after meclizine treatment. **Conclusion:** Pcyt2 modulation in A549 cells both genetic and pharmacological showed the decrease of cancer cells proliferation and viability. On the other hand, supplementation of ethanolamine increase cellular proliferation. Altogether, these preliminary results confirm the importance of PE for cell metabolism and division which is an exciting starting point to deeply evaluate Pcyt2 potential as a target for NSCLC treatment.

Keywords: Targeted therapy, CTP:phosphoethanolamine cytidylyltransferase (Pcyt2), Non-Small Cell Lung Cancer

EP1.14-05 CLINICAL CHARACTERISTICS OF OSIMERTINIB RESPONDER IN NON-SMALL CELL LUNG CANCER PATIENTS WITH EGFR-T790M MUTATION

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Background: Osimertinib is a mutant-selective EGFR inhibitor that is effective against non-small cell lung cancer (NSCLC) patients with the *EGFR*-T790M mutation, who are resistant to EGFR-tyrosine kinase inhibitors (EGFR-TKIs). However, the factors affecting response to osimertinib treatment are unknown. **Method:** In this retrospective study, 27 NSCLC patients with the *EGFR*-T790M mutation were enrolled at 5 institutions in Japan. **Result:** Among several parameters tested, the progression-free survival (PFS) associated with the initial EGFR-TKIs was positively correlated with the PFS after osimertinib treatment (p = 0.021). The median PFS following osimertinib treatment and the overall survival (OS) were longer in patients who responded to osimertinib than in those who

did not (17.7 months versus 3.5 months, p = 0.009 and 24.2 months versus 13.5 months, p = 0.021, respectively). A multivariate analysis demonstrated that the PFS with initial EGFR-TKIs was significantly related to the PFS with osimertinib treatment (p = 0.035), whereas osimertinib response was significantly related to the PFS and OS with osimertinib treatment (p = 0.016 and p = 0.006, respectively). **Conclusion:** Our retrospective observations indicate that PFS following the initial EGFR-TKI treatment and the response rate to osimertinib might be promising predictors for effective osimertinib treatment in NSCLC patients with the *EGFR*-T790M mutation.

Keywords: Osimertinib, Biomarker, EGFR-T790M mutation

EP1.14-06 CLINICAL APPLICATION OF AN APPROPRIATE SIZE NGS PANEL IN ADVANCED NON-SMALL CELL LUNG CANCER MANAGEMENT: PERSONAL EXPERIENCE

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Background: Precision medicine plays an important role in patients with advanced non-small cell lung cancer (NSCLC). The targeted genes, EGFR, BRAF, ALK, and ROS1, have become as a standard genetic test in NSCLC. Using multi-gene next-generation sequencing (NGS) technology is an efficient approach compared with the conventional genetic test that can identify hundreds of genetic information simultaneously. In this study, we share our clinical experience of using an appropriate size NGS test in Taiwan NSCLC patients. **Method:** The formalin-fixed, paraffin-embedded (FFPE) were collected from 100 patients with advanced NSCLC. 94 patients had received at least one treatment and six patients were treatment-naïve. The FFPE samples were profiled using a medium size NGS panel on the Ion Torrent system. The single nucleotide variants (SNV) and small InDels were detected in 35 or 40 genes, as well as copy number variations (CNVs) in 14 or 22 genes. The gene fusion status was evaluated by an RNA fusion test in 4 genes. **Result:** In total, the alternation of FDA-approved biomarkers was identified in 70.0% (70/100) patients. Other genetic alterations, including suggested biomarkers in NCCN guideline (ERBB2 mutations and CNVs, MET exon 14 alterations and RET fusions), and other potential actionable mutations (EGFR exon 20 insertions and CNVs, BRAF rare mutations, KRAS mutations and CNVs, ALK CNVs, MET CNVs, mTOR pathway, and cell cycle pathway alternation) were detected in 60.0% (60/100) patients. The co-occurred potential genomic alterations were discovered in 60.7% (37/61) of patients who had EGFR mutations at diagnosis. 78.3% (18/23) patients with post third generation EGFR TKI therapy had at least a co-occurring potential actionable alterations with EGFR mutation. In patients with wild type EGFR and ALK or unknown-status at diagnosis, the targeted alternation was detected in 51.4% (19/37), and 21.6% (8/37) were FDA-approved biomarkers. Furthermore, we report two cases who responding to the targeted drugs followed the NGS testing results. One case had a potentially actionable alteration co-occurred with EGFR mutation and the other had a rare BRAF mutation. **Conclusion:** The data reported here suggest that using genetic test by an appropriate size and cost-effective NGS panel for NSCLC patients at disease diagnosis or disease progression could identify more mutations other than FDA-approved biomarkers for targeted drug selection.

Keywords: Targeted therapy, NSCLC, NGS

EP1.14-07 EFFICACY AND SAFETY OF ALK INHIBITORS IN ALK-REARRANGED NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: First and second generation ALK inhibitors were shown to delay disease progression and improve tumour response in ALK-rearranged advanced non-small cell lung cancer (NSCLC) patients. While a significant progression free survival (PFS) improvement has been consistently reported, no overall survival (OS) benefit was shown in randomized trials. We conducted a systematic review and meta-analysis to assess the efficacy and safety of ALK inhibitors compared to chemotherapy (ALK vs. chemo) and 2nd generation ALK inhibitors compared to 1st generation ALK inhibitors (ALK 2G vs. ALK 1G). **Method:** The electronic databases PubMed and EMBASE, were searched for relevant randomized trials. Pooled hazard ratios (HR) for overall survival (OS) and progression free survival (PFS), and pooled risk ratios for objective response rates (ORR) and grade 3 or higher toxicity were meta-analyzed using the generic inverse variance and the Mantel-Haenszel methods. To account for between-studies heterogeneity, random-effect models were used. Subgroup analyses compared PFS by gender, smoking status, brain metastases, race and age. **Result:** Six trials were included in the analysis of ALK vs. chemo and four in the analysis of ALK 2G vs. ALK 1G. Treatment with ALK inhibitors improved OS compared to chemotherapy (HR: 0.84, 95%CI 0.72-0.97) while a trend toward a better OS was seen with ALK 2G vs. ALK 1G without reaching statistical significance (HR: 0.64, 95%CI 0.36-1.16). PFS was improved with ALK vs. chemo and ALK 2G vs. ALK 1G (HR: 0.44, 95%CI 0.35-0.44 and HR: 0.38, 95%CI-0.29-0.51, respectively). Similarly, ORR was improved with ALK vs. chemo and ALK 2G vs. ALK 1G (RR: 2.68, 95%CI 1.89-3.81 and RR: 1.16, 95%CI 1.08-1.24, respectively). The risk of grade 3 or higher toxicity did not differ between treatments (RR 1.08, 95%CI 0.88-1.33 and RR 0.77, 95%CI 0.56-1.06, respectively). Overall the PFS benefit of ALK vs. chemo and ALK 2G vs. ALK 1G was homogenous across all subgroups with a greater degree of benefit within never-smokers when treated with ALK vs. chemo (*p* for subgroup differences=0.03). **Conclusion:** This meta-analysis is the first, to our knowledge, to report an OS improvement with the use of ALK vs. chemo. A trend toward a better OS was also seen with ALK 2G vs. ALK 1G and this is likely because of crossover effects and limited OS follow-up. Longer follow up and further research are warranted to directly compare ALK inhibitor sequences and to understand the outcomes of 2nd generation ALK inhibitors as initial therapy.

Keywords: ALK, Targeted therapy, advanced NSCLC

EP1.14-08 IRREVERSIBLE SEVERE CARDIOTOXICITIES EXCEPT FOR QTC INTERVAL PROLONGATION ASSOCIATED WITH OSIMERTINIB

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Background: QTc interval prolongation is a known and warning cardiotoxicity associated with Osimertinib. The final summary on the safety profile of Osimertinib (AstraZeneca plc) reports that severe cardiotoxicities except for QTc interval prolongation are 0.8 % (29/3578 patients) and alerts us to such adverse events. Here, we report irreversible severe cardiotoxicities associated with Osimertinib except for QTc interval prolongation. **Method:** We reviewed the medical records of EGFR-mutated Non-Small Cell Lung cancer patients who were treated with Osimertinib at Osaka International Cancer Institute between March 2016 and January 2019. We checked cardiotoxicities associated with Osimertinib based on the medical records. **Result:** We enrolled 123 patients treated with Osimertinib into this study. The median age was 69 (range: 33-86) years. Of 123 patients, 40 (32.5%) were male, all cases except one were adenocarcinoma, EGFR mutation profile was Ex. 19 del/ L858R/ de novo T790M/ others(G719S, L861Q); 62 (50.4%)/ 56 (45.5%)/ 3/ 2. Osimertinib treatment line was 1st line; 23 (18.7%), 2nd line; 30 (24.4%), 3rd line; 18 (14.6%), ≧4th line; 41 (33.3%), 11 pts; switching from other EGFR-TKI during 1st line. Severe cardiotoxicities (CTC-AE Gr.3≧) were observed in 5 pts (4.1%); acute myocardinal infarction (1), irreversible congestive heart failure due to systolic dysfunction (1), exacerbation of tricupid regurgitation (1), decreasing ejection fraction (EF) (2). QTc interval prolongation was observed only in one patient (Gr.1). Histopathological analysis of a myocardial biopsy from one patient with decreased EF (Gr.3) revealed inflammatory cells infiltration into cardiomyocytes. Intriguingly, afatinib switched from osimertinib overcame osimertinib induced cardiomyopathy in the patient. **Conclusion:** We experienced severe cardiotoxicities associated with Osimertinib at a higher frequency (4.1%) than reported before. Considering some patients were forced to quit their chemotherapy due to severe cardiotoxicities. We should pay attention to not only QTc interval prolongation but also other cardiotoxicities in administrating Osimertinib in the clinical setting. Afatinib could be an alternative to Osimertinib for overcoming Osimertinib-induced cardiotoxicities.

EP1.14-09 CHARACTERIZATION OF ACTIONABLE BRAF^{V600E} AND CO-MUTATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Targeting activated-mutations in NSCLC offers unique benefit that outperforms other cancers. Multiplex Next Generation Sequencing (NGS) platform provides opportunity for detection of low-frequency actionable-mutations such as *BRAF* ^{V600E}, which was previously reported in 1-2% of NSCLC and correlated with poorer response to chemotherapy. In this study, we used the NGS platform to determine the prevalence and characteristics of *BRAF* ^{V600E}-mutated NSCLC. **Method:** Tissue archive of stage I-IV NSCLC from Ramathibodi and Phramongkutklao Hospitals during 2012-2015 was retrieved for DNA extraction. Samples were analyzed by NGS with Lung Cancer Panel 45 Genes on Ion Torrent system. Variants from NGS with coverage of higher than 1000X and ≥3% alternate variant frequency were considered as positive. The cutoff-point was validated by Real- time PCR. Clinical data correlation was analyzed. **Result:** Of the 159 FFPE-samples, 16 samples (10.1%) with BRAFV600E mutation were identified. The median age was 66.6 years old. Majority of the patients were female (81.3%) and never-smoker (75%). Seven patients had early stage and 9 patients had stage III-IV disease. Co-mutations with BRAFV600E were found in 13 patients. EGFR mutation was the most common co-mutation (62.5%) follow by co-mutation with KRAS (37.5%), MET exon14 splice-site (18.8%), and PIK3CA (6.3%) (Table1). Advanced-stage patients with KRAS and MET exon14 splice-site co-mutations with BRAFV600E had worse survival (10.4, 10.4 months) compared to patients with EGFR co-mutation (41.1 months). Survival of patients with single BRAFV600E is better than patients with other co-mutations (not reach vs 60.5 months) in all stages. Table 1: Baseline characteristics of 16 patients with BRAFV600E mutation and their co-mutated gene including palliative treatment in stage IV patients

Conclusion: Our data demonstrated high prevalence of *BRAF* ^{V600E} and coexisting-actionable mutations. *BRAF*^{V600E}-mutated NSCLC are common in female and never-smoker. Co-mutations with other actionable-mutations patients showed worse survival compared to single *BRAF*^{V600E} patients. Integrating the sensitive multiplex NGS method into the clinical practice will help broaden the opportunity for superior treatment efficacy in the future.

Keywords: BRAFV600E, EGFR, NSCLC

Patient ID	Gender	Age	Smoking status	Staging	Co-mutation				First line treatment	Second line treatment	Current status	OS (mo)
					EGFR	KRAS	MET	PIK3CA				
1	Female	62	Never	IA	*L858R*						Alive	
2	Female	73	Never	IA	*Del19, L858R*	*G12D*					Alive	
3	Female	50	Never	IA	*Del19*	*G12C, G12D, Q61R*					Alive	
4	Female	67	Never	IA	*G719S*	*G12D*					Alive	
5	Female	62	Never	IB		*G12S*					Alive	
6	Female	67	Never	IB	*G719A, del19*						Alive	
7	Female	75	Never	IIA							Alive	
8	Female	80	Ex-smoke	IIIA		*G12D, G13S*	*C2888-1G>A**				Death	10.4
9	Male	63	Ex-smoke	IIIA							Alive	
10	Female	75	Never	IV			*C3028G>T**		Gemcitabine	-	Death	7.9
11	Female	60	Never	IV	*Del19*				Carbo/Pac	Bevacizumab	Death	12.6
12	Female	59	Never	IV	*L858R*		*C3028G>A**		Carbo/Pem	Erlotinib	Death	48.9
13	Female	89	Never	IV	*L858R*				Erlotinib	Osimertinib	Death	60.5
14	Male	74	Ex-smoke	IV	*Del19*	*G12D, Q61L*		*H1047R*	Carbo/Pac	Gemcitabine	Death	27.1
15	Female	58	Never	IV					Carbo/Gem	Carbo/Gem	Death	34.9
16	Male	71	Current smoke	IV	*L858R*				Gefitinib	Carbo/Gem	Death	41.1

EPOSTERS

EP1.14-10 INVESTIGATION OF MECHANISMS OF ACQUIRED RESISTANCE TO AFATINIB WITH PLASMA DNA IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Afatinib, the 2nd generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has been evidenced better efficacy compared to 1st generation EGFR-TKI by phase III studies, but the problem is to acquire resistance approximately one year after treatment. The detail mechanisms of acquired resistance to afatinib has not clarified, although T790M was also detected at time to acquired resistance. Recently, the 3rd generation EGFR-TKI, osimertinib has been approved as the first line setting. As for the mechanisms of acquired resistance to osimertinib as 1st line, various kinds of pathway beside EGFR contributed, suggesting difficulty to select next treatment strategy after osimertinib. Considering how to use 1st, 2nd and 3rd approximately, it has been reported that longer PFS was shown among the patients who were treated with osimertinib following afatinib, compared to 1st generation EGFR-TKI. Based on these evidences, we hypothesize that mechanisms of acquired resistance to afatinib may be less genetic alterations compared to osimertinib, and these alterations could be limited to EGFR pathway, resulting in EGFR-TKI sequencing, from afatinib to osimertinib showed better prognosis. Because the concept of tumor evolution showed that the number and kind of genetic alterations were increased after treatment modifications, comprehensive assay system is indispensable for evaluation of acquired resistance. Moreover, non-invasive assay system such as liquid biopsy is needed since distant metastases are often observed in advanced lung cancer patients. Guardant360™, a high sensitive digital sequencing system with plasma DNA has been developed by Guardant Health, enable to detection of SNV of 73 genes, in/del of 23 genes, amplification of 18 genes, and fusions of 6 genes. The assay system enables us to detect 0.03% allele fraction. The purpose of this study is to clarify mechanism of acquired resistance to afatinib with liquid biopsy to determine best EGFR-TKI sequencing. **Method:** Study Design Prospective observational study Primary objective To determine mechanisms of acquired resistance to afatinib with plasma DNA Target sample size 40. We are planning to compare with the results of patients who acquired resistance to osimertinib with liquid biopsy performed in FLAURA. So far, 29 patients acquired resistance to afatinib, and we collected these blood samples. Sample preparation Collection of samples 1. before afatinib treatment and at PD to afatnib 2. collection of 5ml blood with sodium citrate collection tube Genomic examinations NGS is performed in Guardant Health. **Result:** This study had finished enrollment and under analysis now. **Conclusion:** Comprehensive analysis are needed to clarify the mechanisms of acquired resistance to afatinib to facilitate consideration of the best sequence of EGFR-TKI.

Keywords: Afatinib, Acquired resistance, EGFR-TKI sequencing

EP1.14-11 REAL-LIFE DATA OF OSIMERTINIB IN PRETREATED PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER HARBORING EGFR T790M MUTATION

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Background: Several clinical trials have demonstrated the efficacy and safety of osimertinib in pretreated patients with advanced non-small cell lung cancer (NSCLC) harbouring EGFR T790M resistance mutation. However, clinical real-world data on patient characteristics and efficacy of the drug is limited. **Method:** We reviewed the medical records of T790M mutation-positive lung cancer patients treated with osimertinib between May 2016 and February 2019 in our institution. We calculated progression-free survival (PFS) and overall survival (OS) from osimertinib initiation. **Result:** The study included 22 patients with a mean age of 59.6 years. 59% (13/22) were female and 100% had adenocarcinoma histology. We had an unusual high frequency of tobacco use in our series as 40.9% (9/22) of our patients were smokers (3/22) o former-smokers (6/22), with a mean of 35 pack-year (sd, 28.5). 45.5% (10/22) had exon 21 L858R mutations, whereas 54.5% (12/22) harboured exon 19 deletions (19del). One patient simultaneously had an exón 19 deletion and exon 20 S768I mutation. Osimertinib was used in second, third and fourth line in 50% (11/22), 27% (6/22) and 23% (5/22) of patients, respectively. All patients had liquid biopsy blood samples obtained prior to the start of the treatment, and T790M mutation could be detected in 86.4% (19/22), with a mean mutant-allele fraction of 4,11% (standard deviation 8.65, min 0, max 37.7). T790M was detected only in tissue in 2 patients and exclusively in cerebrospinal fluid in 1 of them. At the time of starting osimertinib, patients had a median of 3 metastatic sites (min 1, max 6), being the most frequent locations the lung (73%), the bone (64%), the pleura (59%), the central nervous system (23%) and the peritoneum (14%). Median follow-up duration was 10 months (IQR, 4.7-22.67). To the date, 63% (14/22) have experienced progression of the disease. Median PFS in our series was 8.9 (95% CI, 4.9-17.9) months, whereas median OS since osimertinib initiation was 18.2 (95% CI, 8.8-NE) months. Regarding to toxicity, 12 patients referred adverse events, 82.6% of which were mild (G1), being the most frequent toxicities neutropenia (9%), diarrhoea (9%), hypertransaminasemia (9%) and asthenia (9%). Only 1 G3 event was recorded (asymptomatic hyperamilasemia). **Conclusion:** The efficacy of osimertinib in real-world practice was similar the observed in clinical trials, with a favourable adverse effect profile. Liquid biopsy is an effective non-invasive method to assess the presence of the T790M resistance mutation prior to the start of osimertinib.

Keywords: Osimertinib, Real-world data, EGFR mutant NSCLC

EP1.14-12 KRAS EXON 2 MUTATION - A RESISTANCE PATHWAY TO 1ST AND 2ND GENERATION EGFR TKIS

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Background: The most common resistance pathway to first and second generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in advanced non-small cell lung cancer (aNSCLC) is acquired EGFR T790M mutation. Other resistance mechanisms composed of amplifications of MET, HER-2 and small cell transformation. Acquired KRAS mutation is known as resistance mechanism to 3rd generation EGFR TKIs, but not to 1st or 2nd generation. **Method:** Patients with EGFR positive NSCLC had molecular profiling done upon resistance to 1st or 2nd generation EGFR TKIs, done by next generation sequencing on FFPE tissue or cfDNA from plasma including EGFR exons 19, 20, 21, KRAS exon 2 and BRAF exon 15. Treatment outcomes and prognosis data were taken from the medical records. **Result:** Fifty-three EGFR positive NSCLC patients had molecular profiling done upon resistance to 1st or 2nd generation EGFR TKIs since August 2017, of them 48 had KRAS exon 2 mutation tested. Six (12.5%) patients had KRAS exon 2 mutation, found on plasma in 5 patients and in tissue in 1 patient. Of the 6 patients, the original EGFR mutation was found in 3 patients (50%), and 2 had concurrent EGFR T790M mutation. One patient had KRAS mutation on the initial EGFR testing, although had prolong response to EGFR TKIs. All patients responded to 1st line EGFR TKIs. Upon progression- the 3 patients tested positive for EGFR T790M mutation were treated with osimertinib, although only 1 patient with concurrent KRAS and EGFR T790M mutation responded, and 2 patients with no EGFR T790M mutation were treated with chemotherapy with progressive disease. **Conclusion:** We found acquired KRAS mutation as resistance mechanism for EGFR TKIs in 12.5% of patients with EGFR positive NSCLC treated with 1st or 2nd generation EGFR TKIs. The patients with NSCLC tested positive for KRAS as resistance mechanism for EGFR TKIs were characterized by poor response to either TKIs or chemotherapy. Therefore, testing for KRAS exon 2 mutation is advised upon disease progression during EGFR TKI therapy.

Keywords: EGFR resistance, Metastatic EGFR positive NSCLC, K-RAS mutation

EP1.14-13 EGFR MUTATION IN LUNG ADENOCARCINOMA: REAL WORLD STUDY FROM A SINGLE INSTITUTE

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Background: To investigate the EGFR mutation in lung adenocarcinoma of real world. **Method:** Patients diagnosed lung adenocarcinoma and performed EGFR mutation analysis in Liaoning Cancer Hospital & Institute from June 2014 to April 2018 were collected retrospectively. Gender, age, EGFR mutation status of patients were analyzed. **Result:** There were 779 patients included in the study. Of all patients, 365 were male, 414 were female, median age was 60 years-old (range 29-80). EGFR mutation analysis showed that there were 417 mutation cases, 362 were negative, the overall mutation rate was 53.5%. For male patients, the mutation rate was 37.0% (135/365), and 68.1% for female patients (282/414). Seven hundred and sixty-one patients had one EGFR mutation type, 17 had two types, and 1 had three types. The most common type of EGFR mutation was Exon 21 L858R (204/436, 46.8%), and the second common was Exon 19 deletion (175/436, 40.4%), other mutation types were significantly less, including Exon 20 insertion (20/436, 4.6%), Exon 18 G719X (19/436, 4.4%), Exon 20 S768I (10/436, 2.3%), Exon 21 L861Q (5/436, 1.1%). Primary resistance of T790M mutation were found in 3 patients (0.7%), however, all the 3 cases had two types of mutations besides T790M mutation (2 Exon 19 deletion and 1 Exon 21 L858R). **Conclusion:** The overall EGFR mutation rate was over 50% in our institution, and higher in female patients, about 70%. The most common mutations were Exon 21 L858R and Exon 19 deletion, and other mutation types were rare. Finally, T790M mutation often combined with the other type of EGFR mutations.

Keywords: real world study, EGFR, lung adenocarcinoma

EP1.14-14 MUC1 CONFERS CHEMOTHERAPY RESISTANCE OF TUMOR-INITIATING CELLS THROUGH EGFR-IL-6 AXIS

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Background: Tumor initiating cells (TICs) are responsible for causing chemotherapy resistance and tumor relapse, but the mechanisms have not been elucidated. This study aims to explore the role of mucin 1 (MUC1) in chemotherapy resistance of TICs and its clinical significance. **Method:** The relationships between expression of MUC1 and clinical outcomes were analyzed by multiple databases. The MUC1 expression and function in chemoresistant TICs were investigated *in vitro* and *in vivo* through gain-of and loss-of function strategies. The potential downstream targets of MUC1 were analyzed using chromatin immunoprecipitation and luciferase reporter assay. The prognostic value of MUC1 signaling was evaluated using IHC. **Result:** High expression of MUC1 positively related with poor outcome of cancer patients. Elevation of MUC1 in chemoresistant cancer cells concomitant with TICs enrichment. Mechanistically, MUC1 induces the expansion of TICs population through activation of EGFR, which augments interleukin-6 (IL-6) transcription. Inhibition of EGFR-IL-6 signaling significantly abolishes expansion of chemoresistant TICs. Furthermore, coadministration of EGFR inhibitor overcomes the resistance of TICs to paclitaxel both *in vitro* and *in vivo*. Analysis of cervical cancer patients reveales that the expression of MUC1, EGFR and IL-6 are considerably increased after chemotherapy, showing a positive correlation between the expression of MUC1, EGFR and IL-6. Consistently, mining TCGA datasets uncovered a significant positive correlation between activation of MUC1-EGFR-IL-6 signaling pathway and poor disease-free survival in chemo-treated cervical cancer patients. **Conclusion:** MUC1 confers chemotherapy resistance of TICs through EGFR-mediated transcriptional regulation of IL-6.

Keywords: chemoresistance, EGFR, tumor initiation cells

EP1.14-15 REAL WORLD CLINICAL EXPERIENCE OF THE GALICIAN LUNG CANCER GROUP: AFATINIB IN PATIENTS WITH EGFR POSITIVE MUTATION

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Background: Treatment with tyrosine kinasa inhibitors has been a revolution for the patients with non-small cell lung cancer and EGFR positive mutation, especially in patients with exon 19 deletions. Afatinib seems one of the best options of treatment. **Method:** Retrospective study on patients from differents hospitals in Galicia (Spain) diagnosed of metastasic lung adenocarcinoma with EGFR positive mutation who have received first line treatment with afatinib between July 2015 and September 2018 were included. Main objective was to compare our clinical experience concerning response rate, progression free survival and toxicity with published data. **Result:** 45 caucasians patients were included in our analysis (33 women, 12 men). Median age was 71.2 years (range 39-91 years) and 29 patients had never smoked. Exon 19 deletion was the most common mutation (41 patients, 91.1%). The objective overall response was 68.9% (95% CI: 82.4-55.3), complete responses were observed in 6 patients (13.3%) and partial responses were found in 25 patients (55.6%). Stable disease was observed in 8 patients (17.8%) and disease progression in 1 patient (2.2%), 5 patients have not been reevaluated (11.1%). Median progression free survival (PFS) was 27 months (95% CI: 14.8-39.1) and overall survival was not reached. Common adverse events grade 3/4 were mucositis and skin toxicity in 11 patients (24.4%) and diarrhea in 6 patients (13.3%), respectively. The dose was reduced in 28 patients (62.2%) and treatment was discontinued in 8 patients (17.8%) owing to adverse events. **Conclusion:** Median PFS in our patients is 15 months longer than the information retrieved from differents studies with similar response rates and toxicity. This might be due to a majority of population with exon 19 deletion which, according to published data, seems to benefit more from afatinib than from other EGFR mutations.

Keywords: NSCLC, Afatinib, EGFR mutation

EP1.14-16 USE OF DIGITAL DROPLET PCR FOR DETECTING EGFR T790M RESISTANCE MUTATION IN PLASMA AT PROGRESSION ON TKI THERAPY

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Background: Therapy surveillance is a corner stone in advanced lung cancer clinical management. Due to the ease of sampling, analysis of tumor derived circulating DNA in plasma for treatment monitoring and decision making is desirable. Patients with tumors harboring a sensitizing *EGFR* mutation benefit from targeted therapy using tyrosine kinase inhibitors (TKIs). Unfortunately, the majority of patients develop resistance towards the initially administered TKI either through intrinsic mechanisms of *EGFR* or mutations of additional genes such as amplification of *MET*. Osimertinib can be administered at disease progression due to the resistance mutation T790M in *EGFR*. In this study we used liquid biopsy at progression after TKI treatment to assess mutational status of sensitizing and T790M mutations. In some cases, a tumor biopsy was analyzed in parallel as part of clinical management. **Method:** Six 10 ml Streck Cell free BCT® tubes were collected and plasma was isolated. Cell free circulating DNA was purified and used in an ultra-sensitive ddPCR assay IBSAFE (George et al, manuscript in preparation). Both the sensitizing *EGFR* mutation and T790M was analyzed. In some cases, a solid biopsy was analyzed in the clinic in parallel to our plasma analysis. Patient outcome data will be collected from patient files. **Result:** Eighteen of 25 patients tested positive in plasma for the previously known sensitizing *EGFR* mutation (72%). Twelve of 25 tested positive in plasma for T790M mutation (48%). Among plasma samples positive for the sensitizing mutation, 67% were also positive

for T790M. The minor allele frequency (MAF) fraction of T790M in comparison to the sensitizing mutation varied extensively from 0.01% to 90% and also the MAF compared to total DNA varied (0.005% to 23%). Updated clinical follow up data will be presented. **Conclusion:** For a subset of patients were a tumor biopsy is not feasible, a liquid biopsy could provide information about the mutational status. As the MAF vary considerably and can be very low, a highly sensitive assay such as the IBSAFE ddPCR assay, capable of confirming a mutation at a MAF as low as 0.005% is advantageous. Further, a large plasma input volume may aid in identifying patients positive for mutations at a low MAF. Updated clinical follow up data will be discussed.

Keywords: plasma, EGFR, ddPCR

EP1.14-17 ACQUIRED T790M MUTATION IN PATIENTS FAILING TREATMENT WITH FIRST OR SECOND-GENERATION EGFR-TYROSINE KINASE INHIBITORS

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Background: The majority of patients with epidermal growth factor receptor (*EGFR)*-mutant advanced non-small cell lung cancer (NSCLC) develop resistance to first- or second-generation *EGFR*-tyrosine kinase inhibitor (TKI) after a median treatment period of 12 months. This study aimed to determine the prevalence and predictors of acquired *T790M* mutation as a resistance mechanism among these patients. **Method:** This was a retrospective study of patients with sensitising *EGFR*-mutant advanced NSCLC who experienced disease progression (PD) while on first- or second-generation *EGFR*-TKI treatment and underwent investigations to determine the resistance mechanisms in University of Malaya Medical Centre from 1st January 2015 to 31st December 2017. **Result:** Of 87 patients, acquired *T790M* mutation was detected in 55 (63.2%) patients at PD. *T790M* mutation was significantly more frequent in patients who achieved partial response (PR) as the best response (p = 0.008) or had new lung metastasis (p = 0.048); and significantly less frequent in patients who developed new symptomatic brain metastases (p = 0.021). Patients with *exon 19* deletion were more likely to acquire *T790M* mutation compared to those with *exon 21 L858R* point mutation (p = 0.077). In multivariate analysis, PR with *EGFR*-TKI treatment was a significant independent predictor of acquired *T790M* mutation (p = 0.021) while having new symptomatic brain metastases (p = 0.034) or new lymph node metastases (p = 0.038) were significant independent predictors against acquired *T790M* mutation. **Conclusion:** Acquired *T790M* mutation was a common resistance mechanism leading to first- or second-generation *EGFR*-TKI treatment failure. Patients with tumours harbouring *exon 19* deletion mutation were more likely to acquire *T790M* mutation. A best tumour response of PR to *EGFR*-TKI treatment was an independent predictor of acquiring this resistance. This information is helpful to clinicians in the early prognostication and management planning for patients with *EGFR*-mutant NSCLC.

Keywords: EGFR-TKI, T790M mutation, Acquired resistance

EP1.14-18 NGS-MOLECULAR CHARACTERIZATION OF LUNG ADENOCARCINOMAS FROM HISPANIC PATIENTS: LEVEL OF EVIDENCE FOR THERAPEUTIC ACTIONABILITY

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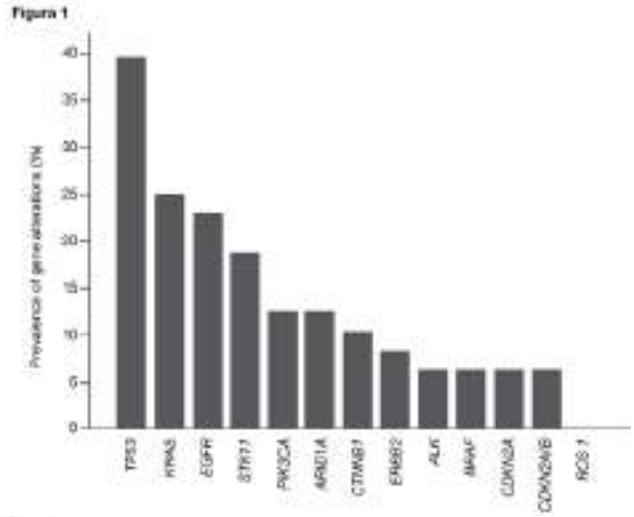
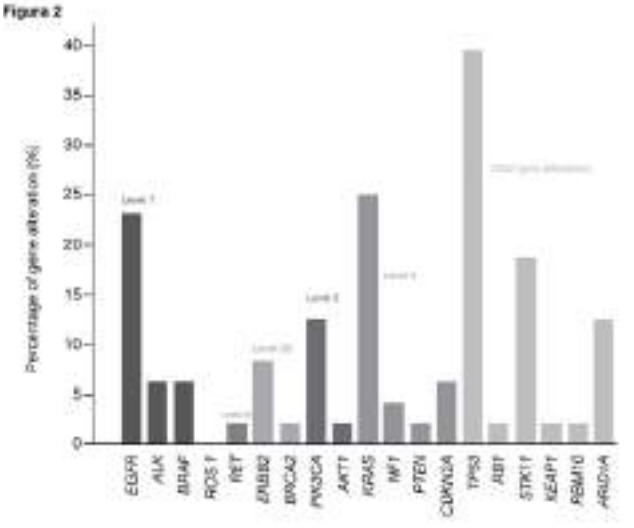
Background: Several studies have shown that NSCLC genomic background among Hispanics differs from other populations, therefore genotyping tumors in order to assess their molecular profile is adamantly needed in the current era of targeted therapy. Panel-detected oncodriver mutations can drive therapeutic approaches, and can help classify the information in order to propose strong evidence-based interventions in treatment guidelines. In this study we sought to understand the landscape of genomic drivers in a cohort of patients with lung adenocarcinoma of Hispanic ancestry. **Method:** Tumor samples were collected from 48 patients with lung adenocarcinoma from march 2017 until march 2019. Samples were submitted for testing to Foundation Medicine and hybrid capture NGS was performed. **Result:**





A total of 282 samples were sent for evaluation, among which 48 (17%) with lung adenocarcinoma were tested by FoundationOne (FO) in tumor tissue. Among the patients included, 54.2% were men and 79.2% were >50 years of age. Most patients had a previous negative report for *EGFR* and *ALK* (in tumor tissue). Results for tumor mutation burden (TMB) were obtained from 48 (100%) samples. Median TMB was 4 mutations/Megabase (m/Mb). High TMB (>10 m/Mb) was identified in 9 (18.8%) samples. The most frequently detected alterations were in *P53*, *KRAS* and *EGFR* genes (Figure1). In terms of the level of evidence for therapeutic actionability, level-1

was 33.5 %, level-2 was 12.5%, level-3 14.6% and level-4 37.5%. (Figure 2). **Conclusion:** Despite an initial assessment of actionable alterations (EGFR and ALK), through a NGS-approach we were able to detect a high amount of genomic alterations linked to a high-level of evidence for therapeutic actionability (33.5%), possibly due to higher sensitivity and a higher number of genes tested in the panel, increasing therapeutic options in this molecular-driven era. This research work was conducted with the support of Roche Foundation Medicine.

Keywords: Targeted therapy, Next-generation sequencing, Genomic profile

EP1.14-19 EFFICACY AND SAFETY OF AFATINIB FOR ADVANCED LUNG ADENOCARCINOMA PATIENTS WITH SENSITIVE EGFR MUTATIONS IN CHINESE POPULATION

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Background: Afatinib is an irreversible ErbB family blocker that improves progression-free survival (PFS) of advanced EGFR-mutant lung adenocarcinoma, comparing with chemotherapy. However, afatinib leads to more adverse events than first-generation EGFR inhibitors. Hence, exploration of optimal afatinib initial dose and its efficacy and safety for Asian patients has drawn extensive attention. **Method:** We retrospectively investigated advanced NSCLC patients treated with afatinib from February 27, 2017 to October 30, 2018. Demographic and clinical information, survival data and adverse events were collected and evaluated. **Result:** A total of 60 patients were included into this study. Thirty-nine (65%) patients received afatinib as first-line treatment. Median PFS for first-line afatinib treatment was 15.64 months [95% confidence internal (CI), not reached] and median OS has not been reached. When including age, sex, smoking history, baseline brain metastasis status, afatinib starting dose and mutation types into a multivariate COX regression analysis, PFS of patients with common sensitive EGFR mutations only was significantly longer than that of patients with uncommon mutations [hazard ratio (HR), 0.256; 95%CI, 0.080-0.823; p=0.022]. No significant difference was observed in median PFS between patients treated with a starting dose of 40mg and 30mg (11.18 vs. 5.25 months, p=0.060). The incidence of all grades rash/acne (92.5% vs. 61.1%, p=0.011) and paronychia (82.5% vs. 50.0%, p=0.010) of 40mg group was significantly higher than that of 30mg group.

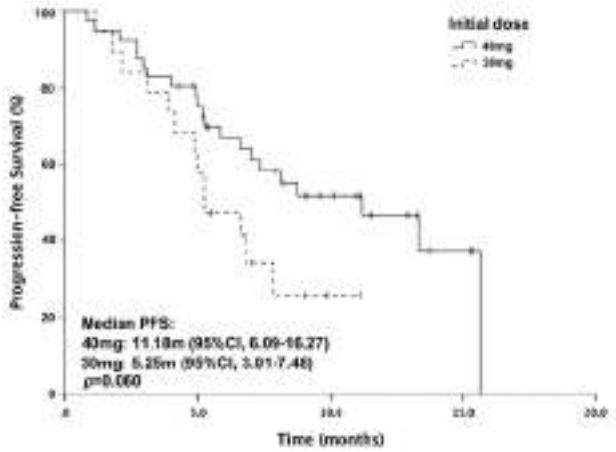

Table 1. Afatinib-Related Adverse Events

Adverse events	All Patients N=58		Afatinib 40mg N=40		Afatinib 30mg N=18		
	N	%	N	%	N	%	p
Diarrhea	50	86.2	36	90.0	14	77.8	0.402
≥Grade 3	6	10.3	5	12.5	1	5.6	0.736
Rash/acne	48	82.8	37	92.5	11	61.1	0.011
≥Grade 3	2	3.4	2	5.0	0	0.0	1.000
Paronychia	42	72.4	33	82.5	9	50.0	0.010
≥Grade 3	2	3.4	2	5.0	0	0.0	1.000
Stomatitis/ mucositis	41	70.7	29	72.5	12	66.7	0.652
≥Grade 3	0	0.0	0	0.0	0	0.0	-
Dry skin	22	37.9	16	40.0	6	33.3	0.628
≥Grade 3	0	0.0	0	0.0	0	0.0	-
Pruritus	9	15.5	7	17.5	2	11.1	0.818
≥Grade 3	0	0.0	0	0.0	0	0.0	-

Conclusion: First-line afatinib treatment is beneficial to advanced lung adenocarcinoma with sensitive EGFR mutations. Initial dose and baseline brain metastasis status do not impact PFS significantly.

Keywords: Carcinoma, Non-Small-Cell Lung, Afatinib, Molecular targeted therapy

EP1.14-20 EGFR T790M MUTATED CELLS ARE NOT A NEW EMERGING SUB-CLONAL POPULATION IN LUNG ADENOCARCINOMA AFTER THE TREATMENT OF TARGETED THERAPY

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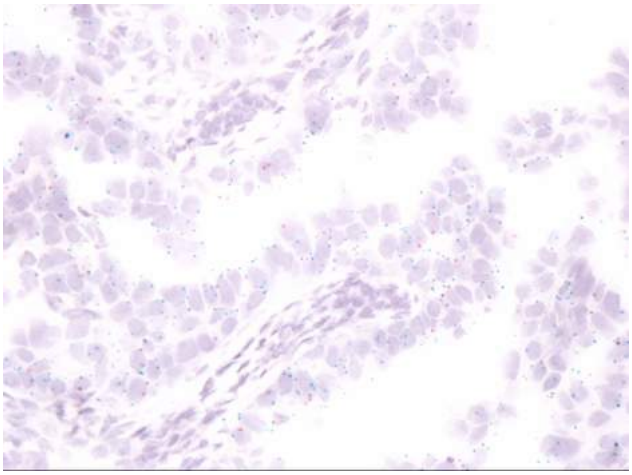
Peking Union Medical College Hospital, Beijing/China

Background: EGFR TKI targeted therapy has improved prognosis for lung adenocarcinoma patients. Almost all patients inevitably develop acquired resistance to these agents, mainly through EGFR T790M mutation. Lung adenocarcinoma patients retained the sensitive mutation and simultaneously acquired the T790M resistance mutation. Whether the acquired T790M mutation is in a newly formed cell groups, or they co-exist with the sensitive mutation in the same cell remained unknown. **Method:** RNA *in situ* hybridization (ISH) methods were employed to examine EGFR T790M and L858R mutations. EGFR L858R mtation probe was labelled with blue color and T790M was labelled with red color. EGFR mutations were also assessed using PCR methods. **Result:** s of RNA ISH and PCR analyses were identical in the majority of examined tissues. We observed that the T790M and L858R mutations co-expressed in the same cell in both the primary and acquired resistance tissue samples. For the two cases with tissues available following third generation TKI therapy, we observed that the T790M mutation disappeared in the repeated biopsy specimen.



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Conclusion: The EGFR sensitive mutation is a trunk and drive mutation, while T790M is a gatekeeper mutation that can appear or disappear under the pressure of TKI therapy. EGFR T790M mutation isn't a new emerging cell clone and co-existed with the sensitive mutation in the same cell.

Keywords: EGFR, T790M, lung adenocarcinoma

EP1.14-21 IMPLEMENTING PRECISION MEDICINE IN A COMMUNITY CANCER CENTER TO IMPACT OUTCOMES IN LUNG CANCER

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Background: With the majority of cancer patients being treated at community cancer centers, it is important to recognize the need for implementation of a Precision Medicine program in community-based oncology programs (Levit et al, 2019; Madhavan et al., 2018; Davis et al, 2018). Increasing indications for targeted therapies and immunotherapies drive the need for molecular testing so patients receive personalized treatment to impact quality outcomes (Gagan & Allen, 2015; Freedman et al., 2018). **Method:** Retrospective review of Precision Medicine program and use of molecular testing. **Result:** The Precision Medicine program was established October 2016 recognizing the need for structure and administrative support. Several key committees were formed including: Steering Committee with administrators and medical staff; Scientific Advisory Board for approval of genomic test; and Operations Committee for review, approval, and accountability, which are responsible for promoting and implementing Precision Medicine. A Precision Medicine team was formed to educate, expand testing availability, and establish policies and procedures within the healthcare system. The Scientific Advisory Board has reviewed and approved genomic test based on scientific validation. The multidisciplinary Lung Advisory Board has evaluated NCCN and College of American Pathologist guidelines to approve lung biomarker reflex testing for lung cancer patients. Currently PD-L1, *EGFR*, *BRAF*, *ROS1*, and *ALK* are reflexed for diagnosis of lung adenocarcinoma, and for squamous cell lung, PD-L1 is reflexed. Since January 2017, 2% *ALK* positive, No *ROS1*, 3% for *BRAF*, and 10% for *EGFR* mutations. PD-L1 combined positivity of high and low expression has been >41%. The population reviewed has an 85% current or past smoker rate. Next-generation sequencing (NGS) is physician ordered, and has increased utilization, 164 in 2017 to 225 in 2018, and trending to over 300 in 2019. For patients with NSCLC stage III and IV, about 20% have NGS. Education and recognition of limited tissue has led to increased use of liquid biopsy, 1 in 2017, 5 in 2018, to 21 in the first quarter of 2019, with lung cancer being 45% of cases. **Conclusion:** A Precision Medicine program provides education, resources, and processes to the healthcare system and multi-disciplinary team to ensure appropriate genomic testing is used to guide personalized medicine and quality outcomes. The approval of reflex testing for non-small cell lung cancer diagnosis allows identification of key targetable mutations for treatment decisions.

Keywords: Genomics, Molecular Testing

EP1.14-22 AMPLIFICATION AND OVEREXPRESSION OF MET IN BRAIN METASTASES OF NON-SMALL CELL LUNG CANCER

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Background: Non-small-cell lung carcinoma (NSCLC) with *MET* amplification may respond to c-MET inhibitors. **Method:** We investigated *MET* gene amplification status by fluorescence in-situ hybridization (FISH) and c-MET protein expression by immunohistochemistry of 42 NSCLC brain metastases (34 adenocarcinoma, 4 squamous cell carcinoma, 4 NSCLC-NOS). **Result:** We found *MET* gene amplification in 7/42 (21.6%) and c-MET protein expression in 9/42 (21%) of evaluable brain metastasis. There was no correlation between the presence of *MET* gene amplification and c-MET protein expression ($p<0.1$, Chi square test). One patient with *MET* amplification also had *EGFR* mutation. Three patients with c-Met overexpression had *ALK* rearrangement. **Conclusion:** c-MET overexpression and *MET* amplification are commonly found in brain metastasis of NSCLC and may represent a promising therapeutic target.

Keywords: MET, NSCLC, driver mutation

EP1.14-23 COMPARISON OF MOLECULAR TESTING USING VARIOUS SPECIMENS FOR NON-SMALL CELL LUNG CANCERS

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Tokyo Medical University, Tokyo/Japan

Background: The effectiveness of various molecular target drugs such as EGFR-TKI for non-small lung cancers came to be shown. So we performed a genetic tests to make plan for suitable therapy individually. For the cases that an operation was carried out for the lung cancer, I inspected the usefulness of the liquid biopsy. The somatic cell variation rate of detection in blood was low, and, in the relatively early non-small-cell lung cancer patient targeted for the operation, the tumor volume was shown in the rule factor when it was. I examined it including the lung cancer case that moved an object as well as an early case this time. **Method:** Patients provided written informed consent for use of the samples were participated in this prospective research. EGFR mutation was examined using blood, a liquid cytological specimen, biopsy specimen. These patients was suspected lung cancer and bronchoscopy was performed. We collected blood, the cytodiagnosis specimen using liquid fixed vial for Cellprep and biopsy specimen. I examined EGFR mutations by three kinds of specimens using Cobas EGFR variation detection kit v2.0. We compared results of EGFR mutation, **Result:** One-hundred fifty-eight patients were registered to this study. Among those patients, 77 patients with matched set of samples were enrolled to this study. EGFR mutation rates in tissue, cytology, and plasma were 37.7, 29.9 and 16.9 %, respectively. Overall agreement rate of the cytology specimens and the plasma specimens against the tissue samples were 87.0 and 75.3%, respectively. All eightT790M mutation positive cases were perfectly matched between tissue and cytology specimens. **Conclusion:** We previously reported that detection of mutations in cfDNA of patients with disease at stage IA or IB or at T2a or lower is difficult. Tumor volume is a determining factor for the feasibility of mutation detection with cfDNA. In this study, advanced lung cancer patients were included. Biopsy specimen were the most feasible sample for detecting mutations. Since high specificities were confirmed in both cytology and plasma specimens, the results are reliable if the mutation results were positive. Choosing cytology or plasma specimens for EGFR testing can be the considerations for the patients who have difficulties in collecting tissue samples in the real world setting.

Keywords: Lung cancer, EGFR mutation, liquid biopsy

EP1.14-24 LENVATINIB FOR RECURRENT METASTATIC ADENOID CYSTIC CARCINOMAS (ACC) OF THE LUNG

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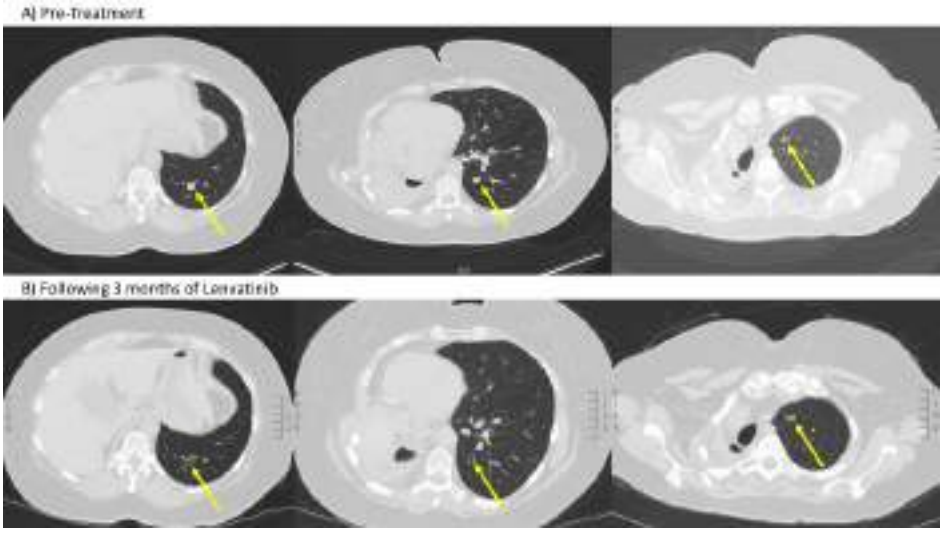
Background: Adenoid cystic carcinoma (ACC) is a rare malignant neoplasm that frequently originates from the salivary glands of the head and neck, but may also arise in the mainstem bronchus and major airways. The tumor is characterized by a tendency for both local and distant recurrences. Surgical resection remains the mainstay of treatment and radiotherapy is offered in select cases. Palliative systemic chemotherapy offers only modest benefit and is minimally effective. In preclinical studies, ACC has been shown to overexpress the oncogene MYB, which is involved in cell proliferation, apoptosis, differentiation and in upregulation of several growth and angiogenetic factors contributing to the autocrine activation of the FGFR and VEGFR-mediated angiogenesis. Two phase II studies have demonstrated that targeting salivary gland ACC with Lenvatinib, an oral multiple kinase inhibitor targeting VEGFR-1-3, FGFR-1-4, RET, c-KIT, and PDGFR, produced objective partial responses and tumor stabilization. Here we present a case of a patient treated with primary pulmonary ACC treated with Lenvatinib. **Method:** A 62-year-old female underwent a right pneumonectomy for a localized endobronchial ACC of the right lung followed by post-

operative radiotherapy for microscopic involvement of the resection margins. Two and a half years after primary therapy, she was noted on surveillance imaging to have multiple lung nodules in her left lung concerning for recurrent metastatic disease. Subsequently, she initiated palliative therapy with Lenvatinib 24mg daily. **Result:** Tumor assessment by chest CT performed three months after start of Lenvatinib revealed partial response per RECIST V1.1 criteria with interval cavitation of several pulmonary nodules reflecting treatment response. She experienced the typical adverse events associated with Lenvatinib, including CTCAE V4.05 grade 3 hypertension that was managed with three anti-hypertensive medications and grade 3 diarrhea, which required dose reduction.



Conclusion: Consistent with other early phase clinical trials of Lenvatinib in salivary gland ACC, Lenvatinib may exert therapeutic activity in primary pulmonary ACC as has been demonstrated in this case.

Keywords: lenvatinib, adenoid cystic carcinoma, Targeted therapy

EP1.14-25 DEVELOPMENT OF NEW LUNG CANCER THERAPIES BASED ON GENE-EDITING TECHNOLOGIES

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Background: Genome editing has enriched our understanding of mechanisms of the human pathology. Genome editing took a significant advance with the recent development of the CRISPR-Cas9 technology. CRISPR is an acronym for: Clustered Regularly Interspaced Short Palindromic Repeats and it is an adaptation of a prokaryotic functional system. It uses a single guide RNA to direct Cas9 activity to a specific part of the genome, therefore, this system can be used for gene editing and regulation. Cancer is a genetic disease where some DNA-damaged cells begin to divide without stopping and spread into surrounding tissues. Interestingly, in some tumors there is a dependency of a single oncogenic activity (oncogene addiction). This phenomenon indicates that mutations in key oncogenes (driver mutation) are able to drive carcinogenesis and maintain the tumor phenotype. Suggestively, if we can prevent or disrupt these mutations, we can difficult carcinogenesis or damage an established tumoral phenotype **Method:** We seek out for using Crispr-Cas9 technology to target driver mutations and evaluate its therapeutic and preventive value. To develop a proof of concept, we focused on *KRAS* gene which represents the most frequently mutated family across all cancer types. About one-third of human lung adenocarcinomas, the most prevalent form of lung cancer, carry *KRAS* mutations. Most of these mutations are located on codon 12; the mutations *KRAS* c.34G>T (G12C) and *KRAS* c.35G>A (G12D) are the most frequent and important ones. **Result:** We designed specific targeting strategies using HiFiCas9 nuclease which induced *KRAS* G12C and G12D edition while leaving KRAS WT untouched. Disruption of these *KRAS* mutations with the specific gRNA-guided-CRISPR-Cas9 decreases viability and proliferation of mutated cells such as H23 and A427. The generation of a transgenic mouse expressing Crispr-Cas9 designed to target these mutations will allow us to test the potential cancer-resistant phenotype. **Conclusion:** Crispr-Cas9 can be engineered to specifically target single nucleotide oncogenic mutations of *KRAS*. Edition of *KRAS* oncogenic mutations G12C and G12D led to a reduction in the viability of mutated lung adenocarcinoma cell lines.

EP1.14-26 UNCOMMON EGFR MUTATIONS SENSITIVE TO FIRST-GENERATION EGFR-TKI, ICOTINIB

D. Yue[1], B. Sun[1], B. Zhang[1], N. Li[2], R. Lin[2], T. Wang[2], C. Wang[1]

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Background: The first-generation EGFR-TKIs are the standard of care for non-small cell lung cancer patients withEGFR activating mutations. Patients with EGFR L858R (p.L858R) or exon 19 deletions are the most prevalent subgroup sensitive to EGFR-TKIs. Previous reports showed that the minority of lung cancer patients with rare EGFR mutations still achieved clinical benefit with EGFR-TKIs. Here, we profiled the landscape of gene mutations in lung cancer patients who responded to Icotinib (a first- generation EGFR-TKI approved in China) treatment without classic EGFR activating mutations. **Method:** We performed a comprehensive sequencing study by a NGS-based panel on a cohort of eleven lung adenocarcinoma patients without common EGFR sensitive mutations and receiving Icotinib treatment in a previous clinical trial (ICOGEN, NCT01040780). The pre-treatment FFPE tissues from all eleven patients were sequenced using a 500-gene panel. **Result:** Six patients responded to Icotinib treatment including three patients with partial response (PR) and three patients with stable disease (SD). The other five patients showed immediate disease progression (PD) after the treatment of

Icotinib. Rare EGFR mutations in the EGFR tyrosine kinase domain, including EGFR mutations W731C (exon 19), M793I (exon 20), and V845L (exon 21), were detected in the PR and SD groups but not in the PD group. EGFR somatic mutation M793I has been detected in the lung tissue of a patient according to the COSMIC record (COSM1716335). In the PR and SD groups, ERBB2 I655V and JAK2 R215Q were identified as potential mutations which could relate to Icotinib sensitivity.

Mutation Information

Gene	p.HGVS	COSMIC ID	P1 (PR)[a]	P2 (PR)[a]	P3 (PR)[a]	P4 (SD)[a]	P5 (SD)[a]	P6 (SD)[a]
EGFR	p.W731C	-	-	5.7%	-	-	-	
EGFR	p.M793I	COSM1716336	-	-	-	-	6.8%	
EGFR	p.V845L	-	2.9%	-	-	-	-	
ERBB2	p.I655V	COSM4000121	-	95.5%	21.5%	-	54.1%	47.5%
JAK2	p.R215Q	COSM275614	1.3%	6.7%	1.0%	-	25.3%	-

a-patient ID and best clinical response per RESIST criterion in the parenthesis.

Conclusion: This study uncovered potential new biomarkers predicting the clinical benefit to Icotinib. With further validation and evidence, it may expand the current patient populations which benefits from the first-generation EGFR-TKIs.

Keywords: icotinib, rare EGFR mutations, gene panel

EP1.14-27 RETROPERITONEAL PSEUDOTUMOR INDUCED BY CRIZOTINIB TREATMENT FOR CMET EX14 SKIP MUTATION NCSLC

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Background: MET-exon-14-skipping(METex14) mutations have been described in 0.6-7% of non-small-cell-lung-carcinomas(NSCLC). METex14 enhance MET receptor pathway signalling through increasing MET protein stability. Patients with NSCLC harboring METex14 mutations may respond to MET tyrosine-kinase-inhibitors(TKI) such as crizotinib. A.E. Drilon et al presented in the Profile-1001 study that crizotinib also demonstrated clinical activity in NSCLC with MET amplification and further data were associated with METex14 skip mutation. **Method:** A 63-year-old, non-smoking, female presented with right-upper-lobe (RUL) mass, Lymphangitis spread and bilateral mediastinal nodal involvement (figure 1). Lung adenocarcinoma (TTF1(+), PDL>20%) was diagnosed. The patient refused radiation nor chemo-therapy and therefore treated by pembrolizumab (KeyNote-042). Upon the presence of CMET ex 14 skip mutation detected on ctDNA (Gaurdnat360™), crizotinib was started with a significant response that allowed a RUL lobectomy with free surgical margins (R0), 4 months later (pT1aN0M0). Following the surgery, she has continued crizotinib therapy and a retroperitoneal pseudotumor was seen on the 9th months post-surgery (figure 2). Needle biopsy indicated a fibrocollagenous tissue, bundles of striated muscle and mixed acute and chronic inflammation without malignant cells. Considering the pathological report, a cyst drainage was performed (figure 3) and crizotinib treatment continued in a lower dose of 250 mg X 1 with no evidence of disease until this report. **Result:** Crizotinib has been shown to act clinically as a targeted selective inhibitor of ALK activity in NSCLC. It is a multi-kinase inhibitor of c-MET and ROS1 oncogenic tyrosine kinase. C-MET receptors are normally present in renal tubular epithelium. Previous publications have described complex renal cyst development as a side effect of crizotinib treatment[iv] [v]. It is not clear yet whether its target of c-MET may explain the crizotinib relation to pseudotumors and renal cysts development. Therefor cases of renal cysts should be registered and reported as rare side effects of crizotinib treatment. **Conclusion:** "Section not applicable"

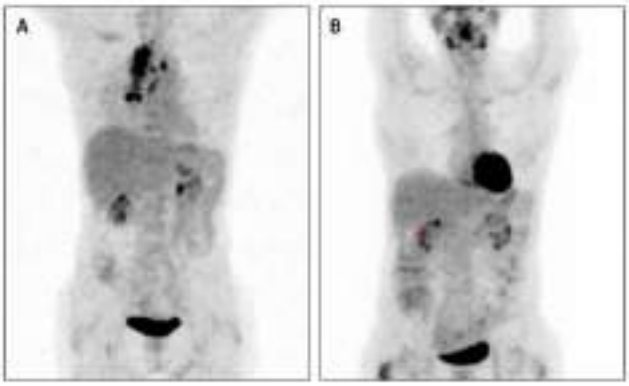

Figure 1: (A) The patient's PET-CT demonstrates right upper lobe mass with multiple mediastinal nodes (02/2017). (B) The Patient's PET-CT post crizotinib treatment present complete response (08/2018).

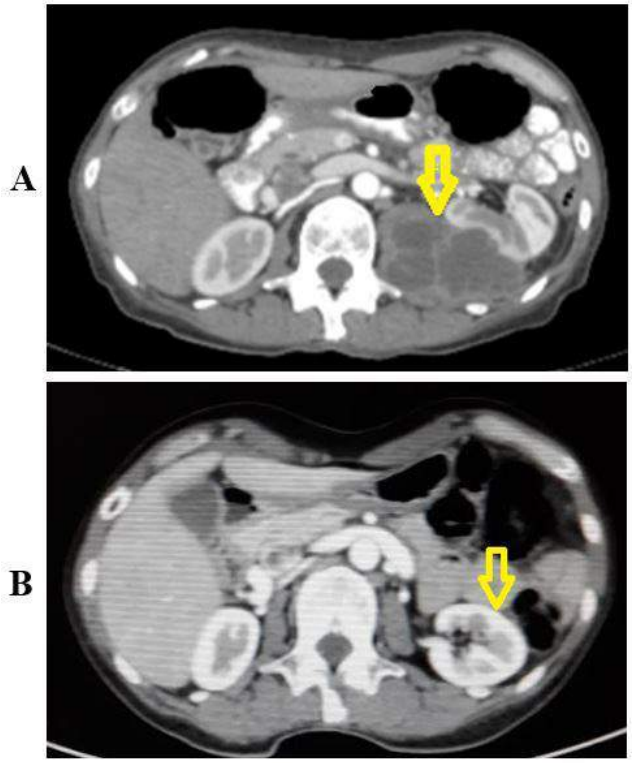

Figure 2: (A) Computed Tomography demonstrates left renal pseudotumor cysts before drainage. **(B)** Normal Computed Tomography after cysts drainage.

Keywords: METex14 Mutation NSCLC, crizotinib, Pseudotumor side effect

EP1.14-28 A DELPHI CONSENSUS ON TKI SEQUENCING IN TREATING ADVANCED EGFR-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard of care for first-line therapy in patients with EGFR mutation-positive (EGFR M+) non-small cell lung cancer (NSCLC). However, many patients with EGFR M+ NSCLC eventually acquire resistance to first and second generation TKIs, which commonly occurs with the onset of a T790M mutation.[1,2,3,4] Due to the different resistance mechanisms caused by first- and second-generation TKIs versus third-generation TKIs, and the subsequent availability of targeted treatment options, the sequence of TKIs in EGFR M+ NSCLC must be considered. Previous studies have shown the effectiveness of afatinib followed by osimertinib in delaying later chemotherapy, but there is not yet agreement on wider use of this sequencing strategy. The aim of this survey was to establish a global

expert consensus on TKI sequencing strategies in EGFR M+ NSCLC. **Method:** The global panel (7 expert oncologists) reached consensus by a modified Delphi approach (e-surveys). The panellists voted on each statement: disagree, agree, agree with changes (consensus defined as ≥85% agree). Statements without consensus were refined as per suggested changes (through freeform answers to the 'agree with changes' option) and re-voted on. Voting was electronic. The project was funded by Boehringer Ingelheim, who had no role in the development of the Delphi questions or the voting process. **Result:** The panel reached consensus that it is important to consider the sequencing of treatments when deciding which EGFR TKI to choose for a patient with advanced EGFR M+ NSCLC, and that optimising TKI sequencing may delay the need for chemotherapy. When choosing the appropriate TKI, the panel reached consensus that a treatment sequence which extends survival, without compromising quality of life, is an important factor when treating patients with advanced EGFR M+ NSCLC. The panel also reached consensus that the sequential strategy of afatinib followed by osimertinib is a viable option to prolong the chemotherapy-free period, in particular for the 75% of patients with an Exon 19 deletion (del19) who acquire T790M mutations after first-line treatment.[2,5] **Conclusion:** The survey confirms the importance of considering the sequencing of treatments when deciding which TKI to choose for patients with advanced EGFR M+ NSCLC, and provides an expert consensus view on the treatment priorities for this patient population. References: 1. Novello S, et al. Ann Oncol 2016;27(Suppl. 5):v1–27. 2. Jenkins S, et al. J Thorac Oncol 2017;12(8):1247–56. 3. Matsuo N, et al. Sci Rep 2016;6:36458. 4. Lau K-S, et al. Poster presented at ESMO 2016 (Poster 1243P) 5. Hochmair M, et al. Targeted Oncology 2019

Keywords: Delphi consensus, TKI sequencing, EGFR M+ NSCLC

EP1.14-29 MUTATIONAL LANDSCAPE IN LUNG CANCER PATIENTS BY TARGETED NEXT-GENERATION SEQUENCING AND DIFFERENCES BY GENDER IN SPANISH POPULATION

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Hm Sanchinarro, MADRID/Spain

Background: Personalized treatment with matched therapies according to genomic alterations improve treatment outcome in advanced NSCLC and some genomic alterations are linked to sex. Next Generation Sequencing (NGS) is reliable tool for genomic profiling. We aim to search clinical and pathological differences by sex in NSCLC patients with a comprehensive genomic profile by NGS. **Method:** We retrospective assess clinical-pathological and molecular characteristics of 73 stage I-IV lung cancer patients and NGS at baseline. NGS was performed in 67% by Oncomine ™, 30% by OCA v3 and 2% by Foundation One. **Result:** The cohort included: 49% of females (F), the mean age was 63 years (40-85), 90% stage IV, 91% adenocarcinoma, followed by squamous cell carcinoma (9.5%) and small cell (2%). Former smoker were reported in 74% and 80% of male (M) and females, respectively. Primary tumor lung biopsy was the main source of sample for NGS in 90% of cases. The majority of somatic genomic alterations were mutations (64% M *vs*. 78% F), followed by CNV (19% M *vs*. 11% F) and rearrangements (17% M *vs*. 11% F). In both genders KRAS mutation (mut) was the most common (M vs. F) (27% vs. 28%), and wild-type tumors was reported in 20% and 9%, respectively. Regarding actionable drivers, there was a higher incidence of *EGFR* mut (18% *vs*. 9%), *ALK* rearrangements (6% *vs*. 4%) and *HER 2* mut (6% vs 4%) in F vs M, respectively. As contrary *BRAF* mut (4% *vs*. 3%), and *RET* rearrangements (4% *vs*. 0%) were more frequent in M. Baseline brain metastases in patients with *EGFR and BRAF* mut was similar regardless of sex (50% and 0%), whereas in *ALK* and *HER2* were more frequent in F (50% F vs. 0% M). Twenty-nine percent of patients received personalized treatment according to these results. **Conclusion:** NGS can identify a significant proportion of therapeutically relevant driver alterations in LC leading personalized treatment. Some clinical features were found by gender in our population probably related to genomic differences linked to sex.

Keywords: Lung cancer, NGS, Gender

EP1.14-30 CEREBROSPINAL FLUID FOR LIQUID BIOPSY IN LEPTOMENINGEAL METASTASES OF EGFR-MUTANT NON-SMALL-CELL LUNG CANCER – A CASE REPORT

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Background: Leptomeningeal metastases (LM) occur in 3-4% of non-small-cell lung cancer patients, especially in 9.4% of those with an epidermal growth factor receptor (EGFR) mutation. EGFR tyrosine kinase inhibitors (TKIs) markedly prolong survival, but LM remain a devastating complication. Since leptomeningeal lesions are difficult to access, resulting in a poor understanding of the resistance mechanisms of LM, greater efforts have been made to trace the evolution of the tumor genome in accessible body fluids including plasma and cerebrospinal fluid (CSF). **Method:** "Section not applicable" **Result:** Case report: The presented clinical case refers to a 69-years-old female, PS 0, with a new right lower lobe nodule submitted to wedge resection surgery. Pleomorphic adenocarcinoma, staging IIB (pT3N0M0), and adjuvant chemotherapy with carboplatin and vinorelbine was done (4 cycles). Eight months after surgery, CT and PET-CT showed relapse with local and distant metastasis, staging IV (rT3N3M1b), EGFR mutation positive, initiating second-line therapy with erlotinib during 31 months, with complete response. By that time she initiated neurologic symptoms with headache and dysarthria. Head CT and MRI didn't revealed any lesions, and there was no evidence of relapse in thoracoabdominal CT. A lumbar puncture (LP) was performed and CSF was sent to cytology (negative for neoplastic cells). Liquid biopsy with CSF and peripheral blood to search for the T790M mutation were both negative. Multidisciplinary decision was to maintain erlotinib, and was oriented to consultation of psychiatry and neurology. Three months later she had another predominant neurologic episode of disorientation, aggression and aggravated dysarthria. Head CT showed progression with multiple foci of leptomeningeal uptake in both cerebral hemispheres, confirmed by MRI. A new LP was performed and infectious etiologies were excluded; cytology was negative and repeated liquid biopsy of CSF and blood were negative for the T790M mutation. Erlotinib dose was increased to 600mg. Ten days after discharge, she returned with diffuse diarrhea and uncontrollable vomiting ending up dying a day later. **Conclusion:** This case highlights the worse prognosis when LM exists and a high correlation between the onset or worsening of neurological symptoms and the development or progression of LM, before imaging; the use of CSF for liquid biopsy to search for T790M mutation, more than one time by the possibility of spatiotemporal heterogeneity; and also is in agreement with the existing literature that the EGFR T790M occurrence in CSF is relatively rare, potentially explained by the low exposure level of first-generation EGFR TKIs in CSF.

Keywords: Cerebrospinal fluid liquid biopsy, leptomeningeal metastases, epidermal growth factor receptor tyrosine kinase inhibitors

EP1.14-31 RETROSPECTIVE STUDY ABOUT EGFR MUTATIONS IN LUNG CANCER: OUR EXPERIENCE IN A SPANISH HOSPITAL

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Background: Mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase are observed in approximately 15% of lung adenocarcinomas and usually occur in nonsmokers. The detection of these mutations can be detected either in liquid biopsies or solid tissue biopsies. EGFR mutations are a predictive biomarker for high response and longer survival (both progression-free and overall) with tyrosine kinase inhibitors (TKIs), namely gefitinib, erlotinib, afatinib and osimertinib. **Method:** We conducted a descriptive and retrospective study including all patients diagnosed with EGFR mutations between January 2007 and September 2018 (both locally advanced and metastatic forms were included). **Result:** Of the 67 patients, the mean age was 67.2 years. The majority were adenocarcinoma (82.5%), with only 7.9% of squamous and 6.4% large cell carcinoma. The main mutations registered were exon 21 deletion (41%) and exon 19 deletion (4.9%). Only 24.6% had history

of smoking. 71.6% of patients present stage IV disease at diagnosis. The main organ involved was the bone (45.8%), followed by the lung (44.1%) and brain (25.4%). Also 13.6% presents pleural, 10.2% liver, 5.1% adrenal and 5.6% lymph node involvement. 84.1% of the patients were treated with TKIs (erlotinib 49.2%, gefitinib 16% and afatinib 19%) while 16% were treated with chemotherapy. With first line treatment, 94.7%presented disease control (41.8% partial response, 41.9% stable disease and 11% complete response). With a mean of 23.6 months, 56.9% of them progressed, mainly involving the lung (28.6%) and the bone (20.6%). Only 9.5% presented brain progression. At the end of the study, 34% had died (overall survival´s mean of 27.5 months). **Conclusion:** In patients with oncogenic driver mutations in EGFR, treatment with TKIs results in a better outcome than standard chemotherapy. This mutation predicts sensitivity to EGFR (our study shows up to 94.7% presents some type of response). Also, this response is longer (23.6 months in our experience) and better tolerated than chemotherapy. Overall survival of these patients is longer too, in our series, round to 27.5 months of overall survival, and mainly related to the tumor stages. More studies will be needed to be able to clarify the prognostic impact of factors such as the smoke status, sex, type of relapse or second line treatment.

Keywords: NSCLC, EGFR, characteristics

EP1.14-32 PATTERN OF EGFR MUTATIONS AND RESPONSE TO FIRST GENERATION EGFR TKIS IN PATIENTS OF METASTATIC LUNG CANCER AT A TERTIARY CARE CENTRE IN INDIA

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Background: EGFR gene mutations, ALK and ROS1 gene rearrangements represent the most common targetable lesions in the era of TKIs for treatment of metastatic lung cancer. Use of TKIs improves overall survival compared to cytotoxic chemotherapy in these patients. The objective of the study was to identify the prevalence and pattern of EGFR mutations and their response to TKIs in Indian patients. **Method:** Histopathologically confirmed cases of metastatic lung adenocarcinoma diagnosed between 2016 to 2018 at Kidwai Cancer Institute, Bangalore were reviewed for their EGFR mutation, ALK and ROS1 gene rearrangement status. DNA was extracted from formalin fixed paraffin embedded tissue and tested for EGFR hotspot mutations (Exon 19 deletions, exon 20 insertions and substitution mutations G719X, S768I, T790M, L858R and L861Q in exons 18, 20 and 21 of the EGFR gene) using ARMS real-time PCR. ALK and ROS1 rearrangement was tested using IHC with primary antibody ALK D5F3 and ROS1 D4D6 respectively. **Result:**

Complex EGFR mutations			
PATIENT ID	**EGFR MUTATION**	**TREATMENT**	**PFS (MTHS)**
51	EXON 19 DEL + T790M	Chemotherapy	6
1626	EXON 19 DEL + L858R	Gefitinib	6
164	S768I + L858R	Gefitinib	2
208	L858R + T790M	Chemotherapy	3
229	EXON 19 DEL + T790M	Chemotherapy	4

A total of 240 patients underwent testing. EGFR mutations were detected in 31.6% (n =76) and ALK and ROS1 rearrangement in 7% (n=17) and 1.25% (n=3) of the patients. The most common EGFR mutation was exon 19 deletions (e19 del) (n=44; 57.9%) followed by L858R mutation in exon 21 (n=23; 30.3%). Double EGFR mutations was seen in 5 patients (6.6%) and 3 patients had L861Q mutation. One patient had upfront T790M mutation. Median age was 54 years (range 35 -78 years). Male to female ratio was 0.9. 43.45% (n=33) were never smokers. Gefitinib was advised in 50 patients (65.8%), Erlotinib in 21 patients (27.6%) and rest were treated with chemotherapy. Median PFS in patients with e19 del, L858R and other mutations was 11, 12 and 4 months respectively. **Conclusion:** The prevalence of EGFR mutations in our studies are similar to those reported from other parts of India, lower than that from other Asian countries and higher than that from Western countries. E19 del and L858R mutations respond favourably to TKIs, but complex mutations do so poorly. Use of TKIs other than Gefitinib and Erlotinib need to be explored in these cases to improve outcomes.

Keywords: EGFR mutations, EGFR TKI's, metastatic

EP1.14-33 INTESTINAL METASTASIS FROM PRIMARY ROS1-POSITIVE LUNG ADENOCARCINOMA PATIENTS RESPONDING TO CRIZOTINIB

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Background: Small intestinal metastases from primary lung cancer are rare. Such patients have a poor prognosis. Early diagnosis of small intestinal metastases is difficult because of the low incidence of clinically apparent symptoms. The standard treatment for small intestinal metastases has not been established. **Method:** A 69-year-old Chinese man presented for evaluation of a tumor in the right lower lung and mediastinal lymph node enlargement on clinical examination. The clinical stage was cT2N2M0 (stage IIIA). Histologic examination of the tumor revealed lung adenocarcinoma. **Result:** He received two chemotherapy regimens. However, the disease progressed. He had bloating after chemotherapy and decreased flatus. An abdominal CT scan showed an intestinal effusion with local intestinal obstruction. Medical treatment was ineffective; hence, he underwent a diagnostic laparoscopy. The pathologic evaluation suggested an intestinal metastatic adenocarcinoma from the primary lung cancer. Based on an real-time PCR assay, the tumor had a ROS1 fusion and responded well to crizotinib. The progression-free survival was 7 months. **Conclusion:** Physicians must be aware of the possibility of intestinal metastases from primary lung cancer. With an accurate diagnosis and thorough evaluation, patients may benefit from targeted therapy.

Keywords: lung adenocarcinoma, ROS1, small intestine

EP1.14-34 ADVANCED NSCLC TREATED WITH GEFITINIB OR ERLOTINIB FOR FIVE YEARS OR LONGER - UPDATED DATA FROM THE RETROSPECTIVE SLOVAKIAN STUDY

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Background: Median PFS in the key phase III trials with gefitinib or erlotinib for advanced NSCLC with EGFR sensitizing mutations was less than 12 months. There are only a few data about the treatment results and toxicity of long-term treatment lasting 5 years or over. Purpose of this study was to find patients treated with either gefitinib or erlotinib for at least 5 years and to evaluate the treatment results in this group of patients. **Method:** Retrospective multicentre study, approved by the Ethics Committee of the Specialised Hospital of St Zoerardus Zobor, Nitra. All thoracic oncology centres in Slovakia were involved. For this update also the other hospitals and oncology outpatient departments were asked to participate. Data regarding patients were obtained from the databases of participating institutions and patient files. Descriptive statistics was used for the data analysis. **Result:** At the IASLC WCLC 2018 we presented data about seven patients included in the study. Here we present the data about another two patients, and updated data about the previously found seven patients. Characteristics of patients and the treatment results are summarised in the Table. Median PFS in this exceptional group was not reached, but it will be over 80 months. There was only one patient with the decreased dose of erlotinib (from 150 to 100 mg QD) due to skin toxicities. All the other patients had the common and manageable grade I – II toxicities only, and there were no unexpected drug-related AEs. Table: Patients characteristics and treatment results

Gender (M/W)	Age (yrs)	Smoking status	PS	Histology, Cytology	NSCLC stage	EGFR mutation	Treatment line/TKI	Response	PFS (mo)
W	72	Ex	2	AC	IV	Del 19*	1st/gefitinib	SD	67
W	53	Smoker	1	AC	IV	NK	1st/erlotinib	SD	112+
W	58	Never	1	AC/SQ	IIIB	NK	2nd/erlotinib	PR	94+
W	69	Never	1	AC	IV	NK	2nd erlotinib	SD	87+
W	72	Never	1	AC	IV	Del 19	2nd erlotinib	PR	75+
W	59	Never	1	AC	IV	L858R	1st/erlotinib	PR	72
M	64	Never	1	AC/SQ	IV	NK	2nd/erlotinib	PR	108+
M	70	Ex	1	SQ	IV	NK	2nd/erlotinib	SD	102+
W	50	Never	1	AC	IV	Del 19	1st/gefitinib	PR	66

*Del 19 and T790M

Conclusion: The treatment was safe and effective in our group of patients with advanced NSCLC treated with gefitinib or erlotinib for over 5 years. The NGS analysis of the available samples will be done after approval of the submitted Protocol by the Ethics Committee.

EP1.14-35 SQUAMOUS CELL CARCINOMA TRANSFORMATION AFTER ACQUIRED RESISTANCE TO OSIMERTINIB

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Background: Osimertinib is a third-generation epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI) for the management of NSCLC carrying *EGFR* T790M mutation after acquired resistance to prior EGFR-TKI and is now the preferred therapy in the front-line. The resistance mechanism of osimertinib, including histologic transformation had been reported, mostly small cell carcinoma. **Method:** Here we a patient with lung adenocarcinoma with uncommon EGFR H835L +L833V + T790M mutation who developed progressive lung atelectasis after acquired resistance to osimertinib. Bronchoscopic biopsy over the endobronchial tumor was done and the pathology report showed squamous cell carcinoma. **Result:** Mutation analysis of the squamous cell carcinoma performed by next generation sequencing (FoundationOne® CDx) was performed and reveled complex genomic alteration including EGFR H835L, L833V and T790M mutation, TP53 mutation and mTOR amplification. Squamous cell transformation after acquired resistance to osimeritinib was diagnosed. Then the patient was treated with a mTOR inhibitor, everolimus (5mg /day) plus osimertinib. One month after treatment an initial tumor response was observed, however, a progression occurred after 3 months of treatment.

Specimens for sequencing	Surgical specimen	CT-guided lung tumor biopsy	Endobronchial biopsy
EGFR mutation profile	L833V & H835L	L833V & H835L&T790M	L833V & H835L & T790M
Cell type	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma
Other genetic alteration			PDL1 0% MTOR amplification STK11 loss CDKN2A/B loss FANCA loss JUN amplification PMS2 R534fs*3 TP53 R175H

Conclusion: Squamous cell transformation is a rare manifestation of osimertinib resistance, further research is need to investigate the underlying mechanism of this histologic change and discover the proper treatment strategy.

Keywords: Osimertinib; tyrosine kinase inhibitor; epidermal growth factor receptor -

EP1.14-36 SUICIDE GENE THERAPY DIRECTED BY MICRORNA ACTIVITY

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Background: Lung cancer is one of the most prevalent types of malignancies worldwide, accounting for 1.6 million deaths every year. Despite last efforts, the overall survival rate at five years after diagnosis is under 15%. Therefore, new approaches are needed to improve the current clinic. Suicide gene therapy is an interesting technology which consists in expressing a toxic gene into tumor cells. The most studied suicide gene system is the Herpes Simplex Virus Thymidine Kinase (HSV-TK) that converts the non-toxic prodrug ganciclovir (GCV) into a guanosine analog, promoting cell apoptosis. However, there are problems regarding the expression of the toxic gene in non-tumor cells, which would cause unwanted cell death. MicroRNAs (miRNAs) have been revealed as one of the most important families of gene expression regulators, acting at a posttranscriptional level by binding messenger RNAs (mRNAs) and blocking protein translation. Alterations in the expression levels of these miRNAs in carcinogenesis have been largely described in the literature, being some of them biomarkers in the diagnosis of cancer. The aim of this work is to improve the selectivity of the HSV-TK suicide gene therapy to target exclusively tumor cells, taking advantage of the alterations in the expression of miRNAs in lung cancer. **Method:** We have constructed a plasmid that expresses the HSV-TK mRNA under the control of an artificial 3'-UTR containing binding sites for different members of the let-7 family, a miRNA family whose expression is frequently lost during lung cancer development. Thus, we could direct the expression of the toxic gene preferably in tumor cells where the levels of let-7 are low, allowing the expression of the HSV-TK. To determine the ability to direct the expression of the suicide gene on this system, we used a lung cancer cell line and a non-tumor, lung tissue one. Both lung cancer and non-tumor cell lines were infected with lentiviruses containing the plasmid construction and then cell viability assays, competitive cell growth assays by immunofluorescence and apoptosis assays were performed to check for differences between the GCV-treated and untreated cells. **Result:** Our preliminary results suggest that miRNA expression can selectively drive the expression of the HSV-TK in lung cancer cells due to their low let-7 expression values, resulting in a decrease of cell viability in lung cancer cells compared to non-tumor cells after treating them with GCV. Ectopically overexpressing let-7 into the lung cancer cells blocked the cell viability decrease caused by the GCV, meaning that our artificial 3'-UTR with binding sites for let-7 is working. **Conclusion:** According to our results, we have successfully directed the expression of a suicide gene to tumor cells using miRNA activity. Thanks to that, our HSV-TK/GCV suicide gene therapy model adds an extra layer of safety by preventing off-target cell death. Differential miRNA expression between tumor and normal

tissues could be used to direct the expression of a gene of our choice to the tumor tissue, which could be an interesting approach and a potential tool to treat this disease.

Keywords: miRNA, suicide gene therapy

EP1.14-37 ANLOTINIB-INDUCED BRONCHO-PERICARDIAL/PLEURAL FISTULA IN PATIENTS SUFFERING FROM LUNG CANCER (FIRST REPORT)

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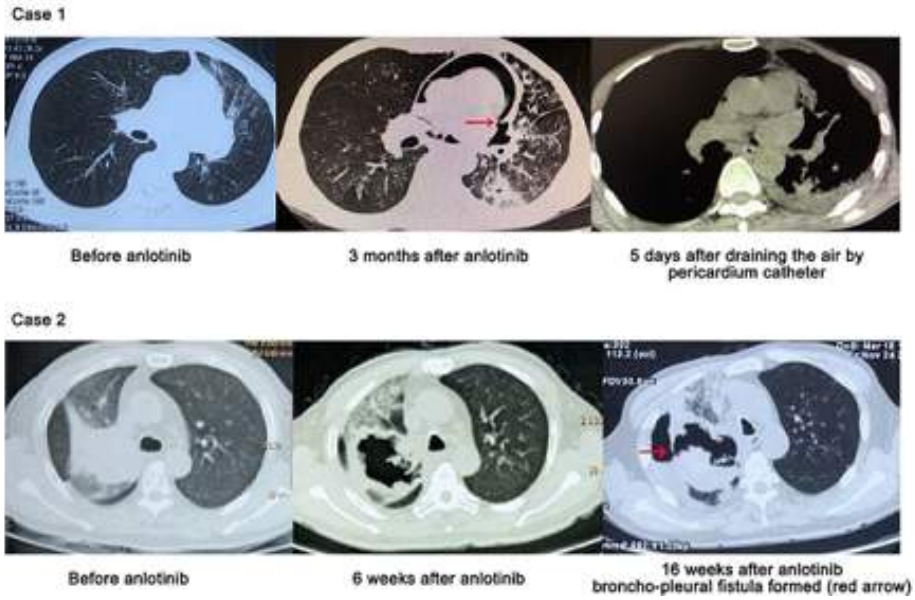
Background: Anlotinib is an small molecule inhibitor of multiple receptor tyrosine kinases, with inhibitory effects on tumor angiogenesis, and approved in China for treatment of patients with non-small cell lung cancer (NSCLC) who have undergone progression after≥2 lines of chemotherapy. The occurrence of bronchial fistula related to anlotinib has not been reported yet. We presented 2 cases of NSCLC patients with bronchial fistula after treatment with anlotinib. **Method:** Case 1: A 69-year-old male diagnosed central squamous cell lung carcinoma(CSCLC) of the left (stage IV) on July 2018, who refused chemotherapy but treated with anlotinib for 3 months, aggravated with short breath, with CT indicating broncho-pericardial fistula. After catheter was set into pericardium and drained for 5 days, CT showed significant reduction of gas and pericardium partially conglutinated. Case 2: 63-year-old male diagnosed CSCLC of the right (EGFR 19del) in 2016, with a history of diabetes, who successively received 2 lines of chemotherapy, target therapy, radiotherapy, shifted to anlotinib in August 2018 for 4 months, then aggravated with coughing pyohemosputum and fever, with CT indicating broncho-pleural fistula. After performed a closed thoracic drainage and anti-bacterium therapy, the patient improved and drainage decreased.



Result: Two cases developed bronchial fistula during the treatment of anlotinib alone, suggesting that the adverse effects mainly related to the antiangiogenics effect of it and causing ischemic necrosis. Other possible factors include: ①central lung cancer, ②squamous cell carcinoma, ③cachexia, ④multi-line treatment, ⑤long diameter of tumor≥5cm) and cavity formation, ⑥radiotherapy, ⑦accompanied with underlying diseases easy to complicated with infection, such as diabetes.

Conclusion: Although the incidence of bronchial fistula caused by anlotinib in NSCLC is extremely rare, it seriously affects the quality of life and overall survival of patients. Therefore, we need to use it selectively and make a close observation of the high-risk patients.

Keywords: Anlotinib, Broncho-pericardial/pleural fistula, Lung cancer

EP1.14-38 PROLONGED SURVIVAL IN A CASE OF NSCLC WITH RECURRENT BRAIN METASTASIS - A CASE REPORT

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Background: Carcinoma lung remains the most common cause of cancer related deaths in men globally.Approximately 10 percent of newly diagnosed patients with advanced non-small cell lung cancer (NSCLC) have brain metastases. Presence of brain metastases is associated with very poor prognosis with decreased survival and compromised quality of life in patients even after intensive treatment with multimodal approach.Though the survival varies according to performance status and presence of other prognostic factors, the survival in non small cell lung cancer with brain metastasis has increased to some extent in last two decades(median survival ranges between 7 -12 months in various studies).Hereby we present our experience with a case of adenocarcinoma lung with brain metastasis on presentation who has received multiple lines of treatment approach and leading a happy and hearty life after 8 years(96 months) of diagnosis. **Method:** Section not applicable **Result:** CASE REPORT A 45 year old nonsmoker male presented with constant headache with memory loss and on evaluation was found to have a SOL in the left temporal region with few other small lesions at other sites in brain along with right lung mass and was diagnosed as primary lung cancer with brain metastasis.CT guided biopsy of the lung mass showed adenocarcinoma lung.EGFR and ALK were non mutated.He received palliative whole brain radiotherapy followed by four cycles of chemotherapy with pemetrexed and carboplatin regimen.Received EBRT to right lung mass. Developed relapse after one year and underwent surgery.After six months,he developed recurrence at brain,for which surgical excision of the brain lesion(metastatectomy) was done followed by reirradiation to brain. Again he developed brain recurrence following which he received six cycles of Pemetrexed and Carboplatin followed by six cycles of maintenance Inj Pemetrexed.Again developed brain recurrence after one year which was surgically resected out following which he received Tab Erlotinib+ Tab Temezolamide. Recurrence of brain lesion was again encountered after four months for which he received six cycles of Inj Bevacizumab+ Nab-Paclitaxel + Carboplatin. Evaluation with whole body PET-CT scan and MRI brain showed complete metabolic response at primary site(lung) and partial response at brain. Then he received maintenance Inj Bevacizumab for six cycles. Then after one year,on recurrence in brain with surgical excision of the tumor and subsequent evaluation it was found that he had T790M mutation and hence was planned for Tab Osimertinib. He

is on Tab Osimertinib since last 26 months. Recent evaluation was done two months back in form of whole body PET-CT scan and MRI brain which showed complete response at both primary(lung) site and brain.Patient is doing fine till date with a followup period of 96 months since upfront presentation with brain metastasis. **Conclusion:** Treatment approach for NSCLC has seen a paradigm shift in last few years with the increased role of targeted therapies which has improved the survival.Hence biopsy and identifying the druggable targets have become of prime importance in managing lung malignancies.Metastatectomy and target oriented approach has always proven to be beneficial in oligometastatic settings.

Keywords: adenocarcinoma lung with brain metastasis, Osimertinib, prolonged survival in carcinoma lung

EP1.14-39 BRG1 DEFICIENT CELLS ARE SENSITIVE TO THE INHIBITION OF SPECIFIC LYSINE DEMETHYLASES (KDMS) IN LUNG CANCER

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Background: The standard treatment of non-small cell lung cancer (NSCLCs) is surgery. New therapeutics, such as tyrosine kinase inhibitors or immunotherapy may improve survival, but these treatments are only effective in small cohorts of patients. Thus, hopes of improving survival of lung cancer patients are related to the advent of novel therapeutic strategies. The classic epigenetic research focuses in the reversion of gene promoter DNA hyper methylation or histone code modifications, using a battery of unspecific drugs addressed to modify the global epigenetic code in cancer cells. In our previous work, we identified frequent inactivating mutations in the epigenetic gene BRG1 (about 20% of NSCLC), which were mutually exclusive with amplifications in the MYC oncogenic family. Unfortunately, BRG1-mutant cancer cells were also not able to respond to certain epigenetic therapies whereas cancer cells carrying MYC amplification, which are BRG1 proficient, appear to be highly sensitive to these combinations of treatments. These results show that MYC amplification could be used as a prognostic biomarker for a specific personalized therapy. In this project we observed that the mutational status of BRG1 directly correlates with the expression levels of several Lysine methyltransferases (KMTs) and Lysine demethylases (KDMs) in cancer cells. We also found that inactivating mutations in KDMs and KMTs tend to be mutually exclusive with inactivating mutations in BRG1, mutations in other SWI/SNF members and mutations in MYC oncogenic genes. Thus, we focused on targeting histone-modifying enzymes, in BRG1 proficient or deficient lung cancers cell lines. **Method:** For this propose we integrate state of the art technology like genome-wide chromatin modification and transcriptome analysis, using human cell lines and preclinical models for lung cancer, including in vivo models of mice such as xenografts, subjected at different concentrations of histone deacetylase inhibitor (HDACi), lysine demethylase inhibitor (KDMi) and EZH2 inhibitor (EZH2i) to design a personalized epigenetic treatment with high efficacy and low toxicity. **Result:** Our results showed that BRG1 deficient cells are not sensitive to HDACi, displaying an unexpected increase in some epigenetic marks after treatment that correlates with a global enrichment of repressive marks and EZH2 occupancy at gene promoter in BRG1-mutant cells. Otherwise, BRG1 directly regulates KDMs expression in lung cancer and demonstrates that inactivating mutations in BRG1 sensitizes cancer cells to the lysine demethylase inhibitor (KDMi). However, EZH2i seems to reverse KDMi activity in the absence of BRG1, exposing an interesting and determining role of this histone lysine methyltransferase in the sensitization of BRG1 deficient cancer cells to the KDMi. **Conclusion:** The results will be of great value for the stratification of lung tumors according to their genetic or epigenetic background for tailored treatments, opening the possibility to use BRG1 mutations as a potential Biomarker for personalized epigenetic target therapy in cancer. The development of an epigenetic-based therapeutic prediction model will hopefully set the basis for future treatment of lung cancer as well as of other epithelial cancers.

Keywords: Epigenetics, Target therapy, BRG1

EP1.14-40 LOCALLY ADVANCED DESMOIDE TUMOR: RESPONSE TO SORAFENIB: CASE REPORT

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Background: Desmoid tumors or deep fibromatoses are malignant connective clonal tissue tumors that do not metastasize, but are at high risk of local recurrence and are associated with morbidity and mortality. There is still no standard for treatment, however the reactions of patients with desmoid tumors with Sorafenib are promising. The objective of this work is to highlight the contribution of sorafenib in the treatment of desmoid tumors. **Method:** Our study is a case report conducted in the oncology department of IBN ROCHD CHU of Casablanca, focusing on the analysis of the Sorafenib response in patient with locally advanced desmoid tumor. **Result:** Our case is a 60-year-old patient with no comorbidities who had presented in 2012 a left dorsal parietal mass, he was operated on, the histopathological examination concluded to a desmoid tumor. He presented in 2015 a tumor recurrence for which he was again operated and put under Celecoxib for one year, after the clinical and radiological progression, he was put under Tamoxifen, for 2 years. Currently, he presents a tumor increase. In fact he has a posterior dorso lumbar parietal mass, measuring clinically about 15 cm, very painful, the initial thoracic CT scan as well as the MRI of the soft tissues showed left lateral vertebral parietal mass, hypodense coming into contact with the last 3 ribs without bone lysis, measuring 12 * 11 * 7 cm. The surgery was considered dilapidated by the surgeons, the decision was to put the patient under Sorafenib 400 mg per day, the assessment after two months found an excellent clinical and radiological response, with a total disappearance of pain and 50% decrease in the size of the initial injury on the chest CT scan. **Conclusion:** This case study allowed us to support the efficacy of Sorafenib, currently being tested (Study Alliance A91105) in the treatment of recurrent or locally advanced desmoid tumors.

Keywords: Desmoid, Sorafenib

EP1.14-41 CASE SERIES: LUNG NEUROENDOCRINE CARCINOMA WITH EGFR MUTATION

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Background: Lung Neuroendocrine Tumor derived from neuroendocrine cells in the lung and could be classified as well differentiated (low-grade typical carcinoids [TCs] and intermediate-grade atypical carcinoids [ACs]) and poorly differentiated (high-grade large cell neuroendocrine carcinoma or SCLC). Little is known about EGFR mutation in LCNET although EGFR mutation were frequently found (about 40%) in Indonesia NSCLC population. **Method:** We reviewed 3 cases from our hospital of large cell neuroendocrine tumor (LCNET) with EGFR mutation testing available. Clinical data and therapeutic responses were retrospectively evaluated. **Result:** Case#1 was a 53 years heavy smoker male with shortness of breath since 6 months, stg 4 T4N3M1a/pericardial effusion, Trans-thoracal Core biopsy showed LCNEC and harboring EGFR mutation in Exon 18 G719S. He was given Gefitinib, but the diseased progressed within 2 months and continued with Platinum based regimen with survival of 9 months. Case#2 was a 64 years old heavy smoker male with shortness of breath and chronic fatigue since 6 months, stg IV T3N3M1a, biopsy from neck lymph nodes showed LCNEC and harboring EGFR mutation in Exon 19 INS/DEL. He was given Erlotinib, but the diseased progressed within 2 months and refused to be given chemotherapy, with survival of 5 months since diagnosis. Case#3 was a 48 years old Non Smoker male with shortness of breath and chronic cough since 3 months, stg IIIB T4N3M0, biopsy from supraclavicular lymph nodes showed LCNEC and harboring EGFR mutation in Exon 21 L858R and L861Q. The disease remain stable for 13 months with Erlotinib, and followed by platinum based chemotherapy thereafter. He survived 20 months after diagnosis. **Conclusion:** De-novo EGFR mutation were found in LCNEC, but the response of the TKI is variable.

Keywords: Lung Neuroendocrine Tumor, EGFR mutation, tyrosine kinase inhibitor

EP1.14-42 DE NOVO EMERGENCE OF ISOLATED CNS T790M MUTATION AS A MECHANISM OF RESISTANCE TO FIRST GENERATION EGFR-TKI ERLOTINIB

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Background: A 57-year-old female never-smoker presented in 07/2009 with persistent cough and hemoptysis. Diagnostic imaging studies revealed 5.5-cm left upper lobe/hilar mass with mediastinal adenopathy, CT-guided biopsy revealed a TTF-1 positive pulmonary adenocarcinoma. Brain MRI identified a solitary 4mm metastatic lesion in the left superior precentral gyrus. Given her respiratory symptoms and hemoptysis, she proceeded with a platinum doublet and concurrent EBRT. Follow-up imaging revealed partial response. Tumor mutational analysis became available during radiation therapy and revealed an EGFR exon-19 deletion; she subsequently started treatment with erlotinib 150mg daily. Imaging performed six months after starting erlotinib revealed resolution of her residual lung disease and left precentral gyrus brain metastasis and she continued erlotinib for the next 7-years until 03/2017, when she presented with headaches and ataxia. Brain MRI identified a new 3.9cm left cerebellar mass, as well as reappearance of the left precentral gyrus lesion (Figure 1). Resection of the cerebellar mass identified metastatic lung adenocarcinoma with molecular analysis revealing the same exon-19 deletion plus T790M resistance mutation. Repeat PET/CT imaging failed to identify extracranial disease (Figure 2). She received post-operative stereotactic radiosurgery to the involved sites and started therapy with osimertinib 80mg daily. At the time of this writing, she remains in remission almost 10 years after initial diagnosis of metastatic NSCLC. This report presents an unusual clinical scenario, where visceral disease achieved durable remission on erlotinib while an isolated T790M acquired resistance mutation emerged de novo in the CNS. T790M often emerges as a resistance mechanism under selective pressure from early-generation EGFR-TKI. However, due to low BBB penetrance of 1st/2nd generation EGFR-TKI at standard dose, erlotinib concentration that frequently drives the de novo development of T790M mutation in visceral organs is rarely achieved in CNS metastases. In rare occasions where T790M is detected in the CNS, it is often metastatic from a distant visceral organ. In our patient, low concentration of erlotinib in the CNS might have created a permissive environment for the development of drug-tolerant "persister" cells that remained dormant for several years before eventually acquiring *de novo* T790M-mutation. The latter enabled accelerated growth of CNS metastatic disease in the presence of continuous treatment with erlotinib.

Figure 1.

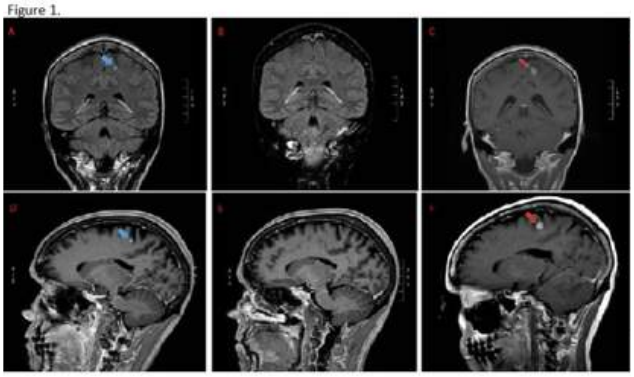
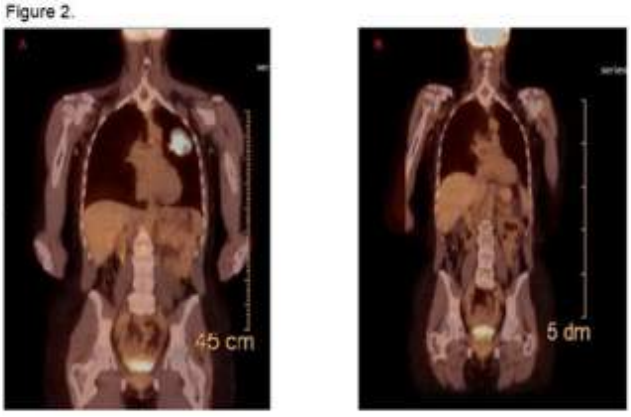


Figure 2.



Method: Section not applicable **Result:** Section not applicable **Conclusion:** Our case report illustrates a real-life example of how spatiotemporal differences in the tumor micro-environment could give rise to intra-tumor heterogeneity and shape response to therapy.

Keywords: CNS metastases, EGFR exon 19 deletion, T790M

EP1.14-43 THE SAFETY OF FIRST-LINE AND SUBSEQUENT MONOTHERAPY OF PD-1/PD-L1 INHIBITORS IN NSCLC: A META ANALYSIS

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Background: With the application of PD-1/PD-L1 inhibitors for non-small cell lung cancer (NSCLC), some agents (pembrolizumab, nivolumab, atezolizumab and durvalumab) were approved not only in subsequent but also first-line therapy. However, the spectrum of side effects in different therapy time might exist heterogeneity. In this meta-analysis, we assessed and compared the safety of PD-1/PD-L1 inhibitors in first or subsequent line therapy, and the systemic-specific spectrum of treatment-related adverse events (trAEs) were summarized. **Method:** A comprehensive search of online databases was performed. Incidence and its 95% CI were chosen to assess safety outcomes. The incidence of trAEs were calculated, including discontinuation and death results. Besides, the most common trAEs and system-specific trAEs of nivolumab and atezolizumab in subsequent therapy were also collected based on Common Terminology Criteria for Adverse Events (CTCAE) 4.0. **Result:** In total, 13 studies (3180 patients) were included. First-line therapy was associated with more frequent high-grade trAEs and withdrawal rates compared with subsequent line therapy (20.9% vs 14.1%, p=0.000; 8.3% vs 5.1%, p=0.000), while no significantly statistical difference existed according to any grade trAEs or deaths rates (18.9% vs 13.9%, p=0.985; 0.3% vs 0.5%, p=0.554). Basing on CTCAE 4.0, the common system-specific trAEs of first-line and subsequent therapy were semblable, no matter in any grade or high-grade trAEs. For the detailed trAEs, the common trAEs of first-line and subsequent therapy were similar including fatigue, diarrhoea, nausea and the like. However, in the high-grade trAEs, first-line therapy focused more on liver disorders (1.85%), and subsequent therapy was associated with more gastrointestinal disorders (1.73%). **Conclusion:** The incidence of high-grade trAEs and withdrawal rates in first-line therapy were higher than in subsequent therapy, possibly because of the different sensitivity and response of the major organs and immune system to PD-1/PD-L1 inhibitors. Besides, the differences of the common high-grade trAEs may be related to the uneven distribution of targets in various organs. These findings indicate that clinicians should pay more attention to heterogeneous side effects when prescribe PD-1/PD-L1 inhibitors in different time of therapy. Further perspective trials and data are warranted to confirm this conclusion and improve clinical medication guidance.

Keywords: NSCLC, PD-1/PD-L1 inhibitors, treatment related adverse events

EP1.14-44 LUNG ADENOCARCINOMA WITH A RARE BRAF V600E K601_W604DEL MUTATION RESPONDED TO DABRAFENIB PLUS TRAMETINIB TREATMENT: A CASE REPORT

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Background: *BRAF* V600E mutation can be detected in 1% of lung adenocarcinomas, and far more rarely, complex mutations in addition to BRAF V600E have been reported. **Method:** Case presentation: A 42-year-old man was diagnosed with advanced lung adenocarcinoma with stage cT1cN3M1c stageIVB. *BRAF* V600E mutation was found with in-house molecular testing, so we submitted the same specimen to be analyzed with Oncomine Dx Target test for reimbursement of the subsequent treatment. However, the result was negative for BRAF V600E. **Result:** The patient was treated with pembrolizumab (first-line therapy) and then carboplatin, pemetrexed and bevacizumab (second-line therapy). Nevertheless, the disease was progressed, so dabrafenib plus trametinib were used for the third line therapy. One month later CT scan showed a partial response. A subsequent

study showed that the V600E mutation accompanied K601_W604 deletion, three bases after the V600E point mutation. **Conclusion:** Our clinical experience suggested that some tumors with compound BRAF mutations, such as *BRAF* V600E K601_W604 del mutation, could respond to dabrafenib plus trametinib treatment, and that rare compound mutations, like this case, may not be detected with the conventional amplicon sequencing, particularly when the additional alterations are acquired at the positions adjacent to hotspots.

Keywords: braf, K601_W604 deletion, dabrafenib plus trametinib

EP1.14-45 ROS1-ADGRG6: A NOVEL ROS1 ONCOGENIC FUSION VARIANT IN LUNG ADENOCARCINOMA AND THE RESPONSE TO CRIZOTINIB

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Background: *ROS1* rearrangements are validated driver genes in non-small cell lung cancer (NSCLC) and have been identified in a small subset (1%-2%) of patients with NSCLC. To date, 18 different fusion genes of *ROS1* in NSCLC have been identified. The ALK inhibitor, crizotinib, exhibits therapeutic efficacy against *ROS1*-rearranged NSCLC. In addition to immunohistochemistry, real-time PCR, and fluorescence *in situ* hybridization, next-generation sequencing (NGS) technology represents a novel tool for *ROS1* detection that covers a wide range of fusion genes. **Method:** A 55-year-old female with stage IV was detected with a novel *ROS1* fusion afther treated with gefitinib due to detection of an *EGFR* mutation (L858R). Histological examination was consistent with lung adenocarcinoma. **Result:** A NGS assay showed that the tumor had a novel *ROS1-ADGRG6* rearrangement generated by the fusion of exons of 1-33 of *ROS1* on chr6: q22.1 to exons of 2-26 of *ADGRG6* on chr6: q24.2. The predicted ROS1-ADGRG6 protein product contained 3075 amino acids comprising the N-terminal amino acids 1-1853 of *ROS1* and C-terminal amino acid 1-1222 of *ADGRG6*. The patient had a favorable tumor response to crizotinib. **Conclusion:** *ROS1-ADGRG6* is a novel *ROS1* fusion gene in NSCLC detected by NGS and should be considered in *ROS1* detection assays.

Keywords: lung adenocarcinoma, NGS, ROS1 rearrangement

EP1.14-46 THE KIF5B-RET FUSION AS A NOVEL MECHANISM OF ACQUIRED EGFR TYROSINE KINASE INHIBITOR RESISTANCE IN LUNG ADENOCARCINOMA

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Background: Lung cancer is a common malignancy and a leading cause of cancer deaths worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. And most NSCLC patients with epidermal growth factor receptor (EGFR) mutations respond well to the treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Unfortunately, almost all patients with effective EGFR-TKIs therapy eventually develop drug resistance in about 1 year. The most common mechanism of acquired resistance to first-generation EGFR-TKI treatment is the development of the *T790M* mutation in exon 20 of the *EGFR*, which occurs in almost one half of cases of acquired resistance. **Method:** In this case report, we present a 72-year-old male non-smoker patient with an *EGFR* exon 19 deletion diagnosed with lung adenocarcinoma (LADC), who initially responded to first-generation EGFR-TKI treatment, but developed acquired resistance, and was shown to have gene detected by the next generation sequencing. **Result:** Repeated liquid biopsy showed the *KIF5B-RET* fusion gene by next generation sequencing. Therefore, cabozantinib was added to the treatment, and stable disease (SD) was achieved. Unfortunately, the patient did not acquire long-term benefits and the progression-free survival (PFS) was only 2 months **Conclusion:** Our results suggested that the *KIF5B-RET* fusion gene is a possible novel cause of acquired resistance to first-generation EGFR-TKIs.

Keywords: Epidermal growth factor receptor, Non-Small Cell Lung Cancer, icotinib

EP1.14-47 LUNG ADENOCARCINOMA WITH CONCURRENT KRAS MUTATION AND ALK REARRANGEMENT RESPONDING TO CRIZOTINIB

Y. Zhu[1], W. Wang[2], C. Xu[3], X. Li[1], W. Zhuang[3], K. Du[1], G. Chen[3], M. Fang[2], T. Lv[4], Y. Song[4]

[1]*Zhejiang Rongjun Hospital, Jiaxing/China,* [2]*Zhejiang Cancer Hospital, Hangzhou/China,* [3]*Fujian Cancer Hospital, Fuzhou/China,* [4]*Jinling Hospital, Nanjing/China*

Background: Chromosomal translocation resulting in the fusion between the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene has been considered as a novel oncogenic fusion in a subset of non-small cell lung cancer (NSCLC), mostly in non-smokers with adenocarcinoma. EML4-ALK translocations are commonly reported to be mutually exclusive with EGFR or KRAS mutations. **Method:** We reported a rare case of 47-year-old female was diagnosed with lung adenocarcinoma and treated with three cycles of chemotherapy. A biopsy acquired after disease progression revealed concurrent *KRAS* mutation and *ALK* translocation by a NGS assay. **Result:** Based on molecular findings, treatment was initiated with crizotinib in September, 2016. After 2 months of therapy, the patient achieved a partial response. Afterwards, the patient was further administrated with crizotinib for 9 months with a stable disease before tumor progression. **Conclusion:** A further understanding of the molecular biology with multiple oncogenic drivers will promote the optimal treatment for NSCLC.

Keywords: ALK rearrangement, KRAS mutation, lung adenocarcinoma

EP1.14-48 EFFICACY AND SAFETY OF AFATINIB PLUS APATINIB COMBINATION THERAPY FOR A LUNG ADENOCARCINOMA PATIENT WITH HER-2 V659D MUTATION

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The First Hospital of Jilin University, Chang Chun/China

Background: In lung cancer,several literature report the rare transmembrane domain mutations occur in V659D of Her-2 may be effective for afatinib. This is a successful case of a lung adenocarcinoma patient with a novel Her-2 V659D mutation but unsatisfactory efficacy with afatinib treated with afatinib plus apatinib. **Method:** A 73-year-old Chinese man with a heavy-smoking history came to our hospital due to"Intermittent cough"in eary March 2017. He was diagnosed with stage IB(T2aN0M0)lung adenocarcinoma by pathology of left upper lobectomy in 29th Mar 2017(Fig.1). An HER-2 mutation(V659D mutation)was detected in the surgical specimen by Next-generation sequencing (mutation abundance is 44.6%).

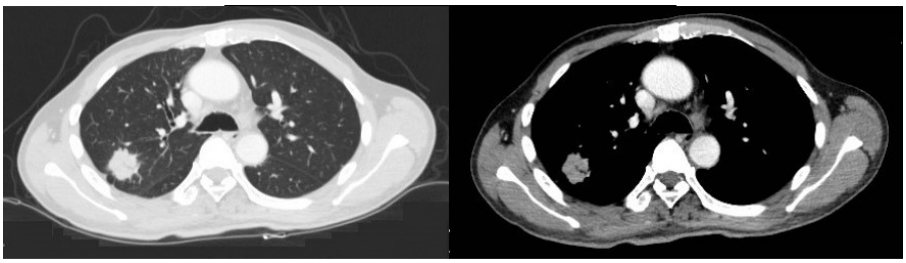

Fig.1 Preoperative pulmonary CT revealed a right pulmonary nodule

Recurrence of lung cancer occurred after 16 months on 30th July 2018. Pulmonary CT revealed multiple nodules in both lungs(Fig.2). The patient had no intention of chemotherapy. Daily oral doses of 40mg of afatinib were given on 31st July 2018. Twenty-two days later, a CT scan revealed the bilateral pulmonary nodules were slightly smaller, however cough symptoms were worse than before(Fig.3). On 23rd Agu 2018, considering the efficacy and side effects, he started taking afatinib(reduced to 30mg)combined with apatinib(500mg/day). The chest CT scan revealed the metastases continued to shrink after 1 month, and necrotic cavities appeared in the middle of the lesions(Fig.4). Cough symptoms improved obviously. Therapeutic evaluation was stable. He had no progression of the disease for months.

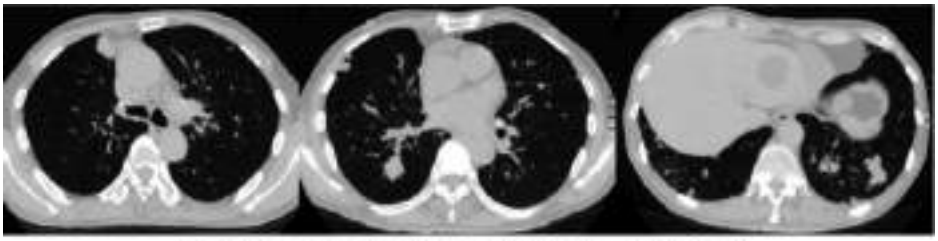

Fig. 2 Pulmonary CT revealed multiple nodules in both lungs

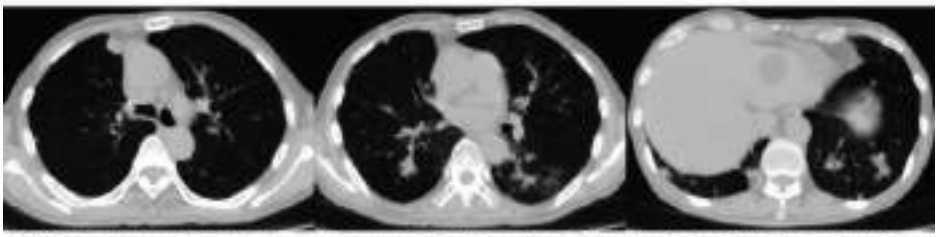

Fig. 3 The bilateral pulmonary nodules were slightly smaller, and the curative effect was evaluated as SD. New patchy shadows in the left lower lobe of the lung are more likely to be inflammatory.

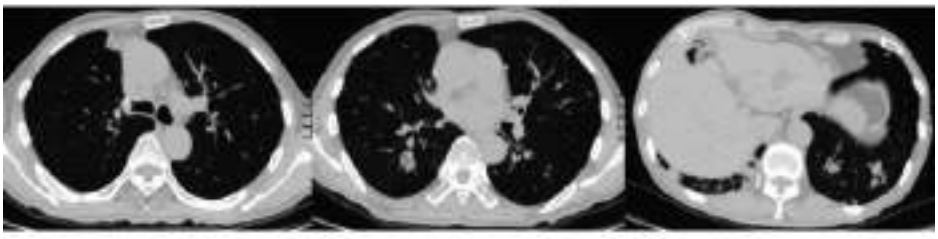

Fig. 4 Bilateral pulmonary nodules shrank , and necrotic cavity appeared in the lesions. The curative effect was evaluated as SD. The patchy shadow of the left lower lobe disappeared.

Result: On 21st Feb 2019, lung CT indicated enlargement of bilateral pulmonary nodules and new lesions suggesting disease progresses. Progression-free survival is 6.1 months. As for the side effects, he had two-grade rash on the face, three-grade oral mucositis with afatinib monotherapy. And he had one-grade rash on the face, two-grade oral mucositis and two-grade hand-foot syndrome in the combined treatment of afatinib and apatinib. **Conclusion:** Afatinib combined with apatinib is a safe therapeutic method for rare mutation of HER-2 V659D that can increase the efficacy.

Keywords: Her-2 rare mutation, Combined targeted therapy, lung adenocarcinoma

EP1.14-49 A PHASE IIIB OPEN-LABEL STUDY OF AFATINIB IN EGFR TKI-NAÏVE PATIENTS WITH EGFRM+ NSCLC: EXPLORATORY BIOMARKER ANALYSIS

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Background: The safety and efficacy of EGFR TKIs in patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC have previously been demonstrated. Here, we present results of a biomarker analysis from a subset of patients in a Phase IIIb study of afatinib in EGFR TKI-naïve patients with locally advanced/metastatic *EGFR*m+ NSCLC. The aim was to explore the relationship between tumor mutation type, and patients' response to afatinib in terms of efficacy and tolerability. **Method:** Patients with EGFR TKI-naïve *EGFR*m+ NSCLC received 40 mg/day afatinib until lack of clinical benefit (determined by investigator). The primary endpoint was incidence of serious adverse events (SAEs). Secondary endpoints were number of patients with drug-related AEs, and time to symptomatic progression (TTSP). Further endpoints included progression-free survival (PFS). For biomarker analysis, peripheral blood samples were collected during scheduled visits from patients entering the study at Beijing Cancer Hospital. DNA extracted from samples collected at Visit 3 and baseline was analyzed for *EGFR* and pre-specified non-*EGFR* mutations, respectively, using an amplification-refractory mutation system. **Result:** In total, 64 patients were included in the biomarker analysis. Baseline characteristics: Chinese, 100%; female, 70.3%; mean age, 57.4 years; *EGFR* mutations: L858R, 50%; Del19, 42.2%. All patients experienced ≥1 drug-related AE, most commonly (grouped terms; any grade/≥3): diarrhea (n=63/9, 98.4%/14.1%) and rash or acne (n=52/5, 81.3%/7.8%). SAEs were reported for 15 patients (23.4%), most commonly cerebral infarction (n=3, 4.7%), malignant neoplasm progression, CNS metastases (both n=2, 3.1%). Median TTSP was 13.5 months (95% CI: 10.9, 18.0). At baseline, 19 of 42 patients analyzed (45.2%) had additional non-*EGFR* mutations; 17 (89.5%) progressed/died. Median PFS was 8.1 months in these patients, versus 12.5 months for patients with EGFR-only mutations (HR, 1.72; 95% CI 0.88, 3.36; p=0.1054). At Visit 3, mutation status had changed from *EGFR*m+ to *EGFR* mutation-negative in 33 of 40 patients analyzed (82.5%). Of these, 29 (87.9%) progressed/died; median PFS was 11.0 months versus 5.5 months for patients who remained *EGFR*m+ (HR, 1.25; 95% CI: 0.47, 3.30; p=0.6556). **Conclusion:** In this analysis, safety data were consistent with the known safety profile of afatinib. Median PFS was twice as long in patients who became *EGFR* mutation-negative compared with those who remained *EGFR*m+; however, the difference was not statistically significant. There was no significant difference in PFS for patients with additional non-*EGFR* versus those with *EGFR*-only mutations. This exploratory analysis suggests that afatinib has clinical benefit for patients with *EGFR*m+ NSCLC across all the subgroups assessed.

EP1.14-50 THE EFFECTIVENESS OF THE COMBINED THERAPY OF OSIMERTINIB AND VEMURAFENIB IN A PATIENT WITH COEXISTANCE OF EGFR AND BRAF MUTATION

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Background: With the widely application of gene detection techonology in lung cancer, more rare genetic alterations are indentified, including the coexistance of double driver mutations. The coexistance of EGFR and BRAF mutations in lung cancer is rare and its treatment strategy has not been systemetically explored. Synergistic inhibition of the tumour cells by EGFR-TKI combied with BRAF inhibitor has been proved in a vitro trail. If there's clinical benefit of the combined tharepy targeting EGFR and BRAF pathways is unclear. **Method:** We present an adenocarcinoma lung cancer patient harboring 19 exon deletion and T790M mutation of EGFR who progressed on osimertinib with an emergence of BRAF VE600 mutation. The treatment of single-agent vemurafenib is effective for the metastatic leision but make the primary leision progession. Given the progression of primary leision the was noted, osimertinib was added to vemurafenib for treatment. **Result:** During the first week of combined therapy of osimertinib and vermurafenib with oral dose of 80 mg qd and 960mg bid respetively, the patient developed intolerable palpitation and fatigue (grade 3), which were related to drugs. Therefore, the dose of vemurafenib was reduced to 960mg qd, and osimertinib was taken with the original dose (80mg qd). Subsequently, aboved adverse events were obviously relieved (grade 1). After three months of combined therapy, the size of the priamry leision reduced significantly and the patient achieved a partial reponse, suggesting the the effectiveness of the combined therapy of osimertinib and vemurafenib. Currently, the follow-up of the patient is ongoing https://cpaper.ctimeetingtech.com/wclc2019/submission/mediafiles/view?id=1295&type=mediafile **Conclusion:** This case provides an example of the successful treatment of the combination of vemurafenib and osimertinib, and highlights the potential value of BRAF inhibitor combined EGFR-TKIs in the treatment of advanced lung cancer harboring BRAF mutation and EGFR mutation.

Keywords: Combined Therapy, BRAF mutation, EGFR mutation

EP1.15 THYMOMA/OTHER THORACIC MALIGNANCIES

EP1.15-01 SPONTANEOUS MEDIASTINAL HEMATOMA RESEMBLING MEDIASTINAL TUMOR IN A HAEMOPHILIAC PATIENT

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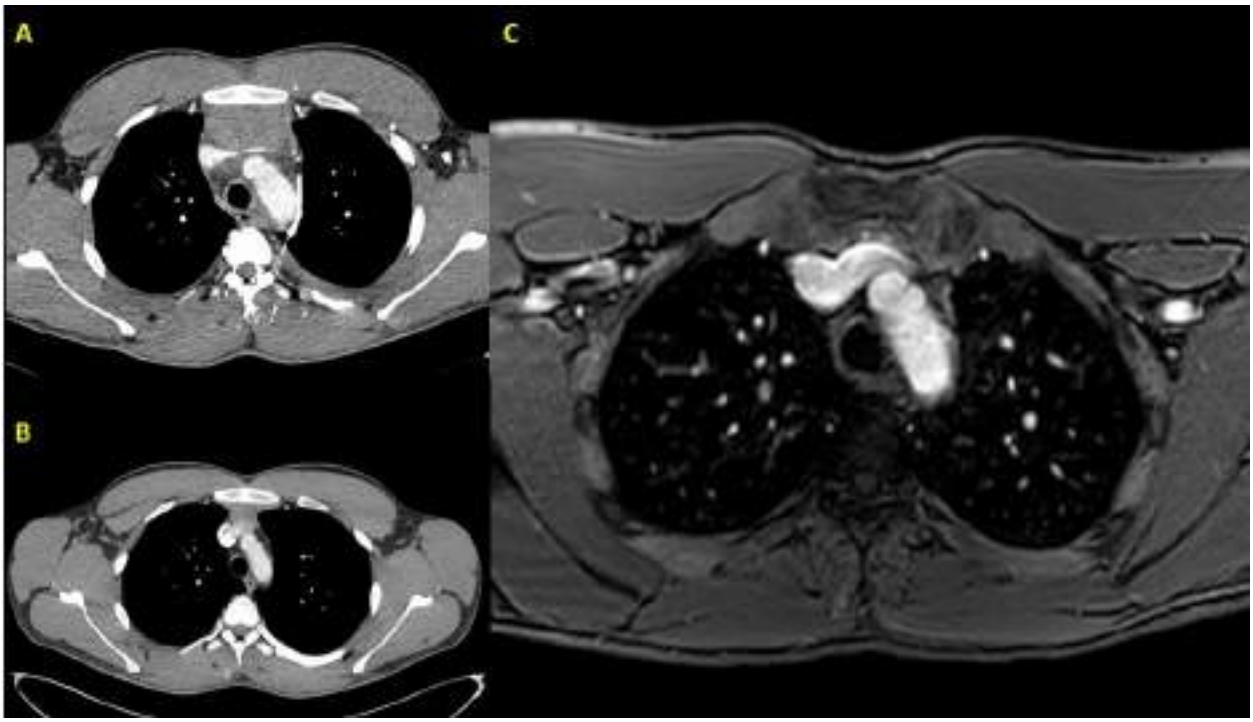
Background: To describe an extremely rare case of spontaneous mediastinal hematoma secondary to a thymic cyst bleeding and its surgical treatment in a patient with haemophilia A. **Method:** A 22-year-old male was admitted to the Emergency Department for chest pain, fever and haematuria arisen four days before. He was a heavy smoker with a previous diagnosis of haemophilia A (factor VIII deficiency). Vital signs showed tachycardia (110 beats per minute) and fever (37.5°C); physical examination showed a superior vena cava syndrome with oedema of the neck and the left harm. Hematological examination revealed only a prolonged clotting time compatible with his hemophilic disorder. A chest X-ray was performed and a mediastinal widening was revealed. A subsequent chest CT-scan showed a mediastinal mass of 77x35x85mm with compression of the left subclavian vein and superior vena cava (Fig. 1A). A suspect of lymphoma was posed and a surgical biopsy was planned. **Result:** Through a right uniportal VATS, the anterior mediastinal pleura was incised to reach the mass, and suddenly 400ml of hematinic liquid leaked out and multiple biopsies of the remnant mediastinal tissue were performed. A mediastinal hematoma was then suspected. Post-operative chest X-ray showed a reduction of the mediastinal widening. A chest CT scan performed a few days later revealed an impressive reduction of the mass (Fig. 1B). Histological examination was consistent with a thymic cyst surrounded by a large amount of haemorrhagic and inflammatory tissue. A chest MRI at 3 and 6 month after surgery demonstrated a gradual and complete reduction of the mediastinal mass (Fig. 1C).



Conclusion: Spontaneous mediastinal hematoma is a very rare condition that could radiologically be misdiagnosed with a mediastinal tumour. A suspect must be posed in patients with bleeding disorders presenting with a mediastinal widening.

Keywords: mediastinum, mediastinal cancer, mediastinal hematoma

EP1.15-02 THYMIC EPITHELIAL NEOPLASM: A 15-YEAR EXPERIENCE TREATMENT IN RAJAVITHI HOSPITAL, THAILAND

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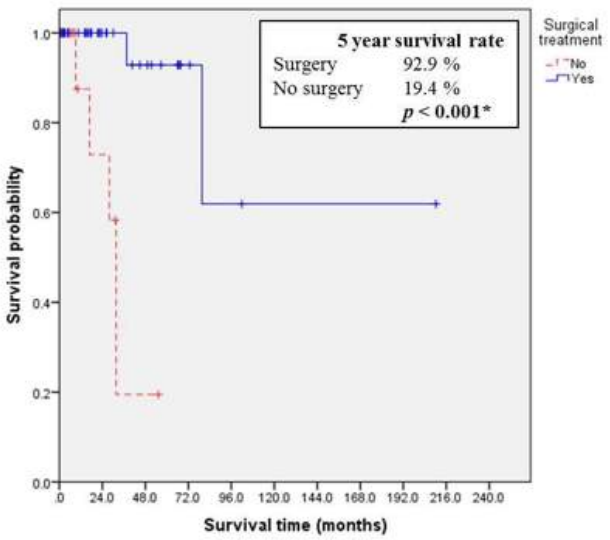
Background: Due to the rarity and indolent natural history of thymic tumors, the prospective randomized trials have been lacking. Surgery is the primary treatment for localized disease and chemotherapy may be indicated in advanced disease. We performed a retrospective review of all cases over a 15-year period at our institution. **Method:** We retrospectively evaluated all patients who were diagnosed as thymoma and thymic carcinoma during 2003-2017 at Rajavithi hospital. Clinical characteristics, staging, treatment, and outcomes were collected and analyzed. **Result:** Thymic epithelial neoplasms were identified in 60 patients: 52.0% male with a median age 56.5 years (range, 22-83 years), 87.0% with Eastern Cooperative Oncology Group performance status of 0 to 1. Paraneoplastic syndromes were presented in 21.7%. The distribution by WHO histologic classification was A, 3.3%; AB, 8.3%; B1, 25.0%; B2, 15.0%; B3, 15.0%; C, 1.7%; and thymoma unclassified, 31.7%. The majorities (55%) of patients were stage 1-3. Of 40 patients who underwent operation, 47.5% underwent R0 resection. Nineteen patients received adjuvant radiation and 5 patients received adjuvant chemotherapy. Palliative chemotherapy and radiation were given in 12 and 7 patients, respectively. The overall response rate to palliative chemotherapy was 10/12 (83.3%) with majority (75.0%) of patients received carboplatin plus paclitaxel. After a median follow-up of 26.8 (1-180) months, 53 (88.3%) patients remain alive. Median overall survival (OS) was 79.6 months with OS rate at 5-year being 73.6%. Ability to received surgical resection was the only significant (p = 0.003) prognostic factor on multivariate analysis. Figure Kaplan-Meier curve for overall survival in thymic malignancy patients (N=60), comparison by the ability to receive surgical treatment



Conclusion: Although surgical resection is the mainstay of treatment, it remains clear that these tumors are chemo-sensitive diseases. Traditional cytotoxic agents remain the standard of care in patients with advanced disease. Multidisciplinary approach should be offered in all patients.

Keywords: THYMOMA, thymic tumors, Chemotherapy

EPOSTERS

EP1.15-03 SMARCA4-DEFICIENT THORACIC MALIGNANCIES: A UNIFYING GENETIC ABERRATION ACROSS TUMORS OF DIVERGENT DIFFERENTIATION

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Background: Mutations in ATPase-dependant chromatin remodelling units are one of the most common genetic alterations observed in human cancer. Germline mutations in *SMARCA4* encoding for Brg-1 protein, a subunit of the SWI/SNF chromatin modifier unit, are well recognised as the causative genetic event in rhabdoid tumor predisposition syndromes that occur in infants and young children. In recent years, somatic mutations in *SMARCA4* have been increasingly identified in many adult-onset malignancies ranging from well differentiated carcinomas to poorly differentiated high grade sarcomas in a variety of anatomical sites, including thorax. Documentation of such tumors is essential to our understanding of the pathogenesis and possible mechanisms of therapeutic targetting. **Method:** Case 1: A 60-year-old male smoker presented with chronic emphyema thoracis of non-tubercular etiology which was treated by intercostal drainage. He had repeated episodes of blockade of chest drain over the next 6 months and eventually a thoracic window was surgically created. Five months following thoracotomy, patient presented with a mass growing at the site of the thoracic window. No other masses in the lung parenchyma or mediastinal lymphadenopathy was seen. Patient underwent an excision of the granulation tissue-like mass. Formalin fixed paraffin embedded sections were subject to microscopy and immunohistochemistry for vimentin, CD34, MIC2, p53, SALL4, pan-cytokeratin (AE1/AE3), EMA, p40, TTF-1, cytokeratin-7, Hepar-1, desmin, myogenin, CD31, S100, Melan-A, HMB-45, GATA-3, calretinin, WT1, INI-1, brg-1 and hematolymphoid markers. Case 2: A 58-year old male smoker presented with hemoptysis and cough. On evaluation, an endobronchial mass was identified and was excised. Formalin fixed paraffin embedded sections from excised tumor mass was subject to microscopy and immunohistochemistry for cytokeratin 7, cytokeratin 19, epithelial membrane antigen, chromogranin, synaptophysin, cytokeratin 20, CD117, TTF-1, NUT1, Her2neu, GATA3, p40, S100, INI-1 and brg-1. **Result:** Case 1: Microscopy revealed a tumor centred in the soft tissue of the chest wall ulcerating the overlying skin. No lung parenchymal involvement was seen. The tumor was arranged in sheets composed of monomorphic large tumor cells with abundant eosinophilic cytoplasm and prominent nucleoli showing frequent mitoses and foci of necrosis. No squamous or glandular differentiation was seen. Tumor cells were only immunopositive for vimentin, CD34, MIC2, p53, and SALL4, very focally immunopositive for CK (AE1/AE3) and showed retained INI-1 protein expression. Brg-1 expression was lost in tumor cells leading to a diagnosis of SMARCA4-deficient thoracic sarcoma. Case 2: Microscopy revealed a high grade tumor arising from the main bronchi with parenchymal and tracheal extension ulcerating the overlying squamous epithelium. Tumor cells were arranged in lobules with peripheral palisading and central necrosis. The tumor cells were large with frequent cytoplasmic clearing and frequent mitoses. Tumor cells were immunopositive for CK-7, CK-19, EMA, CG while were negative for others. INI-1 was retained while brg-1 was lost leading to a diagnosis of SMARCA4-deficient carcinoma. **Conclusion:** Two independant studies have delineated SMARCA4-deficient thoracic sarcomas and SMARCA4-deficient lung carcinomas as distinct clinicopathological entities. Despite a unifying genetic alteration, these tumors appear to show varied histomorphology and immunoprofiles. Long term follow-up and molecular analysis of such tumors is necessary.

Keywords: SMARCA4, lung, chest wall

EP1.15-04 HUGE INTRA THORACIC MESENCHYMAL TUMORS. ABOUT 19 CASES

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Background: Mesenchymal tumors represent a heterogeneous group of tumors, which may be benign or malignant and are developed from supportive tissues: connective, vascular, nervous or adipose tissues. They often reach large volumes making their care very difficult. **Method:** Our work consists of a retrospective study of 19 cases, collected in the department of thoracic surgery of Rabat; over a period of 7 years from January 2011 to December 2018. The purpose of this work is to update the diagnostic approach of this type of tumor, and also their anesthetic and surgical management. **Result:** We counted 19 cases including 12 women and 7 men, with an average age of 49 years. Dyspnea and chest pain are the main symptoms found in all our patients. All the patients received an X-ray and thoracic CT scan, 13 patients underwent a transparietal biopsy and were inconclusive in 3 patients. The surgical approach was a posterolateral thoracotomy for 16 patients, a mean lobectomy completing tumor resection was performed on one patient. The average size of the operative pieces was 16 cm. In operation 5 patients presented hemodynamic instability, 12 patients required a transfer to the intensive care unit in the immediate postoperative. The anatomopathological study of operative specimens returned to solitary fibrous tumor (8 patients) Neurogenic tumors (4 patients) Teratoma (2 patients) Liposarcoma (1 patient) Metaplastic thymoma (1 patient) Synoviosarcoma (1 patient) Pneumoblastoma (1 patient)) fibromatosis (1 patient). **Conclusion:** The diagnosis of an intra-thoracic mesenchymal tumor is very difficult, but it must in no way delay surgical management as long as it is possible.

Keywords: Huge, mesenchymal tumors, Intra-thoracic

EP1.15-05 SURGICAL OUTCOMES OF PULMONARY METASTASECTOMY FOR HEAD AND NECK CANCER: A SINGLE INSTITUTIONAL RETROSPECTIVE STUDY

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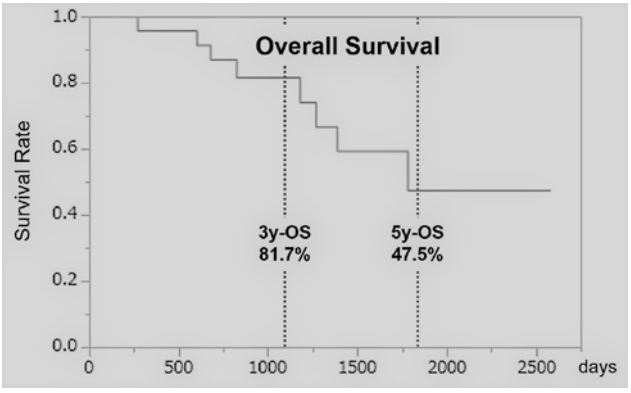
Background: Pulmonary metastasis is often observed during clinical course of head and neck cancer (HNC). Five-year survival rate after pulmonary metastasectomy of HNC has been reported to be around 60%, however, proper indication of metastasectomy remains unclear. We aimed to clarify clinicopathological features and surgical outcomes of HNC patients who underwent with pulmonary metastasectomy. **Method:** A total of 25 patients underwent pulmonary metastasectomy at Chiba University Hospital during from January 2011 to December 2016. Prognostic factors related to overall survival after pulmonary metastasectomy were retrospectively examined using the univariable Cox proportional hazard models. **Result:**



Median follow-up period was 39.5 ±22.5 months. Mean age of the patients was 64.5 ±13.4 years, and they included 23 males. Primary lesions arose in pharynx in 12 patients, oral cavity and nasal cavity and paranasal cavity in 6, larynx in 4, and salivary gland in 3. Seventeen patients were diagnosed as stage IV due to tumor size and/or lymph node metastasis in the first presentation. Primary lesions were resected in 19 patients, and chemotherapy and/or radiation therapy were added in 15 out of these patients. The mean tumor diameter of pulmonary metastases was 15.4 ±10.3 mm. A single pulmonary nodule was detected in 15 patients and double in 6, triple in 3 and four in 1 patient, respectively. Among the 40 lesions, partial resection was selected for 30, segmentectomy for 7, lobectomy for 3. Squamous cell carcinoma was the most predominant (76%). Recurrent site after pulmonary metastasectomy was most frequently observed in the lung (72%). Eight patients survived without recurrence, 10 patients survived with recurrent disease, and others died of the diseases. After pulmonary recurrence, 3 patients underwent repeated metastasectomy, and eventually achieved cancer free status for 4.43

±1.64 years. Following pulmonary metastasectomy, 6 patients were suffered from other cancers. Three- and 5-year survival rates were 81.7% and 47.5%, respectively. In the univariate analysis, disease free survival (< 140 days) and age (< 60) were independent predictors of poor prognosis. **Conclusion:** Surgical treatment for pulmonary metastasis of HNC can offer favorable survival. The number of cancer-bearing patients after pulmonary metastasectomy is increasing possibly due to the advance of novel chemotherapy. It is important to provide a careful observation considering that the most frequent site to redevelop recurrence after pulmonary metastasectomy is the lung and that other organ cancers often arise in those patients.

Keywords: metastasectomy, head and neck cancer, pulmonary metastasis

EP1.15-06 ASKIN TUMOR: A CASE REPORT

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Background: Askin's tumor is a rare highly malignant tumor that originates from the soft tissue of the chest wall, rarely in the lung. It is observed with predilection in the young subject and still raises many questions about his own individualization and his links with Ewing's sarcoma. **Method:** We report the case of child Y. I, 12 years old, who had left chest pain with dyspnea stage 1 6 months before his admission **Result:** The chest CT objectified 2 contiguous formations of the left chest base (30mm and 92mm) with peripheral calcification that contrasted homogeneously with a left pleural effusion. After a multidisciplinary meeting, a biopsy was indicated and its examination found an aspect of round cell tumor proliferation infiltrating muscle tissue and expressing intensely anti CD99 Ac, in favour of a primary peripheral neuro-ectodermal tumor (PNET) Askin type. The patient was then referred to haematology where he received 6 cycles of neo-adjuvant chemotherapy (VIDEprotocol). The thoracic CT evaluation showed a regression of the 2 formations with a slight thickening in the mid-arc of the 9th left rib. The patient therefore benefited from a one-piece resection of the left lateral arches of Co8, Co9 and Co10. The post-operative history was simple. The patient left the ward the fourth day after the surgery. The anatomopathological examination of the resected piece concluded that there was a residual site compatible with the Askin tumour representing 10 to 50% of the tumor mass and evaluated as grade II of Huvos and Rosen with the presence of necrotic and fibrohyaline changes. The resection was complete. After an adjuvant chemotherapy and 8 months before surgery, the patient is regularly followed in consultation and shows no sign of recurrence. **Conclusion:** The therapeutic management of Askin's tumor is not yet well codified and patients are most often treated on a case-by-case basis. All decisions should therefore be taken within the framework of a multidisciplinary meeting.

Keywords: askin tumor, surgical treatment

EP1.15-07 A MUTATIONAL ANALYSIS OF EPIDERMAL GROWTH FACTOR RECEPTOR PATHWAY GENES IN THYMIC CARCINOMA

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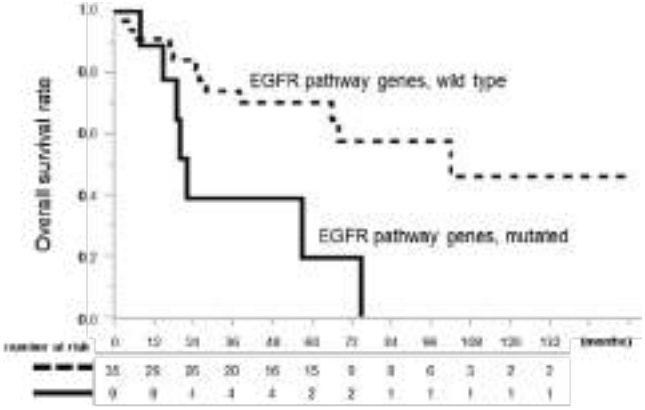
Background: Thymic carcinoma is rare and usually has a fatal outcome. In many malignancies, gene mutations in the epidermal growth factor receptor (EGFR) signaling pathway are important for predicting a patient's prognosis and as targets in molecular-targeted therapy. However, these mutations have not been well analyzed in thymic carcinoma. **Method:** We examined a large cohort of thymic carcinoma and looked for gene mutations in the EGFR pathway genes; *RAS* family, *EGFR*, *PIK3CA*, *AKT1*, and *BRAF* using a highly sensitive single-base extension multiplex assay, SNaPshot assay. **Result:** Among 54 thymic carcinoma cases, 13 (24.1%) showed 14 mutations: *RAS* family mutations in 10 cases (18.5%; KRAS in 6 [11.1%], HRAS in 3 [5.6%], and NRAS in 1 [1.9%]), *EGFR* in 2 (3.7%), *PIK3CA* in 1 (1.9%), *AKT1* in 1 (1.9%), and *BRAF* in 0. All of these mutations were of the missense type, and mutations were mutually exclusive in all cases except in one case that harbored *HRAS* and *AKT1* mutations. A prognostic analysis focusing on squamous cell-type thymic carcinoma cases (n=44, 9 mutation-positive cases) showed that the overall survival (OS) was significantly shorter in patients with EGFR pathway mutations than in those without in a univariate analysis (median OS time, 22 months vs. 102 months; p=0.0173) (Figure 1). Subsequently, EGFR pathway mutations were selected as an independent factor for a poor overall survival (p=0.0389).



Conclusion: In the present study, gene mutations in the EGFR pathway in thymic carcinoma were found more frequently than in previous studies. Gene mutations in the EGFR pathway may be associated with a poor prognosis in thymic carcinoma patients. Therapeutic significance of the gene mutations in thymic carcinoma should be further clarified.

Keywords: gene mutations, EGFR pathway, Thymic carcinoma

EP1.15-08 ASSOCIATION OF PERIOPERATIVE CHEMOTHERAPY WITH SURVIVAL IN THYMIC MALIGNANCIES

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Background: Patterns of perioperative chemotherapy utilization and its association with survival in thymic malignancies are largely unknown. **Method:** We queried NCDB from years 2004-2014 and identified 3,788 patients with non-metastatic thymic carcinoma (TC) and thymoma who received surgery. We compared patients who received perioperative chemotherapy to those who didn't and used a Cox proportional hazards model to determine predictors of mortality. **Result:** 764 patients (20%) received chemotherapy: 287(38%) neoadjuvant (NAC), 347(45%) adjuvant (AC), and 130(17%) unspecified. 184(24%) had TC; the rest had thymoma. Patients who didn't receive chemotherapy (N=3024) had older age (median 62 vs 47, P<0.01) and earlier stage (51% versus 24% stage I-IIA, P<0.01). In multivariable analysis, patients who received AC versus no chemotherapy had a similar overall survival(OS); however, NAC predicted a worse OS. For separate thymoma and TC subsets, median OS did not differ between those who received AC and those who didn't in either group. AC did not improve OS for patients with R1/R2 margins (114 months, 95%CI 94-NR vs 131 months, 95%CI 118-NR)

Characteristic	Hazard ratio for mortality (95% confidence interval)[1]
Age	1.03 (1.03-1.04)
Thymoma vs. TC	0.50 (0.43-0.58)
Charlson-Deyo score>0	1.40 (1.21-1.63)
Chemotherapy None Adjuvant Neoadjuvant Unclassified	1 1.13 (0.89-1.44) 1.77 (1.37-2.27) 1.60 (1.16-2.19)
Masaoka-Koga Stage I-IIA IIB III Unknown/other	1 1.08 (0.88-1.34) 1.59 (1.34-1.90) 2.71 (2.01-3.65)
Radiation	0.78 (0.67-0.91)
Positive margin	1.55 (1.33-1.81)

[1]Model included sex, academic center, insurance, and race/ethnicity

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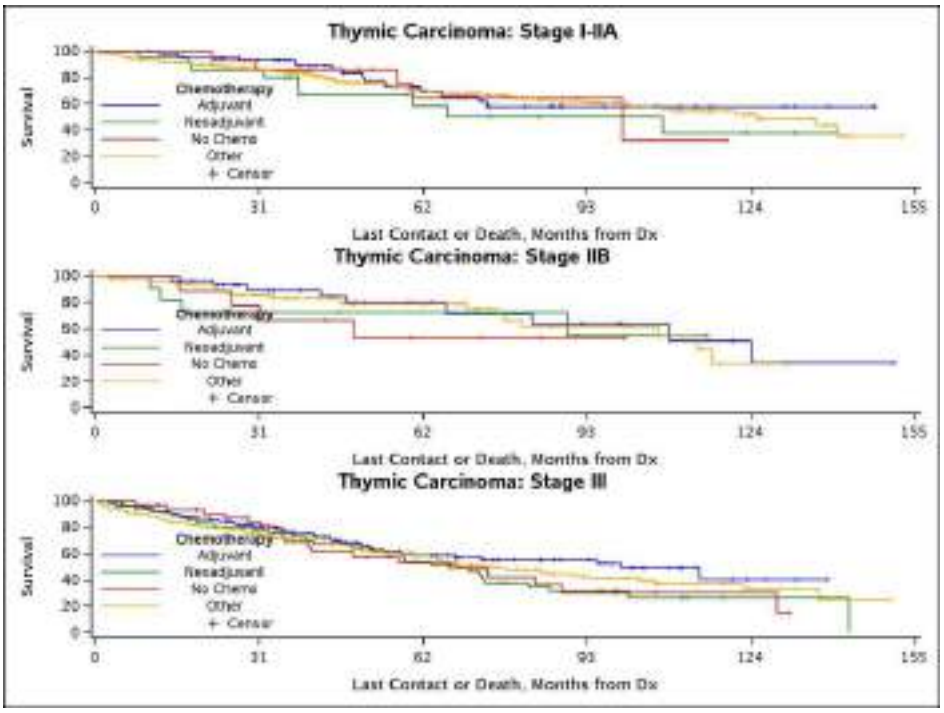

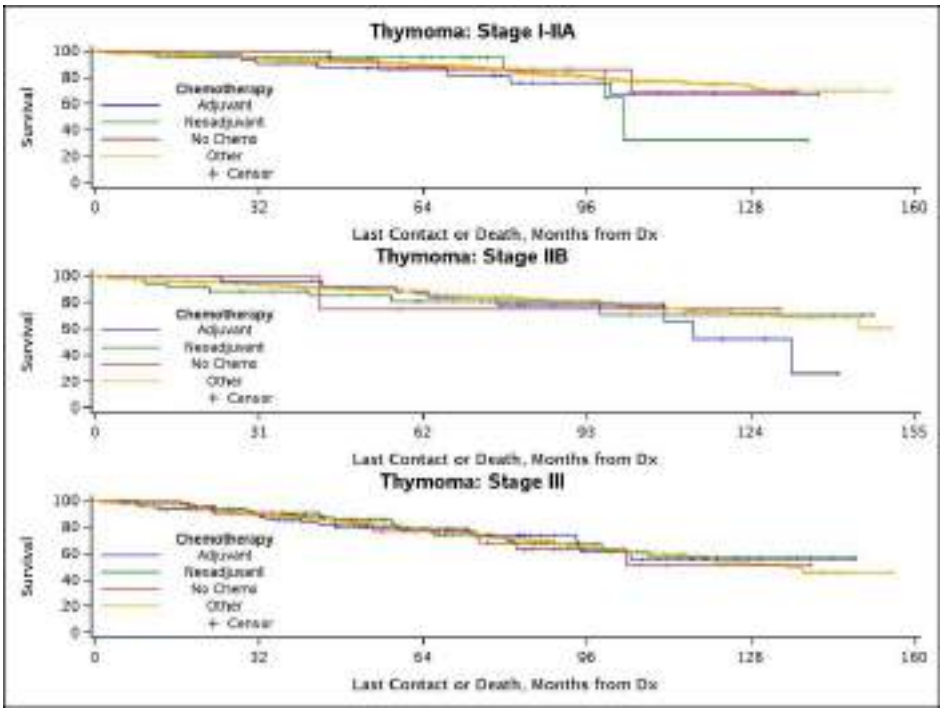

Conclusion: Chemotherapy in the perioperative setting was not associated with improved OS in either TC or thymoma. Prospective controlled studies are needed to determine the role of perioperative chemotherapy in thymic malignancies.

Keywords: thymic carcinoma chemotherapy NCDB, thymoma chemotherapy NCDB

EP1.15-09 SURGICAL RESECTION OF PULMONARY METASTASES FROM HEPATOBILIARY AND PANCREATIC CANCERS

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Background: Hepatobiliary and pancreatic cancers account for 22% of all cancer deaths in Japan. Although these cancers have had a high mortality rate and have been poorly responsive to chemoradiation therapy, the survival of patients have been gradually improved with recent advances in diagnosis and treatment. Pulmonary metastases derived from hepatobiliary and pancreatic cancers have been a rare event and the management in such patients remains controversial. The aim of this study is to review our experience of pulmonary resection for metastatic hepatobiliary and pancreatic cancers, and to assess the feasibility of pulmonary metastasectomy. **Method:** Clinical data of 7 patients who underwent pulmonary resection for metastatic hepatobiliary and pancreatic cancers from April 2010 to March 2019 at Ehime University Hospital were retrospectively reviewed. Disease-free interval was defined as the time between operations for the primary cancer and the metastatic lesion. **Result:** The median follow-up period was 61 (range, 7 to 110) months. Primary diseases of these patients were hepatocellular carcinoma in 2, cholangiocarcinoma in 1, gallbladder cancer in 2 and pancreatic cancer in 2. There were 5 men and 2 women with mean age of 69 (range, 47 to 82) years. The median disease-free interval was 19 (range, 6 to 59) months and one patient with solitary metastasis was treated by lobectomy, the other 6 patients (3 solitary, 3 multiple) were treated by wedge resection. 5 surgeries were operated by VATS and the other 2 were operated by thoracotomy. There were 3 patients with incomplete resection. Additional treatments after metastasectomy were performed in 4 patients. Although no surgical complications and operative mortalities occurred, 2 patients died of primary diseases. Recurrence after pulmonary metastasectomy developed in 1 of 4 patients without incomplete resection. The longest survivor was still alive more than 5 years without recurrence after lung resection and the median survival period was 45 months. **Conclusion:** Surgical resection of pulmonary metastases from hepatobiliary and pancreatic cancers are feasible and the postoperative survival is acceptable. But there are highly selective patients in our study, further study is needed to evaluate the efficacy of pulmonary metastasectomy.

Keywords: hepatobiliary and pancreatic cancer, metastatic lung tumor, pulmonary metastasectomy

EP1.15-10 SURVIVAL IMPACT OF NON-SURGICAL TREATMENT IN THYMIC EPITHELIAL TUMOURS: A RETROSPECTIVE STUDY

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Background: The management of thymic epithelial tumours, although poorly defined due to their rarity, remains multidisciplinary in order to offer patients multimodal treatment with surgery as the therapeutic pillar. Our main objective is to highlight the impact of non-surgical treatments on the overall survival and the progression free survival of patients treated for these tumours at the Mohamed VI center. **Method:** We carried out a monocentric, descriptive and retrospective study using databases from the oncology, the thoracic surgery and anatomopathology departments of the Ibn Rochd University Hospital in Casablanca. We identified all patients with thymoma or thymic carcinoma whose histological diagnosis was made on a biopsy or a surgical excision piece between July 2006 and February 2016 After exclusions, 42 patients were identified and we used a farm sheet to specify for each patient, epidemiological data, data related to histological type, Masaoka-Koga staging and progress under treatment (complete or partial response, stabilization or progression) For our analysis, we used Microsoft Office, Excel 2007 and Kaplan Meier Software to assess overall ans progression free survival. **Result:** 42 cases of thymic epithelial tumours were reported between 2006 and 2016 with apredominance of type B1 in patients aged between 25 and 77 years. The radiological assessment carried out before treament showed that 9.5% of the diseases were metastatic from the outset, while the others had an intra – thoracic locoregional extension Half of the patients were resectable from the outset, wich made it possible to perform primary surgery leading to carcinological resection with generally simple post-operative outcomes. In our series, CAP D1 = D21 chemotherapy was the preferred regimen to be indicated as a pre operative treatment to reduce the size of the tumor and increase its resectivity rate in 11 patients (26,2% of cases). This chemotherapy was indicated as adjuvant treatment in 06 cases of incomplete resection (14,3% of cases) Two patients (4,8% of cases) received first chemotherapy followed by exclusive radiation therapy at 66 Gy while more than 25% received a post-operative radiation therapy at variable doses ranging from 50-54Gy for R0 tumours or microscopic disease to 60-70Gy for macroscopic disease. The overall and progression free survivals at 22 months were 94,6% and 68,4% respectively. The prognostic factors are, in univariate analysis, the performans status, the histological type, the Masaoka-Koga stage and the quality of surgical resection. The multivariate analysis could not be performed due to a lack of statistical power, due to the small number of patients and the retrospective nature of the study. **Conclusion:** The thymic epithelial tumours treatment is a real challenge given the absence of randomized prospective studies on this subject Surgery remains the mainstay of management but neo-adjuvant and or adjuvant treatments can be considered in case of poor prognostic factors in order to reduce the risk of recurrence or death from the disease.

Keywords: Adjuvant, neoadjuvant, thymic epithelial tumors

EP1.15-11 OUTCOMES OF THYMOMA AND DETERMINANTS OF SURVIVAL: 16 YEARS EXPERIENCE OF A TERTIARY CANCER CENTER

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Background: We aimed with this study to explore the demographics and clinical outcome of patients with thymoma. **Method:** A total of 203 patients with thymoma (Masaoka stage II-IV) treated from 2002-2018 were included in this retrospective analysis. IBM-SPSS statistical software version 20 for Windows (IBM, NY) was used for analysis. Survival analysis were estimated by the Kaplan–Meier method and compared by the log-rank test. $p<0.05$ was considered statistically significant. Cox-regression tests used for multivariate analysis. **Result:** Male:female ratio was 105:98 with median age 49 years (Range 11-77). At presentation, patients with stage II, III and IV disease were 90, 67 and 45, respectively. A total of 123 patients(60,6%) had myasthenia gravis, and 56,1% of these patients had presented with myasthenia related symptoms. Majority of the patients were operated with sternotomy(n=103), and mean hospital stay was 8,34 days (Table 1). A total of 76 patients had received adjuvant radiotherapy, and 31 patients and 35 patients had received adjuvant and neoadjuvant chemotherapy, respectively. At mean follow-up of 218,6 months(95%CI:201,8-235,3), 5-year and 10-year OS rates were 93,8% and 89,2%. 30 patients had recurrence after surgery, and 5-year and 10 year DFS rates were 76,5% and 68,3%. Masaoka-Koga stage($p<0.0001$), postoperative hospital stay more than 10 days($p=0,004$) and needing neoadjuvant chemotherapy($p=0,003$) were significant effects on DFS. Among patients who had given neoadjuvant chemotherapy, comparing cisplatin with etoposide or doxorubicin based combinations did not change DFS($p=0,34$) or OS ($p=0,48$). Adjuvant radiotherapy and chemotherapy also have no survival effect on DFS and OS. On univariate analysis, age($p=0.013$), Masaoka-Koga stage($p=0.001$), postoperative hospital stay more than 10 days($p=0,006$) and having recurrence($p=0,013$) were significant effects on OS. Stage ($p=0,001$) and age ($p=0.007$) retained its prognostic significance on multivariate analysis (Table 2).

Table 1: Patient demographics and summary of the treatment approachs.	
Age n = 203 <=50 >50	111 (% 54,7) 92 (% 45,3)
Gender n = 203 Male Female	105 (% 51,7) 98 (% 48,3)
Myasthenia Gravis n = 203 Yes No	123 (% 60,6) 80 (% 39,4)
Acetylcholine Receptors n=123 Yes No	113 (% 91,87) 10 (% 8,13)
Masaoka Stage of Thymoma n = 202 II III IV Unknown	90 (% 44,3) 67 (% 33) 45 (% 22,2) 1 (% 0,5)
Pathology n = 203 Type A Type AB Type B1 Type B2 Type B3 Mixed Micronodular Thymoma Unknown	15 (% 7,4) 20 (% 9,9) 40 (% 19,7) 67 (% 33,0) 32 (% 15,8) 25 (% 12,3) 1 (% 0,5) 3 (% 1,5)
Surgery type VATS (Thoracoscopic) Sternotomy Thoracotomy RATS Inoperable	54 (% 26,6) 103 (% 50,7) 37 (% 18,2) 5 (% 2,5) 4 (%2)
Treatment Modality Neoadjuvant Chemotherapy Adjuvant Chemotherapy Adjuvant Radiotherapy	35 (% 17,6) 31 (% 15,6) 76 (% 38,2)

Table 2: Five-year overall survival and recurrence-free survival estimates in patient subgroups				
	5-Year Survival Rate			
	OS	**P**	**RFS**	**P**
Age				
≤50	%96,6 +/- 1,9	0,013	%77,8 +/- 4,5	0,510
>50	%84,2 +/- 4,7		%75 +/- 5,4	
Gender				
Male	%91,5 +/- 3,4	0,852	%76,5 +/- 5	0,687
Female	%90,9 +/- 3,3		%76,5 +/- 4,9	
Masaoka stage				
2	%96 +/- 2,3	0,001	%93,1 +/- 3	<0,001
3	%88,4 +/- 5		%77,8 +/- 6,4	
4	%85,4 +/- 6,2		%42,1 +/- 8,8	
Myasthenia Gravis				
Yes	%93,1 +/- 2,6	0,648	%80 +/- 4	0,358
No	%87,3 +/- 5		%69,4 +/- 6,7	
Diagnosed before 2008				
Yes	%97,3 +/- 2,7	0,544	%80 +/- 6,8	0,247
No	%89,1 +/- 2,8		%75,4 +/- 4,1	
Chemotherapy No Neoadjuvant Adjuvant	%93 +/- 2,4 %86,9 +/- 7,2 %75 +/- 15,3	0,74	%86,4 +/- 3,2 %47,7 +/- 10 %21,8 +/- 13,4	<0,001
Radiotherapy Type				
No Neoadjuvant Adjuvant	%90,3 +/- 3,3 %50 +/- 3,5 %93,5 +/- 3,2	0,588	%79,6 +/- 4,5 - %74,9 +/- 5,5	0,436
Time of initiation of adjuvant therapy Early Late	%90,9 +/- 8,7 %89,1 +/- 6,1	0,867	%65,3 +/- 14,3 %72,8 +/- 8,5	0,853
Pathology Type Type A Type AB Type B1 Type B2 Type B3 Mixed Hystology	%88,9 +/- 10 %100 %91,8 +/- 4,5 %93,2 +/- 3,9 %84,9 +/- 8,5 %85 +/- 7,7	0,506	%83,6 +/- 10,3 %87,1 +/- 8,6 %77,4+/- 7,1 %76,7 +/- 6,3 %77,8 +/- 9,3 %57,2 +/- 11,7	0,538
Hospitalisation Days				
<10 days	%95,7 +/- 1,9	0,006	%87,1 +/- 3,1	0,004
>=10days	%78,9 +/- 7,2		%56,9 +/- 8,9	
Recurrence				
Yes	%88,9 +/- 6	0,013	NA	-
No	%91,7 +/- 2,6		NA	

Conclusion: Masaoka-Koga clinical stage and age are the important prognostic factors predicting OS. Postoperative hospital stay is related to DFS and OS.

Keywords: THYMOMA, Survival, Masaoka - Koga Staging System

EP1.15-12 PREDICTIVE VALUE OF PERCENTAGE OF KI 67 EXPRESSION IN BRONCHOPULMONARY CARCINOID TUMORS

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Background: Introduction The determination of Ki67 has not been shown to be useful in the diagnostic discrimination between typical (CT) and atypical (CA) carcinoid tumors. However, the biological behavior of these tumors is not homogeneous. Objective: to establish a Ki67 cut-off point for carcinoid tumors and to determine its prognostic implications in overall survival and disease-free survival in both histological subtypes. **Method:** Material and **Method:** retrospective cohort on 106 patients with diagnosis of carcinoid tumor (OMS 2015) surgically trated. The% of cells expressing Ki 67 was determined manually by two pathologists specialized in the use of a rabbit monoclonal antibody prediluted anti Ki67 (Clone MIB-1). Ki67-positive nuclei were quantified in 2000 consecutive tumor cells in the areas of highest activity (HOT SPOT) at a magnification of 40X. The comparison of continuous variables was made according to its distribution and the categorical variables with the Chi2 test or Fisher's exact test. To evaluate the association between Ki-67 expression and the occurrence of events, logical regression analysis was performed and ROC curves were constructed to evaluate global predictive capacity as per histological subtype, identifying the best cut-off point using the Youden index. Once this point was identified, the regression analysis was repeated using Ki-67 as a dichotomous variable (equal or greater than the cut-off point versus lower). All tests are two-tailed and a value of p <0.05 was considered statistically significant. The analysis was carried out with the program R: A Language and Environment for Statistical Computing version 3.5.1 (Vienna, Austria) **Result:** The data of ki-67 were available in 63/106 patients (59.4%). 40 (65.6%) CT and 23 (34.4%) CA. The 60.3% (n = 38) were women, the average age was 43.7 (SD 15.4) years, 25 (28.8%) were smokers. The median of ki-67 was 0.86 (RIQ 0.50 - 3.25). The presence of lymph node metastases N2 (12.8% vs 38.1%, p = 0.045), recurrence rate (2.5% vs 19%, p = 0.044) and mortality (0 vs 28.6%, p = 0.005) were significantly higher in the group of the CA. The median of ki-67 between the CTs was 0.63 (RIQ 0.44 - 1-93) vs 2.00 (RIQ 0.65 - 4.00) in CA (p = 0.005).The Ki-67 value was not significantly associated to mortality (p = 0.546), nor to risk of relapse, analyzing the entire population (p = 0.489), nor by histological subtype (CT p = 0.677 vs CA p = 0.202). The best cut-off point of Ki-67 on the ROC curve in patients with CA was 1.18. Using this value as a predictive variable, there was no significant association between% Ki-67 and mortality (p = 0.077), but a marginal association with the frequency of relapses (p = 0.054). **Conclusion:** Although we have not been able to demonstrate predictive association between KI 67 and mortality, this could be due to the small number of observed events. In the AC subgroup, the marginal association between relapse frequency and Ki 67 values> = to 1.18 presents clinical relevance and future analyzes are required to determine the real predictive value of this variable.

Keywords: carcinoid tumours, Ki 67, pronostic value

EP1.15-13 PROGNOSIS OF COLORECTAL CANCER CASES THAT UNDERWENT LUNG AND LIVER METASTASECTOMY AND THERAPEUTIC OUTCOMES OF BRAIN METASTASIS

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Background: The resectability is often debated in cases of lung and liver metastases. Further, we had reported previously that the incidence of brain metastasis is significantly higher in colorectal cancer with lung metastasis than cases with liver metastasis (lung: 7.7%, liver: 1.6%). We compared and investigated the therapeutic outcomes of cases of lung, liver and brain metastasis. **Method:** Between 2002 and 2013, we retrospectively studied the prognosis of 90 cases of colorectal cancer cases that underwent lung metastasectomy, and 148 cases that underwent liver metastasectomy. The course of treatment in 8 cases of subsequent brain metastasis was also evaluated. **Result:** The 5-year survival rate (5-SR)for 90 cases of lung metastasectomy overall was 66.7%. 63 cases were initial metastasis and the 5-SR was 66.7%. Out of these, there were 7 cases of synchronous metastasis with a 5-SR of 57.1%, and 56 cases of metachronous metastasis with a 5-SR of 67.9%, indicating no significant difference. The regions of secondary recurrence after lung resection were as follows: lung: 28 (cases), liver: 7, brain: 3, mediastinal lymph nodes: 5, other: 5. The 5-SR for 148 cases of liver metastasectomy overall was 54.7%. 141 cases were initial metastasis and the 5-SR was 55.3%. Cases who underwent lung metastasectomy had a significantly higher survival rate (p=0.0068). Out of these, 70 cases were synchronous metastasis with a 5-SR of 35.7%, and 71 cases were metachronous metastasis with a significantly higher 5-SR of 67.9% (p=0.011). The regions of secondary recurrence after liver resection were as follows: lung: 47 (cases), liver: 66,brain: 2, abdominal lymph nodes: 9, dissemination: 6, other: 7. While there were 5 cases of subsequent brain metastasis after lung resection, no subsequent brain metastasis was found after liver resection. All but one of the 8 cases of brain metastasis after lung resection were treated with surgery or CyberKnife. The total survival period was 1141 - 3848 days (median: 1913.5 days), and the survival period after detection of brain metastasis was 15 - 852 days (median: 401 days). In addition, all cases were experiencing associated symptoms when brain metastasis was detected, and only one patient was undergoing regular examinations to detect brain metastasis. **Conclusion:** While appropriate surgical intervention is recommended in cases of lung metastasis and metachronous liver metastasis,it is debatable in cases of synchronous liver metastasis. Cases of lung metastasis should give attention to brain metastasis and recieve early detection and intervention.

Keywords: lung metastasis of colorectal cancer, Liver metastasis, brain metastasis

EP1.15-14 MEDIASTINAL LYMPH NODE DISSECTION THROUGH MEDIAN STERNOTOMY IN THYROID CARCINOMA

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Background: Recurrent cervical and mediastinal lymph node metastasis after the surgery of thyroid carcinoma is frequently reported. Generally, surgery is the best treatment but there is still no established standard surgical procedure. In our hospital, we perform the operation through median sternotomy. **Method:** Surgical procedure for recurrent cervical and mediastinal lymph node metastasis after thyroid carcinoma varies throughout each institute. Recently, reports of the usage of VATs in these cases are increasing. We report 2 resected cases of cervical and mediastinal lymph node metastasis after thyroid cancer which underwent dissection through median sternotomy. **Result:** A 68-year-old Japanese man underwent left thyroid lobectomy for poorly differentiated thyroid cancer in September 2009. The follow-up CT in 2014 showed a multiple mediastinal lymph node metastases. Therefore, the patient underwent mediastinal lymph node dissection through median sternotomy. Pathological findings showed metastasis in 24 of the 42 lymph nodes. During outpatient follow-up, CT revealed a recurrent mass lesion in the vincinity of the right subclavian artery and common carotid artery. Although I131 was administered, the mass did not respond. Therefore surgery therapy was required. The second operation was cervical incision. The pathological findings showed consistent recurrence. The patient was discharged from the hospital on postoperative day 4. The second patient was a 58-year-old Japanese man who had been treated by subtotal thyroidectomy in May 2008. The patient noticed a gradual increase of a mass near his right lower jaw from 2011. As a result of further examination, mediastinal lymph node metastasis was suspected. The patient underwent mediastinal lymph node dissection through median sternotomy and neck collar incision. Pathological findings showed metastasis in 9 of the 31 lymph nodes. Pathological findings revealed metastasis of papillary thyroid carcinoma. The patient was discharged from the hospital on postoperative day 13. **Conclusion:** Recent reports of recurrent cervical and mediastinal lymph node metastasis after thyroid carcinoma suggests using VATs, which may have less complications. In our hospital, the possibility of micrometastases is also considered in cases of post-operative lymph node recurrence. Therefore, we completely resect the mediastinal lymph nodes by median sternotomy approach. We have been promoting mediastinal

lymph node dissection for lung cancer surgery at our center, but we would like to report the significance of mediastinal lymph node dissection for recurrence cases after thyroid carcinoma.

Keywords: mediastinal lymph node metastasis,median sternotomy,thyroid carcinoma

EP1.15-15 SINGLE-CENTER RETROSPECTIVE ANALYSIS OF OPERATED THYMOMAS

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Background: Thymoma is the most common thymic neoplasm. In the majority of cases, patients are asymptomatic and the diagnosis is incidental. Surgery is the gold-standard treatment whenever possible. The objective of this study was to evaluate retrospectively the surgical outcomes in patients with stage Masaoka-Koga I to IVa thymomas at our department. **Method:** A review of 50 cases of thymomas submitted to surgical excision at our Thoracic Surgery Department was made by accessing their clinical records, in a six-year period, from January 2012 to December 2018. **Result:** From the 50 patients, 38% were males, with an average age of 58 years old, ranging from 15 to 85. In a relatively high percentage of patients, the thymic malignancy was accidentally found in a CT-scan. 24 of the cases were associated with Myasthenia Gravis. All the patients had a CT-scan prior to surgery but just 3 had done a PET-CT scan that seemed to be reserved to those of a higher stage. The histological diagnosis was done by CT-controlled biopsy in 14 cases and in the rest the diagnosis was done by the analysis of the extracted specimen. There were 4 type A thymomas, 12 type AB, 5 type B1, 17 type B2, and 10 type B3, one sclerosing thymoma and one micronodular thymoma with lymphoid stroma. The majority (54%) were in Masaoka-Koga stage II. There were 11 patients at stage I, 9 at stage III and only 3 at stage IV. Only 3 patients did neoadjuvant treatment, 21 patients had adjuvant radiotherapy, 2 patients had adjuvant chemotherapy and 3 had both. The surgical approach was sternotomy in 76% of cases, videothoracoscopy in 18%, thoracotomy in 2%, sternotomy plus thoracotomy in 2%, hemiclamshell in 2%. In all cases was done an en bloc resection, which in some involved lung resection (16), pericardial resection (9), vascular resection (8) and diaphragm resection (1). There was no surgical mortality, but 10 patients had phrenic nerve paralysis and 2 had a myasthenic crisis. The mean of hospital stay was 7 days (+- 8), comprising between 2 and 56 days. After a mean follow-up of 29 months (+- 20 months), there were 2 disease-related deaths and 4 recurrences (2 pleural, one diaphragmatic and one lung and mediastinal). The time to recurrence ranged from 4 to 74 months. There was a 100% survival rate at the post-operative period and overall survival at 5 years of 81%. Regarding the Masaoka classification, the 5-year-survival rate was shown to be of 100% in stage I, 96% in stage II, 44% in stage III and 100% in stage IV. On the other hand, the analysis by the WHO classification showed a 5-year-survival of 100% in thymoma A and AB groups, 40% in thymoma B1 group, 75% in thymoma B2 group and 67% in thymoma B3 group. **Conclusion:** Even though thymic malignancies are rare tumors, thymomas are commonly approached by the Thoracic Surgeon. Surgical resection is the mainstay of treatment, but a multimodality approach is crucial in specific cases.

Keywords: thymoma, surgery, survival

EP1.15-16 TWO CASE REPORT OF MALIGNANT TRACHEAL TUMORS

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Background: Primary malignant tumors of the trachea are rare and uncommon, they represent less than 0.01% of adult tumors and about 0.2% of respiratory ones. They are malignant 90% of the time, with squamous cell carcinoma being the most frequent (50–66%) followed by adenoid cystic carcinoma (10–15%). **Method:** The first case report concerns a 42 years old man with no medical history, that consulted in our unit with cough, wheezing and shortness of breath, the chest computerized tomography (CT) showed a distal tracheal mass with axophytic extension without carinal involvement, the ascertain size was 34 mm × 40 mm. Neither mediastinal lymphadenopathy nor obvious invasion to surrounding structures was noted. During the flexible bronchoscopy, we found tracheal tumor partially blocking. the anatomopathology study of the biopsy reported a squamous carcinoma. The second report is about a 20 years old female with an allergic rhinitis history, who consulted with a dyspnea and vigorous cough persisting for more than year. During this this period the symptoms were attached to asthma and were treated by an association inhaled corticosteroid-beta 2 sympathomimetic. The neck and chest CT showed an endotracheal mass of 26 mm diameter originating from the anterior wall, occluding 70% of the trachea. The bronchoscopy confirmed the same analysis and showed an easy bleeding to the touch. The biopsy revealed an adenoid cystic carcinoma. **Result:** The Multidisciplinary decision (pulmonologist, thoracic surgeon, oncologist and anesthesiologist) advised for a surgical resection for the two patients. The first patient underwent surgery with five tracheal rings resection and end-to-end anastomosis after tree neo-adjuvant chemotherapy with modified 5-fluorouracil and cisaliplatin. A chest CT will be done in 3 months and an endoscopic control in 12 months. The second patient had benefited also from a reaction with end to end anastomosis followed by radiotherapy. After 3 years no tumor recurrence has occurred. **Conclusion:** Careful clinical evaluation, tomography and endoscopic examination are essential for the confirmation and staging of primary tracheal tumors. Surgery remains the best treatment to achieve a long-term survival.

EP1.15-17 GIANT THYMOLIPOMA IN A YOUNG WOMAN: A CASE REPORT

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Background: Thymolipoma is a benign mediastinal tumor composed by adipose tissue and thymic tissue. It is a rare mediastinal tumor, presenting predominantly between 20-40 years, without predilection for a specific gender. Its clinical presentation is variable, from asymptomatic cases to thoracic pain and recurrent respiratory infections. We describe the case of a young female, asymptomatic, with an incidental finding of a mediastinal mass posteriorly diagnosed*as a* thymolipoma. **Method:** Review of the Clinic History. **Result:** A 21-year-old female, previously healthy, presents with a recent history of community acquired pneumonia with radiological alterations in x-rays. She denies respiratory or systemic symptoms; physical exam she has decreased breaths sounds in the bases. Chest CT-scan: a large mass in the anterior mediastinum, extending to the left hemi-thorax, with adipose tissue, surrounding the cardiomediastinum without infiltrating it. Surgical excision is performed describing a large (39x22x8cm) lobulated mass weighing 3378grs with a fatty appearance, encapsulated and with scarce hemorrhagic areas, collapsing the left lung. Histopathology: a mesenchymal lesion composed of mature adipose and thymic tissue, with Hassall´s corpuscles and immunohistochemistry compatible with an encapsulated thymolipoma. **Conclusion:** Thymolipomas are identified typically in the management of other medical conditions. They are associated with chromosomal alterations such as rearrangement of the cytogenetic bands, loss of chromosomal material or supra-numeric chromosomes. Four categories have been proposed for its classification: lipoma with thymic tissue combined adipose and thymic neoplasm, adipose tissue replacement of a thymoma and replacement of a hyperplasic thymus; being the first type the one we found on our patient. Surgical excision is curative, without complications and there are no descriptions of malignant transformation. A few case reports on the literature have associated it with myasthenia gravis, particularly in elderly patients with small masses. Within the differential diagnosis the lipoma, the liposarcoma and the thymic hyperplasia have to be taken into account.

A. Chest radiograph showing bilateral basal opacity with displacement of mediastinal structures to the left. B. H & E staining reveals mature thymic and adipose tissue. C. ST-Scan with anterior mediastinum-dependent lesion extending to the lug bases and occupying them with fat content with soft tissue density. D. Appearance of the thymolipoma at the time of the surgical approach

Keywords: Thymolipoma, Thoracic surgery

EP1.15-18 AN 18-YEAR SINGLE-CENTER EXPERIENCE ON 76 GIANT MEDIASTINAL TUMOR RESECTIONS

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Background: Giant mediastinal tumors are often case reported in sparse and can be difficult for surgical removal. The purpose of this study was to make a comprehensive review of the relevant clinical data in our center, aiming to upgrade our current understanding of the disease. **Method:** A retrospective review of medical record was conducted at our single institution from 2001 to 2019. The preoperative, postoperative characteristics and survival data were retrieved. The patients under 16 years old were excluded. The descriptive statistical analysis and Kaplan-Meier analysis were R-3.5.0. **Result:** A total of 76 patients with mediastinal tumors over 10cm underwent surgery in this period were summarised: the median age is 44; the maximum tumor diameter ranges from 10cm to 35cm; the surgical approaches include median sternotomy, lateral thoracotomy, and with or completed by minimally invasive procedure; the blood loss in surgery ranges from 100ml to 3000ml; average postoperative the hospitalization is 30 days. The average overall survival is 39 months. **Conclusion:** With careful preoperative evaluation, our results indicate that surgical management of giant mediastinal tumor is safe and recommended. Patients with a benign or less aggressive malignant tumor who received surgery have a favorable outcome in terms of long-term survival.

Keywords: Giant mediastinal tumors, Thoracic surgery, surgical outcome

EP1.15-19 PRIMARY ENDOBRONCHIAL HYALINISING CLEAR CELL CARCINOMA PRESENTING IN ASSOCIATION WITH ACTIVE PULMONARY TUBERCULOSIS

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Background: Hyalinising clear cell carcinoma (HCCC) is a rare tumor of putative salivary gland origin that most commonly presents as an oral submucosal lesion in middle aged to elderly adults. With a characteristic histomorphology of infiltrating cords and nests of clear tumor cells set in a hyalinised stroma, these tumors frequently harbour *EWSR1:ATF1* fusions, the latter serving as a useful diagnostic marker in differentiation from other clear cell-rich tumors. Only four cases with primary pulmonary origin have been previously reported, all of which were incidentally detected small (<3 cm) intrabronchial masses in non-smoking middle aged men. We report the fifth case in a 44-year-old non-smoker who presented with hemoptysis and was found to harbour a 3.5 cm intra-bronchial HCCC in association with active pulmonary and mediastinal tuberculosis. **Method:** A 44-year-old male, non-smoker, presented with 2 episodes of hemoptysis. On imaging, a heterogeneously enhancing FDG-lobulated soft tissue mass was noted within the left lower lobe bronchus with lobar collapse. FDG avid nodular lesions were also seen in the left lower lobe parenchyma with enlarged aortopulmonary window and bilateral hilar lymphnodes. No pleural effusion was seen. There was no evidence of any metastatic lesions. He underwent an endobronchial biopsy from the left main bronchus followed by left lower lobectomy and mediastinal lymphadenectomy. Formalin fixed paraffin embedded tumor sections were subject to special stains for detection of acid fast bacilli and fungi, immunohistochemistry for p40, TTF-1, chromogranin, synaptophysin, epithelial membrane antigen, smooth muscle actin, S100 and smooth muscle myosin heavy chain, and fluorescence-in-situ hybridisation for 22q12 locus using the Vysis *EWSR1* dual color, break apart rearrangement probe. **Result:** Microscopic sections from the endobronchial biopsy revelaled a subepithelial tumor arranged in nests, cords and trabeculae within a densely hyalinised stroma. Tumor cells were monomorphic with clear to eosinophilic cytoplasm and occasional mitoses. Left lower lobectomy specimen showed a grossly circumscribed solid tumor in the wall of the left main bronchus abutting the cartilage and demarcated from adjacent lung parenchyma by a thin fibrous capsule. Tumor cells were immunopositive for p40, epithelial membrane antigen, while were negative for TTF-1, and myoepithelial markers. FISH revealed presence of EWSR1-re-arrangement in tumor cells, confirming the diagnosis of HCCC. Numerous mililary parenchymal and pleural nodules with necrotic caseous material containing acid fast bacilli were also seen, consistent with tuberculosis. Further work-up did not reveal presence of tumor elsewhere ascertaining a primary lung origin. Patient was started on anti-tubercular therapy and adjuvant radiotherapy/chemotherapy was not given. Patient is currently on follow-up **Conclusion:** From the limited numbers reported, primary pulmonary HCCCs appear to be indolent slow growing neoplasms with an excellent outcome after surgical excision. The differential diagnoses include the commoner squamous cell carcinomas with clear cell change, clear cell adenocarcinomas, mucoepidermoid carcinomas, metastatic clear cell renal cell carcinoma, and myoepithelial neoplasms. Knowledge of its typical histomorphology aided by prudent immunohistochemistry and demonstration of *EWSR1* gene rearrangement or more specifically, EWSR1:ATF1 fusion transcripts should lead one towards the correct diagnosis.

Keywords: hyalinising clear cell carcinoma, bronchus, Tuberculosis

EP1.15-20 GOOD CONTROL BY RE-ADMINISTRATION OF CARBOPLATIN AND PACLITAXEL AGAINST UNRESECTABLE THYMIC CARCINOMA

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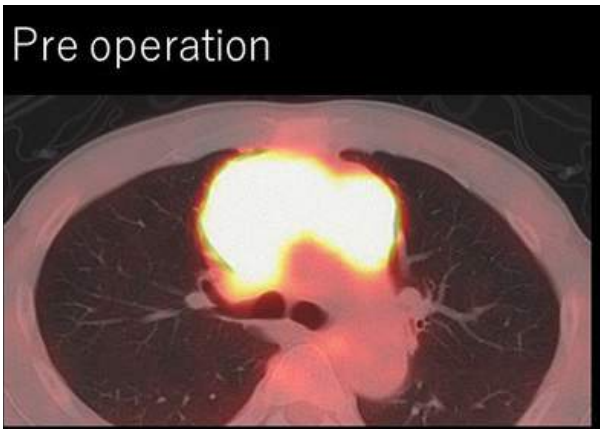
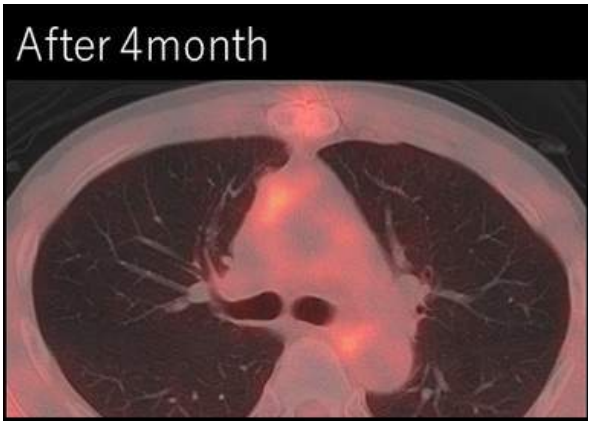
Background: Many chemotherapy regimens have been administered for unresectable and recurrent thymic carcinoma. However, hightly effective standard regimens have not yet been developed. Although carboplatin-based chemotherapy is considered one of the effective options for thymic carcinoma, carboplatin can be used to treat thymic carcinoma up to only 4–6 cycles following guidelines. In addition, there is no scientific evidence for the usefulness of chemotherapy when thymic carcinoma relapses. **Method:** A 48-year-old man who had an abnormal shadow on a chest radiograph obtained during a medical checkup was referred to our hospital. Chest computed tomography (CT) showed a mass measuring 9.3 cm in the anterior mediastinum. Positron emission tomography (PET)-CT showed significant abnormal uptake with a standardized uptake value of 24.5, and there was no evidence of metastasis. We performed median sternotomy, but found pleural dissemination in the right thoracic cavity. We then only obtained a biopsy. Pathologically he was diagnosed with thymic carcinoma. We administered carboplatin and paclitaxel for up to 6 cycles, combined with radiotherapy (60 Gy/30 fr). Six months later, abnormal uptake on PET-CT almost disappeared. However, one year after the chemoradiotherapy, PET-CT showed recurrence of thymic carcinoma. Therefore, we decided to administer the same regimen again for up to 13 cycles. **Result:**





After re-administration, PET-CT showed markedly decreased accumulation and regression of thymic carcinoma. No severe adverse effects were observed. We have subsequently continued monotherapy containing paclitaxel, and until currently there is no evidence of relapse 23 months after surgery. **Conclusion:** Carboplatin has no limitations on its cumulative dose according to its drug package insert, unlike in the case of anthracycline, and the total dose is only limited on the basis of increased side effects regardless of its antineoplasmatic effect. We herein report a case of re-administering carboplatin against unresectable thymic carcinoma beyond the dose suggested by guidelines and achieving good progress.

Keywords: Thymic carcinoma, carboplatin and paclitaxel, Re-administration

EP1.15-21 THYMIC EPITHELIAL TUMORS: REVIEW OF CLINICAL AND PATHOLOGICAL FINDINGS AND PROGNOSTIC FACTORS FOR THE SURVIVAL

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Background: Considered as a very rare malignances (0,15 cases per 100.000), thymic epithelial tumors are also the most commun tumor of the anterior mediastinum. Their treatment is based on multidisciplinary management. The basis of the treatment is a complete surgical and carcinological resection. In locally advanced tumors, neo-adjuvant chemotherapy can be performed. In the case of invasive tumors or incomplete resection, adjuvant radiotherapy is usually recommended. **Method:** We conducted a monocentric, descriptive and retrospective study based on the medical record of 32 patients who underwent surgery for a thymic epithelial tumors in the department of thoracic surgery in the university hospital Ibn Rochd, Casablanca, Morocco. The aim of this study is to review the clinical and pathological findings and also to determine which factors independently predict survival after surgical resection. **Result:** The average age was 48 years and the sex ratio was 0. 88. Of the 32 cases, 32,4% had symptoms consistent with myasthenia gravis. Surgical resection was performed either by sternotomy, thoracotomy or VATS. It was complete in 87,5% of cases. 3 patients (9,4%) received neoadjuvant chemotherapy to reduce tumor size before the surgery. Post-operative radiotherapy was indicated in 31. 2% of patients. We have experienced only one death due to the disease in our series and 2 patients were lost to the follow-up. After an univariate analysis, prognostic factors were: the histological type, the Masaoka-Koga stage and the extent of surgical resection. No multivariate analysis could be done due to small numbers of patients. **Conclusion:** Thymic epithelial tumors present specific problems from anatomical pathology to therapeutic strategy. Their optimal care is still poorly defined because of their rarity and of the resulting difficulty to conceive large clinical trials. Meanwhile, ITMIG, UICC and AJCC are trying to develop a consensus on easier and more universal classification, based on the TNM, to help improve the management.

Keywords: thymic epithelial tumors, prognostic factors, surgery

EP1.15-22 PRIMARY EPITHELIAL - MYOEPITHELIAL CARCINOMA OF THE LUNG WITH UNEXPECTED AGGRESSIVE ONSET

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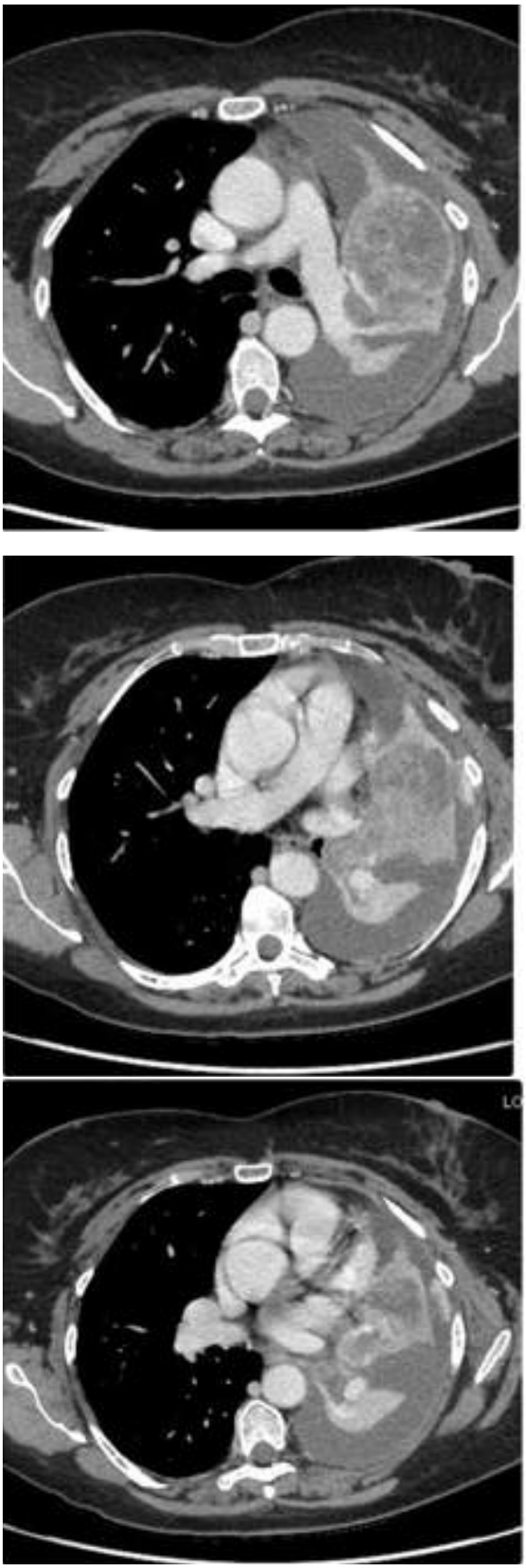
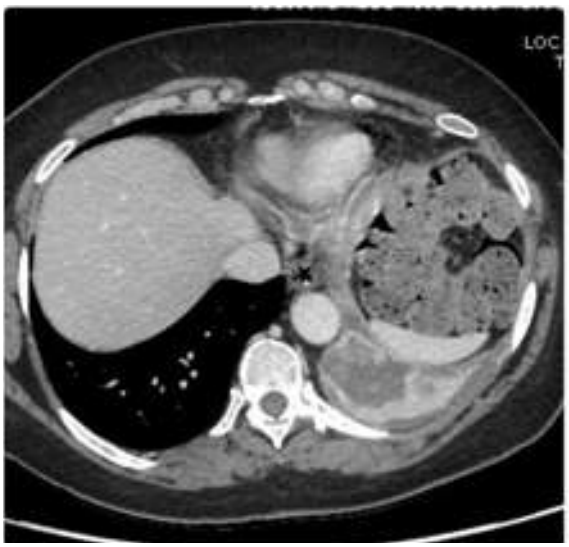
Background: Epithelial-myoepithelial carcinoma (EMC) is the rarest sub-type of primary salivary gland type neoplasms of the lung. It usually arises from the salivary glands in the trachea or main bronchi and it is generally classified as a low-grade tumour, but because of its rarity and the unknown malignant potential, the treatment of choice has not been established. **Method:** A 50-year old Hispanic woman, with no history of previous malignancies or comorbidities, arrived at our institution with cough and dyspnoea. A chest CT showed a lesion of left upper lobe (LUL) bronchus, associated to complete atelectasis of left lung, pleural effusion and two inhomogeneous pleural masses just over the diaphragm. PET/CT revealed increased FDG uptake in LUL and in pleural lesions. Fiberbronchoscopy showed a mass originating from left upper bronchus that occluded left main bronchus. The biopsy of the neoplasm revealed pulmonary EMC. The cytological examination of pleural effusion was negative for neoplastic cells. After cardio-respiratory complete assessment and tumour board evaluation, the patient underwent left pneumonectomy, systematic lymphadenectomy and removal

of two solitary lesions respectively located on parietal pleural and on diaphragm en-block with portion of muscle (repaired with non-absorbable running suture) by thoracotomy





Result: The postoperative course was uneventful (hospitalization: 10 days), however two weeks after discharge the patients was readmitted with pleural effusion and fever. The patient underwent a left thoracentesis (amicrobic, no malignant cells) and a fiberbronchoscopy (regular bronchial suture). After 7 days the patient was discharged. Histopathology confirmed R0 resection of EMC (7x5.5x4 cm), and two solitary metastases on parietal pleura and diaphragm. Ki 67 was <30%. Patient underwent adjuvant chemotherapy, was alive and free of disease 32 months after surgery. **Conclusion:** Primary EMC of the lung is an extremely rare neoplasm with an unpredictable biological behaviour. The surgical resection represents the gold standard if a complete resection can be reached

EP1.15-23 CARDIAC TAMPONADE CAUSED BY A TYPE A THYMOMA: A CASE REPORT

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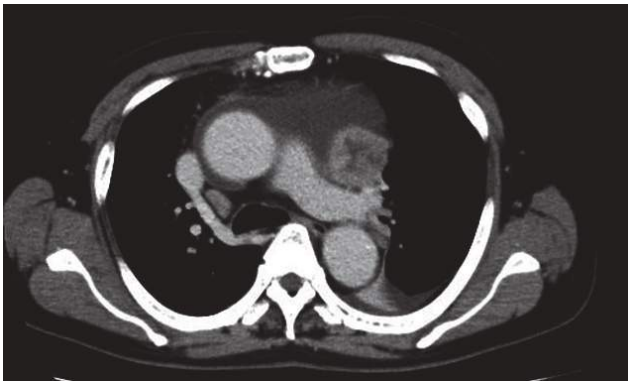
Background: Thymomas, the commonest neoplasm of the anterior mediastinum, are characteristically asymptomatic for prolonged periods. Most patients with disseminated disease have significant signs and symptoms such as chest pain or discomfort, dyspnea, and superior vena cava syndrome. Hemorrhagic pericardial tamponade is an uncommon initial manifestation and it is particularly rare for a thymoma to present with pericardial tamponade. We here present a 73 year-old man who was admitted to our institution with fever and shortness of breath and diagnosed with hemorrhagic pericardial tamponade resulting from a Type A thymoma. **Method:** The patient presented to our emergency department in a stable condition and reported no previous trauma or muscular weakness. Chest computed tomography (CT) showed a cardiac effusion, an anterio-superior mediastinal 40×39×38 mm mass and enlarged mediastinal lymph nodes (image)



After a hemorrhagic pericardial effusion had been drained, PET-CT performed to further investigate the mediastinal mass showed increased uptake in the mediastinum and right gluteus maximus

muscle. Examination of a needle biopsy from the right gluteus maximus muscle mass revealed schwannoma. We therefore suspected the mediastinal mass was a metastatic schwannoma and performed VATS thymectomy combined with partial pericardiectomy. **Result:** Histopathological evaluation of the operative specimen revealed a Type A thymoma that was T3 (cardiac) M1aN0 pStage IVa and Masaoka-Koga stage III. The tumor had invaded the cardiac structures. The patient was discharged on the eighth postoperative day. Radiation therapy (50Gy/25Fr) was started three months later. A chest CT taken 9 months postoperatively did not reveal any metastasis. **Conclusion:** We here present a remarkable case of Type A thymoma extending into the pericardium and causing cardiac tamponade that was successfully resected after evacuating a hemorrhagic pericardial effusion.

Keywords: Type A thymoma, Pericardial tamponade

EP1.15-24 VIDEO-ASSISTED THORACOSCOPY APPROACH FOR RADICAL THYMOMA RESECTION

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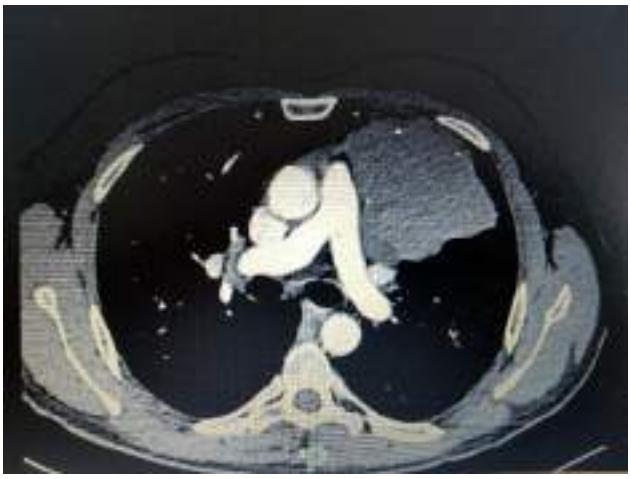
Background: Thymoma is the most common neoplasm of the anterior mediastinum, accounting for 20-25% of all mediastinal tumors and 50% of anterior mediastinal masses. the mean age of patients is 52 years. No sexual predilection. The main treatment is complete surgical resection. Minimally invasive thymectomy (MIT) for thymic tumors remains good opcion in both early and advanced stages, minimizing surgical trauma, improving post-operative course and recovery and pain redusing. **Method:** The aim of this study was to review our experience with VATS surgery for thymoma radical and extended resection. We reviewed data from all MIT cases from December 2009 to February 2019. Patients data was collected regarding demography, perioperative management and clinical outcomes. **Result:** A total of 16 VATS thymectomies were performed in the last 10 years, from December 2009 to February 2019. The median age was 52 years (range: 27 – 83 years) with fimale to male ratio of 1/,1,3.The main pathologic diagnosis was Thymoma and Thymic carcinoma (13%) with 5 % associated with myasthenia gravis (MG). The mean tumor size was 4,09 cm (range: 3 to 11 cm). Figure 1.CT- scan image showing a 11 cm giant anterior mediastinal Thymoma, successfully resected by 2 portal VATS access of the left hemithorax.



Mean blood loss and operative time were significantly lower in the video-assisted thoracoscopic surgery versus open surgery.There was no 30-day mortality. Reoperation was not required. Lenght of hospital stay 3,5 days (range 2 -9 days). Mean follow up was 20 months, with no tumor recurrence. **Conclusion:** Unilateral and bilateral VATS approaches have demonstrated good long-term oncologic and neurologic results with low complication rates. Reduced blood loss, operative time and earlier hospital discharge.

Keywords: mediastinum, minimally invasive surgery, THYMOMA

EP1.15-25 A RARE CASE OF METASTATIC LEIOMYOMA OF THE LUNG

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Background: Leiomyoma is the most common benign uterine tumor. Atypically, it can show with metastatic disease. Lungs are the most frequent metastatic site. Although the benign, metastatic leiomyoma (MLM) has an indolent growth pattern and it may induce pulmonary symptoms and decrease the quality of life. **Method:** We present a case of a 63-year-old woman, former smoker with a past medical history of hysterectomy and bilateral salpingo-oophorectomy due to leiomyoma in 1994. In 2015, the patient showed with a dry cough, chest pain and no fever. Chest X-ray revealed multiple non-specific bilateral pulmonary nodules. Chest and total abdominal CT scans were performed for further evaluation, which confirmed multiple well-circumscribed bilateral pulmonary nodules measuring up to 26mm and 31mm in the right and left lung respectively. No other suspected neoplastic lesions were found. Afterward, she underwent a thoracoscopic resection and pathology determined the neoplastic proliferation of smooth cells favoring the diagnosis of MLM. Tumor markers, including CEA, CA 19.9, CA 125, CA 15.3 and AFP were regular. Patient's symptoms have improved, and she has started a clinical follow-up alternating chest X-ray with chest CT scan every six months. Four years later, lung nodules have increased, measuring up to 37mm (Figure 1). She underwent a lung CT scan-guided biopsy and final pathology showed mesenchymal neoplasia of smooth muscle cells, with a proliferation of spindle cells, with no atypia, absence of necrosis and mitoses. Positive immunohistochemical staining for desmin and smooth muscle actin positive with negative staining for CD34, S100 protein and DOG 1 (Figure 2). **Result:** She remains asymptomatic, and the medical oncology team decided to maintain clinical follow-up with a chest CT scan. Despite the increase of the lesion, the patient was asymptomatic and maintained a follow-up in our service. **Conclusion:** Although MLM is a rare condition, it should be considered in the differential diagnosis in women with a past medical history of uterine leiomyoma. Accurate histopathological and immunochemistry analysis are necessary for the final diagnosis. Due to the slow growth of pattern, most of the patients can be followed with no active specific treatment. There are few similar cases described in the literature and the is no standard treatment in this scenario. Further studies are warranted to evaluate the best treatment option for these patients.

Keywords: spindle cells, immunochemistry analysis, metastatic leiomyoma (MLM)

EP1.15-26 CARDIO MEDIASTINAL TUMORS - DIAGNOSIS AND TREATMENT IN TWO OF OUR CASES

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Background: Malignant cardiac tumors are very rare. Although they are clinically diagnosed and diagnoses very quickly ,but in some cases it is very difficult to diagnose or are diagnosed in the late stages. Objective: To analyze our rarly two cases for diagnosis and treatment in delayed diagnoses for cardiac primary tumor invadation in mediastinum and pericardium tumor wih myocardial and mediastinal invasion in the other case. The diagnosis is based on the clinical history, echocardiography in two cases, and, sometimes, computerized tomography and magnetic resonance imaging, FNAB and mediastinotomy . **Method:** In two cases the diagnosis is based on the clinical history, echocardiography in two cases, and, computerized tomography and magnetic resonance imaging, FNAB and mediastinotomy . **Result:** Patient A. 66 years old ,male patient the diagnosis was established with trans-thoracic biopsies of myosarcoma-derived mass, treated by oncologist and cardiologists.While patient B is a 45 year old female with a pericardiac tumor,with huge pericardial effusion and effusion in the sinister pleural cavity. Liquid cytology with malignant cells. Was performed left mediastinotomy, pericardiotomy ,biopsy of intrapericardial mass, pericardial window and drainage pleural sinister. Biopsy results in pericardial sarcomatous mesothelioma with myocardial and mediastinal invasion. Macroscopically hemorrhagic effusion in pericardial and left pleural cavities. Very large tumor and

quite intrapericardial hemorrhagic disease. **Conclusion:** Malignant cardiac tumors are very rare and early stage diagnosis and adequate treatment is difficult.

Keywords: Malignant cardiac tumor ,pericardial effusion ,pleural effusion.

EP1.15-27 ONE CASE OF MUCINOUS CARCINOMA OF THYMUS CAUSED BONE MARROW METASTASIS

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Background: Primary mucinous adenocarcinoma of the thymus is extremely rare neoplasm. Most thymic carcinomas metastasize to the mediastinal lymph node, pleura, pericardium and diaphragm. And distant metastasis to the extrathoracic organs such as liver, bone or kidney is considered rare. In this case, mucinous carcinoma of the thymus caused bone marrow metastasis and multiple bone metastasis is very rare. **Method:** Case report **Result:** A 51-year-old man. He was pointed out fecal occult blood test positive by medical checkup, and he was diagnosed the sigmoid colon cancer. After undergoing surgery for colon cancer, he was admitted to our hospital for treatment of mediastinal tumor. An anterior mediastinal tumor was pointed out by preoperative examinations. Computed tomography (CT) showed a tumor with maximum diameter of 55mm at the anterior mediastinam, including calcification and contrast effect and swollen lymph node. Thymoma or thymic cancer were suspected, so we surgical resection of mediastinal tumor and lymph node dissection were performed. Result of frozen section diagnosis was adenocarcinoma with mucinous component. Pathological findings showed that most of the tumor was a mucin component, and atypical cells with a small duct formed inside the mucin, signet ring cells were found. Immunohistochemistry, the neoplastic cells were positive for CK7 and CK20. Based on these features, diagnosis of this tumor was mucinous adenocarcinoma of thymus. Pathological stage was T2N1M0 stageIII. Two months after operation, radiation was performed at anterior mediastinum and one week after radiation compression fracture of lumbar vertebra was present. And five months after operation, pancytopenia was present. Examination of bone marrow aspiration biopsy was performed, and the cancer cells were detected. Bone marrow metastasis originated from thymic cancer was diagnosed as a result of comparing pathological features of the colon cancer and thymic cancer. Primary thymic adenocarcinoma is very rare and about 2.7% of all thymic carcinoma. Furthermore, only 16 cases have been reported and there have been no reported cases of thymic mucinous carcinoma caused bone marrow metastasis. **Conclusion:** In this paper, we report a very rare and valuable case with consideration of some literature review.

Keywords: Thymic carcinoma, mucinous adenocarcnioma, bone marrow metastasis

EP1.15-28 SURVIVAL OF THYMOMA IS EXTENSIVE IN LATIN-AMERICAN PATIENTS: RESULTS FROM OVER 10 YEARS OF EXPERIENCE (CLICAP-LATIMUS)

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Background: Thymomas are a group of rare neoplasm of the anterior mediastinum. Due to their low incidence, large cooperative studies are required to evaluate outcomes. The objective of this study is to present the results and experience in treatment of this pathology in Latin-America. **Method:** A retrospective multicenter cohort study was conducted by The Latin-American Consortium for the Investigation of Lung Cancer (CLICaP). Patients with histologically proven thymomas between 1997 and 2018 were included in the analysis. Variables including clinical, pathological and therapeutic outcomes were registered in a centralized manner. **Result:** A total of 105 patients were included. Median age at diagnosis was 54 years old (20-84), and with 60% (n = 38) of the included patients were female. Only 11% (n=7) of the patients had an ECOG performance score >1. Twenty-four patients (22.9%, 95%CI 14.8-30.9) presented with pulmonary or distant metastatic involvement with a median of 2 metastatic sites. Furthermore, 21.9 % of patients (n=23, 95%CI 13.9-29.8%) concurrently presented myasthenia gravis. Surgery was performed in 55 patients (52.3%, 95%CI 42.8 – 61.9%), comprising of 15 tumorectomies, 37 thymectomies and 5 biopsies achieving an R0 resection rate of 78% (95%CI 67.3-89.1%). Adjuvant treatment in the form of either chemotherapy, radiotherapy or both was offered to 3(5%), 7(12.7%) and 5(9%) patients, respectively. Disease progression was documented in 10 cases (9%, 95%CI3.9-15.1%) of which 6 (60%) were locoregional, 1 (10%) distant progression and 3 (30%) both locoregional and distant. Median overall survival (OS) was estimated at around 139.5 months (95%CI 86.1-NA). Cox regression indicated that OS was significantly improved by resection (139.5 vs 25.7 months, HR 4.17 [95%CI 12.6-17.8 months]). **Conclusion:** Survival in patients with thymomas continues to be very favorable, especially in patients who receive adequate local control. The benefit of adjuvant treatment in this setting remains unclear.

Keywords: THYMOMA

EP1.15-29 REAL WORLD CHARACTERIZATION AND TREATMENT OF PATIENTS WITH THYMIC CARCINOMA: LESSONS FROM A LATIN-AMERICAN STUDY (CLICAP-LATIMUS)

L. Mas[1], A. Patané[2], O.G. Arrieta[3], T. Soria[4], A.F. Cardona[5,6,7], C. Martin[8], A. Ruiz-Patiño[9], L.L. Rojas[9,10], R. Ruiz[1], P. Rioja[11], S. Lozano[11], Z.L. Zatarain Barrón[3], M. Corassa[12], H. Freitas[13], V. Cordeiro De Lima[13], L. Corrales[14], C. Sotelo[9], J. Rodriguez[9], L. Ricaurte[9], J. Ávila[9], M. Bravo[9], D. Mayorga[9], P. Archila[9], J. Otero[6,7,9], H. Carranza[9], C. Vargas[6,7,9], R. Rosell[15,16], J. Remon[17]

[1]*National Cancer Institute Peru, Lima/Peru,* [2]*Hospital de Rehabilitación Respiratoria María Ferrer /Instituto Médico Alexander Fleming, Buenos Aires/Argentina,* [3]*Instituto Nacional de Cancerologia, Mexico City/Mexico,* [4]*Oncology Department, Hospital Oncológico SOLCA, Quito/Ecuador,* [5]*FICMAC- Fundación para la Investigación Clínica y Molecular Aplicada al Cáncer, Bogotá/Colombia,* [6]*Clínica del Country, Bogotá/Colombia,* [7]*Molecular Oncology and Biology Systems Research Group (FOX-G), Universidad el Bosque, Bogota/Colombia,* [8]*Instituto Alexander Fleming, Buenos Aires/Argentina,* [9]*Fundación para la Investigación Clínica y Molecular Aplicada del Cáncer-FICMAC, Bogota/Colombia,* [10]*Oncology Department, Clinica Colsanitas, Bogota/Colombia,* [11]*Instituto Nacional de Enfermedades Neoplasicas, Lima/Peru,* [12]*Hospital AC Camargo, Sao Pablo/Brazil,* [13]*AC Camargo Cancer Center, Sao Paulo/Brazil,* [14]*Hospital San Juan de Dios, San José/Costa Rica,* [15]*Germans Trias i Pujol Science Inst., Catalan Institute of Oncology (ICO Badalona), Barcelona/Spain,* [16]*Dr Rosell Oncology Institute. Dexeus University Hospital, barcelona/Spain,* [17]*Hospital Vall d´Hebron, Barcelona/Spain*

Background: Thymic carcinoma is a rare tumor that represents a clinical challenge, especially in resource limited settings. The objective of the present study was to characterize patients who presented this disease in Latin-America. **Method:** From 2014 until 2018, a multinational Latin-American cooperative retrospective cohort study was performed. Patients with histologically confirmed thymic carcinoma were included. Clinical, pathological and treatment variables were collected across 7 participating nations. **Result:** A total of 31 patients were included. Median age at diagnosis was 58 years old (34-69), 48% (n=15) of individuals were women with all but 2 patients (6.5%) achieving an ECOG performance score <2. All patients debuted with Stage IV disease; 24 patients (66%, [95%CI 62-92%]) as stage IVa and 7 as stage IVb (33%, [95%CI 7-37%]) with a median LDH level of 396.5 U/L (153-1529 U/L) and a median of 2 metastatic sites. 13 (41.9%, [95%CI 25-59%]) patients received preoperatory treatment consisting of chemotherapy (n=8, 42%) and chemoradiotherapy (n=5, 16%). Among these patients only 4 (12.9%) were subjected to surgery, two of which underwent a tumorectomy

and 2 a thymectomy. 28 (90%, [95%CI 79.9-100%]) received palliative chemotherapy either with sunitinib (n=7, 25%) or cytotoxic agents. Median overall survival (OS) was reached at 20.2 months (95%CI 19-NA months). Patients who received preoperative treatment had a significantly prolonged OS (17.6 vs 26 months, HR 2.93 [95%CI 1.04-8.27 months], p = 0.03). **Conclusion:** Thymic carcinoma constitutes an aggressive disease that is often diagnosed in advanced stages. These results suggest that multimodal treatment can be beneficial even in locally advanced cases. Larger clinical trial validating these conclusions are warranted.

Keywords: thymic sarcoma, Real world data, Latin America

EP1.15-30 RESECTION ANASTOMOSIS OF MALIGNANT TUMORS OF THE TRACHEA

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Background: Primary malignant tracheal tumors is a rare entity, making only 0.2% of all respiratory tract tumors. Due to their insidious development, their clinical symptom is often late, after a significant reduction of tracheal diameter, which delays the diagnosis that is often misdiagnosed for late asthma. The dominant histological type is adenoid cystic tumor. Wide tracheal resection allowing the release of airways, is the treatment of reference. **Method:** This work is a retrospective study of a series of 7 patients admitted for tracheal stenosis at the department of thoracic surgery of the University Hospital Hassan II of Fes, for a total of 7 years from December 2010 to December 2017. **Result:** There were 6 men and 1 woman, with a mean age of 43 years, 3 of whom were smokers. Dyspnea was the main symtom. All patients received thoracic CT. 6 cases underwent bronchial fibroscopy, the most frequent appearance of which was a tumoral process in 4 patients, most often in the middle part of the trachea in 3 patients, obstructing tracheal diameter almost all in 6 patients. Treatment was surgical with intubation across the operative field in all patients, including 3 resection anastomosis and 4 plasty (V-plasty lateral resection, Kergin-type plasty, Mattey-type tracheobronchial anastomosis, and a V-resection enlarged to carena). The most common histological type was adenoid cystic carcinoma in 2 patients, squamous cell carcinoma in 2 patients, adenocarcinoma in 1 patient, and atypical carcinoid-type neuroendocrine tumor in 1 patient. 2 patients received adjuvant treatment. The follow-up was simple in 6 of our patients who all had postoperative fibroscopy within 9 days on average (8 to 16 days), two deaths, one post-operative death unrelated to tracheal surgery on D4, and a second follow-up to complications of post-radiation tracheal stenosis. The average follow up is 32 months. There was one death at 8 months following post-radiation tracheal stenosis and distant relapse by cervical lymph node metastasis in one patient at 5 years after surgery. He benefited from cervical lymph node dissection + Radiotherapy. He is still alive with controlled disease. **Conclusion:** Despite advances in tracheal surgery, primary malignant tracheal tumors still have an unfavorable prognosis. Endoscopic or radiation disobstruction is a therapeutic alternative for nonoperable tumors.

Keywords: resection-anastomosis; trachea; malignant tumor

EP1.16 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH

EP1.16-01 A SPANISH INITIATIVE TO KNOW THE UNMET NEEDS OF WOMEN WITH LUNG CANCER: "CIRCULOS PROGRAM"

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Background: The personal and family impact of an oncological disease can only be adequately understood and managed from a biopsychosocial perspective. Lung cancer experience has a profound impact on the well-being of both patient and family caregiver and is largely influenced by communication within the family environment. Lung cancer impact can be especially significant when women are affected. **Method:** The objective of this study was to develop an informative program for women with lung cancer, implementing the development of strategies in order to get a deepening knowledge of their perceived needs. Additionally, we aimed to define and design new useful resources that may help other women with lung cancer. A qualitative research allowed to collect data on the experiences in the circle of women and their families, and the identification of the needs and the coping resources used of the participants. The collection of these data was what led to the development of the tools used to develop the support strategies. **Result:** A total of 10 women with lung cancer from Galicia (Spain) participated in 7 sessions. At the personal and psychological level in the women circle, needs were related to improve medical information they get from their physicians, share information and experiences with women in the same situation, more holistic-human care, and the need for more supporting groups. About the social and labor environment, they expressed concern about the social stigma associated with lung cancer, and the culpability for having smoked as well as the concern related to the interruption of working life. The family environment also expressed the need for emotional support and preparation for families and caregivers to be able to support the patient, the need to provide them with strategies to improve the situation, and the need to overcome initial isolation through working groups. Regarding resources, women´s circle was mainly focused on occupying time with new activities, humor and not stigmatizing the disease and the professionals who assist them. **Conclusion:** "Círculos program", even being a pilot program, show the benefits of a more humane approach to the treatment of lung cancer in women, with a better understanding of patients and families needs. More similar programs should be done in order to improve the quality of life of these patients and their transit through this disease.

Keywords: lung cancer, women, unmet needs

EP1.16-02 PROACTIVELY IMPROVING THE MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (IRAES) IN A COMMUNITY CANCER PROGRAM

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Background: As more patients with lung cancer are being treated with immune checkpoint inhibitor (ICI) therapy in community settings, there is a pressing need to properly identify and manage immune-related adverse events (irAEs). Promptly and correctly identifying and managing irAEs can be challenging since clinicians may lack knowledge about irAEs. Furthermore, patients may not know when to report symptoms. For these reasons, an educational research project supported by a grant from Genentech was developed to assess how cancer clinicians may improve the identification and management of irAEs. **Method:** The cancer care team at St. Joseph Hospital Orange (SJO) reviewed 30 patient charts (9 lung cancer, 21 other types of cancers) in early 2018 and assessed the documentation of different types of irAEs, the grading of symptom severity, and how often irAEs led to a visit to an urgent care, ER, or inpatient hospital visit. 37% of patients developed a suspected irAE; the severity of symptoms was documented in 57% of charts; 27% of patients developed irAEs that required care in an ER or hospital. In July 2018, members of the cancer care team held a workshop to discuss their findings and identify opportunities to improve the identification and management of irAEs. Using Plan-Do-Study-Act (PDSA) cycles for improvement, the team at SJO developed and implemented the following process changes: 1) a patient education video explaining irAEs (made in English and Spanish) that is delivered by infusion nurses when patients start ICI therapy; 2) continued use of immunotherapy wallet cards for patients; 3) improving awareness among infusion nurses about irAEs; 4) updates to survivorship care plans to highlight how delayed irAEs may occur after active cancer treatment is completed. **Result:** The project remains ongoing at the time of abstract submission. The patient education video was approved by the oncology council and launched in Jan 2019. The infusion nurses report that patients who watch the video are highly engaged and asking questions about irAEs. Changes to the survivorship care plans were finalized at the end of 2018 and were focused on patients receiving ICI therapy for curative intent (eg,

adjuvant melanoma and lung cancer). **Conclusion:** Since serious irAEs may occur at any time, a proactive approach is required to improve the identification and management of irAEs and ensure optimal patient outcomes. This project demonstrates how one community cancer center developed feasible interventions based on identified needs.

Keywords: Side Effect managment, Immunotherapy

EP1.16-03 TRIAL OF COST-EFFECTIVENESS ANALYSIS OF LUNG CANCER SURGERY-ANALYSIS IN STAGE IIIA LUNG CANCER

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Background: Currently, lung cancer treatment is being treated according to lung cancer treatment guidelines. Most of the guidelines so far have been prepared after studies using the EBM method have been made about treatment effects and disadvantages. On the other hand, recent clinical research has come to examine the QOL of patients and the cost-effectiveness of treatment in chemotherapy, but there has not been any report on the cost-effectiveness of surgical treatment for cancer. We examined the cost-effectiveness of surgical treatment for lung cancer. **Method:** Based on the results of lung cancer treatment at home and abroad, survival time was extracted for each stage, and from this group, surgery was performed at stage IIIA (+ S group) and not performed (-S group) Group data were used. Expenses used domestic data with reference to treatment costs in the United States. Chemotherapy was based on commonly used medications for non-small cell lung cancer. Decision analysis was used for cost-benefit analysis, and effects were calculated from survival rate and quality-adjusted survival year (QALY) using the incremental cost-effectiveness ratio (ICER) as an index. **Result:** If QALY after 5 years is calculated using the life-or-death only QOL score, the ICER of +S group is approximately 5.64 million yen, and the cost-effectiveness is generally superior. If QALY is obtained from the survival curve, the ICER of +S group after 1 year is 4.97 million yen, and the cost utility analysis is even better. **Conclusion:** In this study, performing surgery on patients with stage IIIA lung cancer was also useful in terms of cost-effectiveness. In the future, it is necessary to analyze the cost-benefit analysis of the QALY and the new treatment cost due to deterioration of QOL at relapse and relapse by long-term simulation using Markov model.

Keywords: surgery, cost-effectiveness analysis, Stage IIIA lung cancer

EP1.16-04 REAL WORLD CLINICAL OUTCOMES FOR METASTATIC NON-SMALL CELL LUNG CANCER (MNSCLC) AT IRST ITALY

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Background: This study sought to evaluate the real word clinical outcomes concerning overall survival (OS) for patients in first-line treatment for metastatic non-small cell lung cancer (mNSCLC) prior to the availability of immunotherapies in any line. **Method:** Patients who received systemic anti-cancer treatment for mNSCLC at IRST between Jan2014-Jun2017 with a minimum follow-up of six months were included. The clinical dataset was obtained from data registered in electronic health records maintained during clinical practice. OS was defined as the interval from start of first-line therapy until death or follow-up end, whichever occurred first. Death information was detected from mortality register. OS was estimated using the Kaplan-Meier method stratified by type of first-line treatment. **Result:** Among the 428 first-line patients analyzed, 64.5% were over 65 years old and 62.6% were men (Table 1). A total of 79.0% patients had non-squamous histology whereas 15.0% had squamous histology, with the remaining 6% other histologies. EGFR mutation was detected in 15.7% and ALK translocation in 8.4% of patients. In the first-line the majority (57.0%) of patients received platinum-doublet (mainly platinum+pemetrexed) while single agent chemotherapy was administered in 23.8%, whereas 10.0% received targeted therapy. Conversely overall 9.0% were enrolled in clinical trials, while 0.2% received Immunotherapies. Median OS was 19.9 months (95%CI:9.2-21.7) with targeted therapy, 8.5 months (95%CI:4.8-13.6) for patients enrolled in clinical trials, 6.4 months (95%CI:5.8-7.6) with platinum-doublet and 4.4 months (95%CI:3.7-5.7) with single agent chemotherapy. A total of 34.5% of first-line patients continued to receive second-line treatment.

Table 1. Patient characteristics and real-world overall survival by type of first-line treatment for metastatic NSCLC, Jan 2014 to June 2017, IRST-Italy

Characteristics	Overall N=428	Platinum doublet N=244	Single agent chemo N=102	Targeted therapy N=43	Immuno therapy N=1	Clinical trial N=38
Age >65 years	276 (64.5)	121 (49.6)	99 (97.1)	33 (76.7)	1 (100.0)	22 (57.9)
Men	268 (62.6)	155 (63.5)	75 (73.5)	14 (32.6)	0 (0.0)	24 (63.2)
Current/former smoker	310 (72.4)	188 (77.0)	69 (67.6)	21 (56.8)	1 (100.0)	31 (81.6)
Squamous histology	63 (15.0)	37 (15.6)	19 (18.8)	1 (2.3)	0 (0.0)	6 (15.8)
Stage IV at diagnosis	335 (78.5)	189 (77.8)	75 (73.5)	38 (88.4)	0 (0.0)	33 (86.8)
ECOG PS ≥2	70 (17.3)	30 (12.7)	28 (29.8)	12 (30.8)	0 (0.0)	0 (0.0)
EGFR mutant*	51 (15.7)	2 (1.0)	1 (0.9)	38 (88.4)	0 (0.0)	10 (28.6)
ALK translocated*	21 (8.4)	10 (4.1)	5 (10.9)	3 (8.6)	0 (0.0)	3 (9.7)
Real world overall survival #						
Median (95% CI)	6.4 (5.8-7.5)	6.4 (5.8-7.6)	4.4 (3.7-5.7)	19.9 (9.2-21.7)	-	8.5 (4.8-13.6)
6 months rate (95% CI)	52.1 (47.2-56.7)	53.6 (47.2-59.7)	36.6 (27.1-45.5)	74.4 (58.6-84.9)	-	60.5 (43.3-74.0)

*Done only for 358 patients with not squamous histology
Data cutoff: Dec 2017

Conclusion: In this analysis prior to the introduction of immunotherapies for NSCLC, OS was similar to real world OS in the published literature. The survival was worse in the single agent chemotherapy group while it is superior in platinum doublets group. Overall survival was longest in patients treated with targeted therapy.

Keywords: treatment pattern, real-world study, Outcomes

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EP1.16-05 REAL WORLD OUTCOMES OF ADVANCED NSCLC PATIENTS WITH LIVER METASTASES

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Background: Patients with advanced lung cancer represent a heterogenous population with varying patterns of metastasis. Those with liver metastases may represent a unique cohort with differential response to therapy, including immunotherapy in NSCLC. Novel Natural Language Processing (NLP) and Artificial Intelligence (AI) technology enables automated extraction of real-world data to examine these populations at greater scale than current manual chart abstraction processes, helping clinicians make more informed treatment decisions. **Method:** Patients diagnosed with stage IIIB/IV lung cancer who received first-line systemic therapy at the Princess Margaret Cancer Centre between 2015 and 2018 were reviewed using the DARWEN™ NLP and AI data abstraction platform developed by Pentavere. Data extracted include tumour histology, patient age, sex, ECOG performance status, smoking status, biomarker status, PD-L1 expression, sites of metastases, treatment details and survival. **Result:** Of 615 patients with accessible electronic pathology records, 540 (87.8%) had NSCLC and 333 (54.1%) received systemic therapy. In those patients treated with first-line therapy (immunotherapy 10.2%, targeted therapy 30.9%, chemotherapy 62.7%), 27.3% (91/333) had liver metastasis at any point from baseline to end of follow up (median follow up 8 months). 280 patients had NSCLC and received systemic therapy and were included in subsequent analysis. Of these, 69 (24.6%) had liver metastases at any point and overall survival was worse in those patients 544 vs 715 days (p=0.006). Liver metastases were more commonly seen in those with more metastatic sites (OR: 1.42, 95% CI: 1.19-1.70, p= < 0.001). By contrast, those with *EGFR* mutant lung cancer were less likely to develop liver metastasis (OR: 0.45, 95% CI: 0.23-0.87, p=0.02). Using Cox regression analyses, after controlling for age, sex, baseline performance status, baseline smoking status, first line treatment, total number of metastatic sites and baseline LDH, presence of liver metastasis remained significantly associated with worse survival (HR: 1.78, 95% CI: 1.14-2.76, p=0.01). Elevated baseline LDH, a known poor prognostic factor, was also associated with worse overall survival (HR: 1.58, 95% CI: 10.6-2.35), p=0.02). No differential effect by type of therapy was seen. **Conclusion:** The presence of liver metastases confers worse prognosis in advanced non-small cell lung cancer patients. This effect was observed irrespective of treatment type and highlights the need for additional treatment options which are efficacious in this patient population. Larger cohort studies may help identify patients with liver metastases that may benefit from specific therapeutic strategies in the future. NLP and AI technologies like DARWEN™ can rapidly generate population-based datasets and provide clinicians with timely access to previously unavailable information on treatment patterns and outcomes which can lead to improved care.

Keywords: Real world evidence, AI, Liver metastasis

EP1.16-06 REAL WORLD DIAGNOSIS AND TREATMENT OUTCOMES IN PATIENTS WITH EGFR-MUTANT METASTATIC LUNG CANCER

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Background: We recently showed that lung cancer incidence and mortality rates have steadily decreased in California between 1990 and 2014. Improvements in overall and yearly survivals were most pronounced for Asian and female patients, and for patients with adenocarcinoma after 2004, when molecularly targeted therapy was introduced (Pan et al., ASCO 2018). The objective of this study was to determine the impact of molecular diagnosis and targeted therapy on survival by time interval, gender, race/ethnicity, and smoking status in patients with EGFR-mutant metastatic lung cancer. **Method:** This retrospective study included consecutive cases from patients with locally advanced or metastatic EGFR-mutant NSCLC seen at an academic clinic between 2009 and January 2018 with follow up through February 2019. Allele-specific PCR was used before 2014 (Cohort 1, N=94)) and FoundationOne® was used after 2014 (Cohort 2, N=101). Kaplan-Meier curves were estimated for overall survival and stratified by smoking status, gender, and race/ethnicity. Relative survival rates were calculated for 1 year, 2 years and 5 years. **Result:** A total of 83 and 88 patients with metastatic lung cancer who received ≥1 EGFR TKI were identified in Cohort 1 and 2, respectively. Table below summarizes demographic characteristics, median overall, 1-year, 2-year and 5-year survivals for each cohort. Relative to cohort 1, all cohort 2 subgroups saw improvements in survival. Improvement was most pronounced for never smoker, female, asian and white patients. Survival rates among both cohorts were significantly higher than that of all patients in California during the same periods.

EGFR TKI-Treated Patients	Cohort 1 (N=83)	Cohort 2 (N=88)	HR (95% CI)
Age (mean ± SD) (years)	58.7 ± 11.7	67.2 ± 14.3	
Median Overall Survival (months)	33.5	45.3	0.6 (0.39-0.80)
1-year survival rate (%)	91.5%	93.9%	
2-year survival rate (%)	64.3%	79.5%	
5-year survival rate (%)	16.1%	43.2%	
Never smoker: No. Patient (%)	52 (62.7%)	54 (61.4%)	
Median survival (months)	32.5	60.2	0.4 (0.27-0.71)
Female: No. Patient (%)	51 (61%)	54 (61%)	
Median survival (months)	31.6	78.8	0.4 (0.27-0.71)
Male: No. Patient (%)	32 (39%)	34 (39%)	
Median survival (months)	31.6	78.8	0.8 (0.27-1.39)
White: No. Patient (%)	59 (71.1%)	52 (59.1%)	
Median survival (months)	37.9	45.3	0.55 (0.35-0.87)
Asian: No. Patient (%)	21 (25.3%)	26 (29.5%)	
Median survival (months)	34.4	80.0	0.50 (0.22-1.06)

Conclusion: Advances in the diagnosis and treatment for patients with EGFR-mutant lung cancer have increased patient survival times. Further study is needed to determine the causes of gender and ethnicity differences.

Keywords: Survival, EGFR-mutant lung cancer, treatment outcome

EP1.16-07 NATIONAL, OBSERVATIONAL, MULTICENTRIC STUDY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS IN TURKEY: STONE TRIAL

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Background: In this national, non-interventional study, our aim is to collect stage III non-small cell lung cancer (NSCLC) data derived from medical records in nationwide to capture and consolidate information of treatment patterns, treatment effectiveness and patient outcomes in the real-world setting. This study was carried out with the collaboration of Turkish Society for Radiation Oncology. **Method:** Patients newly diagnosed with primary stage III NSCLC between 01 January 2013 and 31 December 2017 included. A total of 556 patients from 10 hospitals in Turkey were included in this study. Patient characteristics, initial treatment modalities, chemotherapy regimens, overall (OS) and local progression free survival (LPFS), failure patterns and secondary treatments after recurrence for recurrent patients were analyzed. **Result:** Median age was 63 years (range, 56-69 years). 488 patients (%87.8) were male and 68 patients (%12.2) were female. Histopathological type was adenocarcinoma in 197 patients (%35.4), squamous cell carcinoma in 291 patients (%52.3) and others (Large Cell Carcinoma, mixed and unknown) in 68 patients (%12.3). 385 patients (%69.2) received definitive/curative therapy, 23 patients (%4.1) received palliative, 33 patients (%5.9) received adjuvant and 63 patients (%11.3) received neoadjuvant oncological treatment. 54.8% of patients received concomitant chemoradiotherapy, 22.1% of patients received concomitant chemoradiotherapy+ adjuvant chemotherapy, 12.2% of patients received only radiotherapy and, 10.8% of patients received sequential chemotherapy followed by radiotherapy. 75 patients (13.4%) underwent curative resection as primary treatment and, 33 (5.9%) of them received adjuvant chemoradiotherapy and/or radiotherapy. The 2- and 3-year of OS were 57%, and %43, respectively. 2- and 3-year of PFS were %38 and %25, respectively. **Conclusion:** To our best knowledge, this is the first national study representing valuable information about real-life data in stage III NSCLC population in Turkey.

Keywords: national study, Non-Small Cell Lung Cancer, Real world data

EP1.16-08 BEHOBIAMEDIOPULMON: PUTTING FACE AND RUNNING SHOES ON PATIENTS WITH LUNG CANCER

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Background: As lung cancer is one of the most lethal in Europe, it has little presence in the media and social networks. To change this dynamic, a campaign to support lung cancer patients using the hashtag #behobiamediopulmon was planned, where the final event was the participation of patients with lung cancer in the most famous half-marathon in Spain: Behobia-San Sebastián. **Method:** Joining forces between the Spanish Association of Lung Cancer Victims (AEACAP), the organization of the Behobia-San Sebastian and the local government of Gipuzkoa; And with the support of the main scientific societies that treat this pathology (SECT: Spanish Society of Thoracic Surgery, SEPAR: Spanish Society of Pneumology and Thoracic Surgery, SEOM: Spanish Society of Medical Oncology and SEOR: Spanish Society of Radiation Theraphy), it was decided to carry out a campaign of visibility of lung cancer patients. **Result:** During 2018 different actions were carried out: solidary running training (300 participants), children´s race (180 children), charity market, online sale of shirts, creation of a specific song (the protagonists of the videoclip were four patients), production of a documentary-film about lung cancer (presented at a round table with the participation of the daughter of Johan Cruyff). Broadcast of the videoclip in the football matches that Real Sociedad and SD Eibar played at home until the day of the race. In the Behobia-San Sebastian, 3 patients operated on for lung cancer at Donostia Universitary Hospital runned accompanied by 300 people (among them stand out soccer players like Xabi Prieto and Xabi Alonso; musicians of La Oreja de Van Gogh, the journalist Juan-Ramon Lucas or Susila Cruyff). Impact achieved: 3 different national newscast spoke about #behobiamediopulmon, 10 times in regional newscast, 18 radio interviews and 14 newspaper interviews. In YouTube 800,000 reproductions of the song “Sólo si lo hacemos juntos”, 1300 reproductions of the documentary-film #datupaso, Instagram profile (@behobiamediopulmon) with 1000 followers, Prize to the charitable cause with the highest collection in the Behobia-San Sebastian 5000€, solidarity training fund 6600€. **Conclusion:** By joining forces it is possible to perform an action that provides visibility to patients with lung cancer. Joining sport and health, we are able to create a very positive message that reaches to the newly diagnosticated patients, inspiring confidence and life expectancy. The race represents the metaphor of their situation, where patients try to reach the goal, with their ups and downs along the way, accompanied by family, friends and health personnel.

Keywords: patients care, Lung cancer, survivorship

EP1.16-09 DELAYS IN CARE OF LUNG CANCER: A MOROCCAN PUBLIC HEALTH PROBLEM

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Background: For several years, lung cancer, which is responsible for one in five cancer deaths, has been considered the leading cause of cancer death. In Morocco, in 2018, 6488 new cases of lung cancer were reported for both sexes and all ages with 22,9% of all new cases of male cancer (Globocan) It’s a real public health problem The delay between the different therapeutic sequences has a real impact on survival, which makes it’s optimization a real public health issue. The aim of this work was to describe the care pathway for patients treated for lung cancer at the Mohamed VI Center, as well as the different treatment delays in our context. **Method:** To do this, we conducted a monocentric, retrospective study in patients treated for lung cancer between January 2012 and November 2017 at the Mohamed VI Cancer treatment Center. To study this period and obtain significant results, we referred to the statistical rules and retained one month pey year, one year out of two, for a total of six months spread between January 2012 and November 2017 Using the oncology department’s database, we identified all patients with histologically confirmed lung cancer and a usable archived record that was summarized in a farm with pre-established responses coded as numerical variables. The key point of this study was the study of the time between the appearance of the first clinical signs and the initiation of the different therapeutic sequences discussed in a multidisciplinary meeting. **Result:** During the study period, 125 cases of lung cancer were collected. The average age was 57,6 years The average consult time also called patient time was 3.92 months. As for the delays related to the health system there are:An average diagnostic time of 63,5 days A therapeutic delay of 67,9 days on average An average overall delay of 216,3 days The time to diagnosis was therefore close to that recommended by the littérature, while the consultation, treatment and overall time to diagnosis were longer which significantly affects the survival curve **Conclusion:** In several countries, delays in care and access to care services, considered as indicators of system performance, have become a priority in public health policies. The establishment of more specialized oncology and radiation oncology centers should help to reduce them A subsequent reassessment of these delays, after correction, will male it possible to assess the evolution of the quality of the managementof this cancet at the Mohamed VI center

Keywords: Lung cancer, delays, access to care

EP1.16-10 DIFFERENTIATION OF PERFORMANCE STATUS AFTER TUMOR DEBULKING IN MALIGNANT CENTRAL AIRWAY TUMOR VIA RIGID BRONCHOSCOPY

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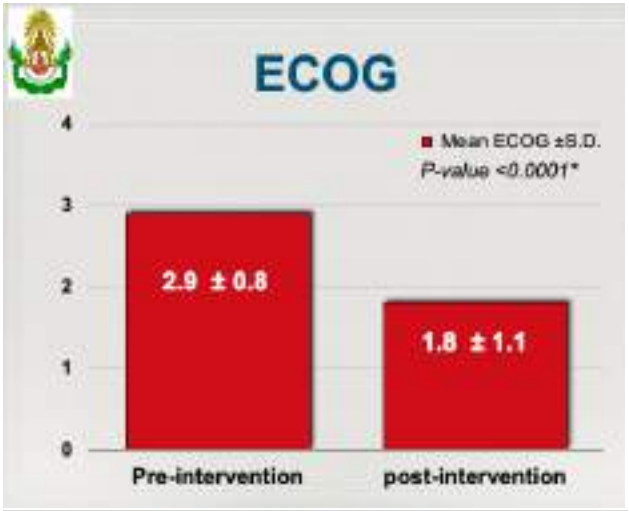
Background: Bronchogenic carcinoma patients havebeen suffered from cancer and its complications. The aim of cancer treatment is for prolonged survival and symptomatic control. Novel multimodality treatment can be relieving symptoms and improve patients' performance status (PS). Malignant central airway obstruction is the most harmful complication that increases morbidity, mortality and decreases PS. Rigid bronchoscopy with tumor resection plays pivotal roles for resolve these problems **Method:** Retrospective Observational study enrolled cancer patients who had beensuffered from malignant central airway obstruction that undergo Rigid bronchoscopy with tumor debulking in Phramongkutklao Hospital during January 2014 – October 2018 **Result:** 64 cancer patients were included in this study. 37(60.7%) were older than sixty. 36 (59%) were male and 38 (62.3%)had primary lung cancer in origin. 30 (49.2%)had left main bronchial obstruction 24(39.3%) had right main bronchial obstruction and 15(24.6%) had thetracheal obstruction. Most of patients 43(70.5%) had intraluminal obstruction and degree of obstruction were grade 4 39(63.9%). Pre-intervention ECOG 2-4 group were 23(37.7%), 24(39.3%) and 14(23%) respectively. Mean pre- intervention ECOG was 2.9±0.8 After rigid bronchoscopy with tumor debulking mean ECOG was decreased to 1.8 ±1.0. 46 of 64 (90.2%) had clinical improvement after successful procedure. 37 (72.5%) had 6-month survival and 33(64.7%) had 1-year survival after successful procedure, compared with 2(20%) and 1(10%) in unsuccessful procedure. 43(95.6%) had opportunity to received other treatment such as chemotherapy, targeted therapy, etc. after ECOG status was improve



Conclusion: Rigid bronchoscopy with tumor debulking improves performance status, increases survival and increases opportunity for other new multimodality treatment in cancer patients who had malignant central airway obstruction.

Keywords: Malignant central airway obstruction, tumor debulking, ECOG

EP1.16-11 IMMUNOTHERAPY IN NSCLC: REAL WORLD EXPERIENCE IN A PERUVIAN POPULATION

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Background: Checkpoint inhibitors drugs, have achieved positive results above chemotherapy in 2nd line and 1st line for specific populations with lung cancer. Nowadays, investigations continue studying biomarkers which could be useful as predictive factors of response as if inflammatory markers might have some role. **Method:** The study design included patients with non-small cell lung cancer (NSCLC) that receivedimmunotherapy with "Pembrolizumab" or "Nivolumab" in two private cancer centers of reference since January 2015 until January 2018. The adverse effects were evaluated by medical oncologists and classified by CTCAE v 4.0. The response were assessed by RECIST criteria. Furthermore, inflammatory markers results were obtained from blood work performed before immunotherapy started. All patients that received at least one dose of immunotherapy were taken into analysis. **Result:** A total of 158 patients with lung cancer were diagnosed in that period, only 18 patients were assessed, the mean age was 62, and the vast majority had adenocarcinoma. The mean number of cycles was 27 (2-52). The ORR was of 28%, 80% had partial response (PR) and 20% had complete response (CR). Thirty-nine percen had stable disease (SD) while 33% had progressive disease (PD). The median of time to achieve a response was of 11.5 weeks. The response according to the PD-L1 expression was stratified, founding clinical benefit in all the groups. The time to progression since immunotherapy was 15weeks. One case was reported as unconfirmed progressive disease by week 10. Markers of inflammation analyzed showed Neutrophil-lymphocyte rate (NLR) and Platelet-lymphocyte rate (PLR) means were 4.37 (1.42 – 21.6) and 270.19 (93.1-650.7)respectively. The values obtained according to response found that the group that progressed to therapy had 4.23 NLR and 343.9 PLR. The group who had clinical benefit, had 4.39 NLR and 229.9 PLR. 33% of the population present toxicity, from which 83% was graded G1-2 and 17% G3-4. **Conclusion:** A high PLR might be associated with an unfavorable prognosis although more studies are needed. This is the first study in Peruvian population that shows results of immunotherapy in lung cancer.

Keywords: Inmunotherapy, NSCLC, Markers of inflammation

EP1.16-12 RIGHT VS LEFT LUNG CANCER – PROGNOSTIC IMPLICATIONS

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Background: Lung cancer is one of the leading causes of death in the developed world. In Ireland alone there are over 2,500 new cases of lung cancer every year. Several studies set to determine prognostic factors that may play a role in optimising the management of patients with lung cancer. One of the factors currently being studied is the location of lung cancer. The interest in this prognostic factor was partially due to the reported implications of tumour 'sidedness' in colon cancer. We conducted a retrospective study to assess if tumour 'sidedness' impacts overall survival in a population of Irish patients with non-small cell lung cancer. **Method:** In this study we selected patients with a diagnosis of non-small cell lung cancer (stage I – stage IV) who received systemic therapy at Sligo University Hospital between 2011-2018. The cut-off date for inclusion was the 1st of March 2019. The primary end point was overall survival. The study was reviewed by the ethics board of Sligo University Hospital who approved data collection and waived consent for this study. **Result:** A total of 76 patients were identified. Of them 41% (n=31) were females and 59% (n=45) were males. 70% (n=53) had a right-sided

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lung cancer and 30% (n=23) had a left-sided lung cancer. There were 3 patients with stage I disease, 13 patients with stage II disease, 26 patients with stage III disease and 34 patients with stage IV disease. Median overall survival for all stages was 19.0 ± 5.0 months (95% CI 9.2-28.8) for right lung cancers and 15.0 ± 7.4 months (95% CI 0.6-29.4) for left lung cancers. For stage III lung cancers median overall survival was 34.0 ± 6.7 months (95% CI 20.8-47.2) for right lung cancers and 13.0 ± 4.0 months (95% CI 5.2-20.8) for left lung cancers. For stage IV lung cancers the median overall survival was 12.0 ± 1.5 months (95% CI 9.0-15.0) for right lung cancers and 13.0 ± 13.4 months (95% CI 0.0-39.2) for left lung cancers. **Conclusion:** We did not observe a significant difference in outcome between right-sided and left-sided lung cancers when assessing patients of all stages combined or for the stage IV sub-group. However, in stage III lung cancer, patients with right lung tumours seem to have a better outcome than patients with left lung tumours. Our data are limited by the fact that this is a single institute study with only a modest number of patients, 76 in total. A larger study will be required to assess if the trend observed holds true, the factors behind it and how it may contribute to optimising the management of lung cancer.

Keywords: NSCLC, Right Vs Left, Prognostic Implication

EP1.16-13 CHARACTERISTICS AND CLINICAL OUTCOMES IN PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA IN FUNDACION SANTA FE DE BOGOTA: 42 MONTHS EXPERIENCE

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Background: The source of information available about lung cancer caracteristics and clinical outcomes in Colombia are poor. **Method:** Observational, descriptive study of a cohort of patients with non small cell carcinoma (NSCL) treated at Fundacion Santa Fe de Bogota (FSFB). We followed patients from August 2015 to January 2019 (42 months) and analyzed clinical and epidemiological characteristics, progression free survival (PFS), overall survival (OSm) and treatment related complications. **Result:** Forty-eight patients were included. 56.2% stage IV, 16.6% stage III, 8.3% stage II and 18.75% stage I. Stage IA (44%) received management with surgery, stage IB (56%) were treated with surgery and adjuvant therapy no patients progressed or died. In stage II all were IIA and received management with surgery and adjuvant therapy, 25% progressed and died OSm 26m and PFS 10m. In stage III group, IIIA (62.5%) treated with surgery and chemo-radiotherapy, 40% progressed PFS 12m, and OSm has not been reached. In stage IIIB (37.5%) received chemo-radiotherapy, 33% progressed PFS 8m and OSm has not been reached. In stage IV, the group without PDL-1 expression and negative for oncogenic addiction (22.5%) received treatment with chemotherapy OSm was 16.9m and PFS 7.5m. EGFR positives (41.9%) received target therapy, OSm was 25.8m and PFS 13.1m. The patients with ALK rearrangement (9.6%) were treated with target therapy OSm was 16m and PFS 12.6m. For PDL-1 >50% (12.9%) all received monoagent immunotherapy OSm was 11m and PFS 10m. For PDL-1 1-49% (12.9%) PFS was 28m and OSm has not been reached, they were treated with inmunotherapy plus chemotherapy. In relation with grade 3 toxicity with adjuvant chemotherapy was 10% diarrhea, 10% kidney failure, 10% hematotoxicity, 10% decompensation of heart failure previously diagnosed. In metastatic disease 7% with chemotherapy had kidney failure, 7% emesis, 7% diarrhea and 7%% hyporexia. Patients with target therapy 17% had diarrhea and 11% hepatotoxicity, 5% hematotoxicity, 5% dermatological complications. 9% with bevacizumab presented hemoptysis and 6% of patients with immunotherapy had autoimmune colitis. Hypothyroidism was the most frequent complication with the immunotherapy 37%. **Conclusion:** We had important proportion of stages I-II (27%). Recurrent disease was more frequent in stage III as had been described. Factors like cigarette, nutritional status and ECOG were no statistically significant for the survival. In metastatic setting the highest OS and PFS was for the group with PDL-1 expression between 1-49%, treated with chemotherapy plus immunotherapy.

Keywords: Colombia, metastatic lung cancer, Real world experience

EP1.16-14 EFFICACY OF FIRST-LINE CONTINUOUS MAINTENANCE OF PEMETREXED THERAPY FOR LUNG ADENOCARCINOMA WHEN ADMINISTERED AT ROUTINE OR EXTENDED INTERVALS

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Background: Lung cancer is the most common cancer and the leading cause of death due to cancer worldwide , The benefit of maintenance therapy with pemetrexed with or without antiangiogenesis inhibitors has been observed in previous studies. However, continuous maintenance therapy with the pemetrexed-antiangiogenesis combination has rarely been evaluated in the real world setting. In real life, patients may not receive maintenance therapy or may receive delayed maintenance therapy (stopping interval of >21 days) owing to many factors. The purpose of this study was to obtain real-world data on the maintenance of local progressive and metastatic non-squamous non-small cell lung cancer (NSCLC) in first-line patients treated with or without pemetrexed antiangiogenesis, and to evaluate the effect of extended interention on clinical outcomes.

Method: 168 patients with stage IIIB or IV lung adenocarcinoma who had not been treated previously received pemetreplatin-induced chemotherapy with or without anti-angiogenesis inhibitors (bevacizumab or rh-endostatin) every 3 weeks for a course of 4-6 weeks.The efficacy and safety of 112 patients without progression after induction chemotherapy were analyzed. **Result:** 70 of the 112 patients received continuous maintenance therapy, with or without an anti-angiogenesis inhibitor, until the disease progressed.42 patients did not receive continuous maintenance therapy.The median duration of maintenance therapy was 4(range 1-26);The median interval of each maintenance treatment cycle was 40 days (ranged from 21 to 77 days).The optimal objective efficiency of maintenance group and non-maintenance group was 48.6% and 33.3%, respectively.At an average follow-up of 14.6 months, the median progression-free survival was 11.5 months (95% CI: 9.8 -13.2 months) and 6.8 months (95% CI :5.4-8.2 months,p < 0.001), and the median overall survival was 40.1 months (22.5 - 57.7 months) and 18.0 months (10.4-25.6 months,p = 0.001) in the maintenance and non-maintenance groups, respectively.The most common grade 3-4 adverse event in both groups was neutropenia (18.6% vs. 19.0%). **Conclusion:** prolongation of maintenance time is feasible, and for patients without progression after first-line induction therapy for lung adenocarcinoma, continuous maintenance therapy with or without combination of pemetrexed with anti-angiogenesis is essential for survival benefits.

Keywords: lung adenocarcinoma, continuous maintenance therapy, pemetrexed

EP1.16-15 SUBCLINICAL INTERSTITIAL LUNG DISEASE IS A RISK FACTOR FOR RADIATION PNEUMONITIS IN PATIENTS WITH LUNG CANCER AFTER THORACIC RADIATION THERAPY

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Background: Previous studies reported that patients with subclinical interstitial lung disease were more susceptible to developing radiation pneumonitis after thoracic stereotactic body radiotherapy or thoracic 3-dimensional conformal radiotherapy. The present study aimed to evaluate the incidence and predictors of RP after TRT in patients with lung cancer with or without preexisting subclinical interstitial pulmonary disease. **Method:** Patients with lung cancer between May 2016 and August 2018, who were treated with thoracic intensity-modulated radiation therapy in our institutions, were prospectively analyzed. Statistical analysis was performed using SPSS software 22.0 for Mac. Univariate and multivariate analyses were used to assess the correlation of subclinical interstitial lung disease with radiation pneumonitis and risk factors of radiation pneumonitis. A P value < 0.05 was considered statistically significant. **Result:** A total of 123 patients with lung cancer were prospectively analyzed. The median follow-up time was 13.9 months. Radiation

pneumonitis was observed in 30, 18, 2 and 1 patient with grades 1, 2, 3 and 5 radiation pneumonits, respectively. No patient suffered from ≥grade 4 radiation pneumonitis. The incidence of ≥grade 2 radiation pneumonitis was 17.1%. Mean lung dose, V10, V20, V30 and subclinical interstitial lung disease before radiotherapy were associated with an increased incidence of ≥grade 2 radiation pneumonits in univariate analysis. Subclinical interstitial lung disease and mean lung dose were significantly associated with ≥grade 2 radiation pneumonits in multivariate analysis (*P*=0.022, *P*=0.018, respectively). **Conclusion:** Preexisting subclinical interstitial lung disease and mean lung dose are predictors of ≥grade 2 radiation pneumonits.

Keywords: Radiation pneumonitis, Lung cancer, interstitial lung disease

EP1.16-16 PEMBROLIZUMAB AS FIRST THERAPEUTIC LINE IN NON-SMALL CELL LUNG CANCER – THE EXPERIENCE OF A PORTUGUESE TERTIARY HOSPITAL

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Background: Pembrolizumab is a humanized monoclonal antibody against PD-1 that has antitumoral activity in NSCLC. It is currently approved by the EMA for the treatment of patients with advanced NSCLC with PD-L1 expression ≥50%. **Method:** A retrospective study was performed in patients with advanced NSCLC proposed for first-line treatment with pembrolizumab. These patients were recruited at our Thoracic Tumor Unit between June 2017 and December 2018. An epidemiologic characterization of patients was performed and a progression-free survival (PFS) was analysed through the Kaplan-Meier method. **Result:** Twenty-two patients were included, with one being excluded due to the presence of synchronous tumor lesions. The majority of patients were male (90,5%), with a mean age of 63±13 years and 85.7% were smokers or former smokers. At the start of immunotherapy, 23.8% had a PS0 and 76.2% had a PS1. The most frequent histology was adenocarcinoma (57.1%), followed by squamous cell carcinoma (33.3%), and the majority of patients were in stage IV (95.2%). The median of PD-L1 expression was 80% (IQR 30). Partial remission was achieved in 47.6% of patients, stable disease in 28.6%, and 23.8% of patients had progressive disease. The median PFS was 10.0 months. Adverse effects were documented in 28,6% of patients, namely hypothyroidism, colitis, hepatitis and sialadenitis. Only one was classified as grade 3 according CTCAE, leading to interruption of the drug. **Conclusion:** The PFS obtained in our study was similar to that described in literature (10.3 months). As we can observe the safety profile of pembrolizumab was also good. Thus, pembrolizumab is increasingly being shown as a well-established drug in 1st line for advanced NSCLC with PD-L1 expression ≥50%.

Keywords: advanced NSCLC, progression-free survival, Pembrolizumab

EP1.16-17 MANAGEMENT OF INAPPROPRIATE USE OF OPIOIDS (IUO) IN PATIENTS (P) WITH LUNG CANCER (LC)

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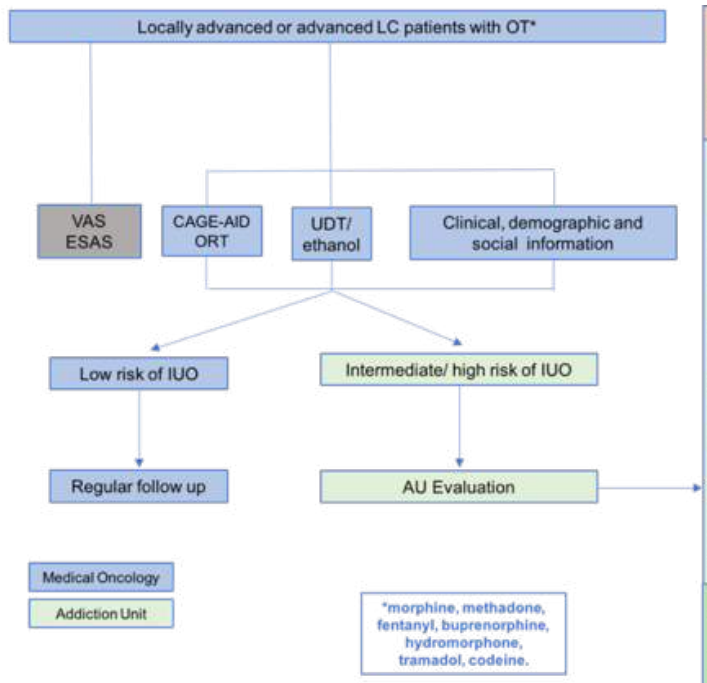
Background: Pain represents one of the main symptoms in patients (p) with lung cancer (LC). Currently, the molecular classification and targeted therapies and immunotherapy for LCp yield a prolonged survival in some p. In this context, analgesia with opioid therapy (OT) requires special caution. The prevalence of IUO LCp is unknown and its assessment is suboptimal. There is no current recommendation to assess IUO risk in cancer p, other than in long cancer survivors with chronic pain. Several scales are validated for the screening of aberrant OT-behaviors. The Addiction Unit (AU) role could be key in the evaluation and minimization of the IUO risk (Fig.1) STUDY DESIGN:Prospective study for the evaluation of IUO risk in LCp. P with intermediate/high risk of IUO will be referred to the AU for evaluation and follow-up (Fig.1) OBJECTIVES:Determine if screening scales are capable of detecting the risk of IUO in LCp. Reduce the impact of IUO in LCp by assessment and follow-up in the AU. VARIABLES: Main: To determine if the Cut down-Annoyed-Guilty-Eye opener (CAGE-AD) and Opioid Risk Tool (ORT) scales are able of detecting the risk of IUO in LCp. Secondary: Determine if the urine and blood drug testing (DT) reinforces the information of such scales. Determine the risk reduction of IUO after the intervention of the AU. **Method:** ELIGIBILITY CRITERIA (Fig.1) SCALES:The MO team will use the following scales for the IUO risk assessment: CAGE-AID, ORT. Visual Analogic Scale (VAS) and Edmonton Symptom Assessment Scale (ESAS) will be used for pain evaluation. LABORATORY: DT (urine/ blood ethanol) ASSESSMENT OF IUO RISK: Proposed timeline and strategies at the AU are summarized in Fig.1. SAMPLE SIZE:Study will include 45 p in a 1-year period. Approved by IRB-Hospital Germans Trias in Pujol, Nov, 23th2018 (UIO-pulmon 2018)



AU, Addiction Unit; CAGE: Cessation-Annoyed-Guilty-Eye opener; ESAS, Edmonton Symptom Assessment Scale; IUO, inappropriate use of opioids; LC, lung cancer; ORT, Opioid Risk Tool; OT, opioid therapy; p, patients; UDT, urine drug testing; VAS, visual analogic scale

Result: Section not applicable **Conclusion:** Section not applicable

Keywords: Lung cancer, pain, Inappropriate use of opioids

EP1.16-18 EGFR MUTATION POSITIVE NON-SMALL CELL LUNG CANCER: MANAGEMENT APPROACH AND SURVIVAL OUTCOMES FROM THE HOSPITAL OF LEON

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Background: Approximately 10-16% of non-small cell lung cancer (NSCLC) cases have the EGFR mutation. Studies have shown that EGFR tyrosine kinase inhibitors (TKIs) significantly prolong progression-free survival (PFS) in patients with advanced NSCLC in comparison to those treated with platinum-based chemotherapy doublets. Our aim is to perform a real world analysis of patients treated with TKI as first line therapy at the Hospital of Leon (CAULE). **Method:** We retrospectively reviewed a total of 74 patients diagnosed with EGFR mutation positive NSCLC between March 2011 to June 2018 in the CAULE. Data was obtained from their medical records. The impact of comorbidities and smoking status on the survival rate were evaluated, in addition to the PFS and overall survival (OS) outcomes in patients treated with first line TKI. The follow-up schedule for computed tomography (CT) imaging was realized every 8 to 12 weeks. **Result:** A total of 74 patients were included in the study, out of which 55 were treated with a first line TKI. Exon 19 deletion was the most prevalent mutation subtype accounting for 53% of cases. 67% of patients were women. The average age was 69 years old. 44% had metastasis to more than 2 sites at the time of diagnosis; 6 patients had brain metastasis, 4 of which received prior whole brain radiotherapy, 1 surgical treatment, and 1 didn't receive local treatment. 22% of patients had no medical comorbidities (including cardiovascular, pulmonary, neurological or psychiatric history). Results revealed that the presence of comorbidities had no statistical significance when analyzing its impact on survival outcomes (HR=0.85, 95%CI 0.37-1.83 p=0.64). Similar results were obtained when non-smokers (71%) were compared to smokers or former smokers, suggesting that smoking had no statistical significance when analyzing survival data (HR=0,94 95%CI: 0.43- 2.02 p=0.87). 50% (n= 28) of patients were treated with first line gefitinib, 32% (n=18) with erlotinib and 10% (n= 6) with afatinib. There was no statistical significance in survival rates amongst patients treated with gefitinib vs afatinib or erlotinib (HR=1.6 P=0.56 95%CI 0.84-3.2). When analyzing best response to treatment, 63% of patient had a partial response, 20% demonstrated stable disease and 10% had progression of disease. Median OS was 31 months (95%CI: 20,5-31,4 months) and the PFS was 17 months (95%IC 13,9-20,6 months). 30% were alive at the time of analysis. The main cause of death was disease progression. **Conclusion:** This real-world analysis of the data gathered from the Hospital of Leon confirms that treatment with TKI is beneficial for patients diagnosed with EGFR mutation positive NSCLC. In fact, our OS outcomes are similar than those reported in clinical trials. We have not observed significant differences amongst TKI treatment options, nor was there an impact on global survival rates in patients with underlying medical comorbidities. Given the prevalence of EGFR mutation positive lung cancer, more clinical data is required in order to expand scientific evidence and determine the best driver mutation therapy option based on patient's profile.

Keywords: EGFR mutation, TKI first line, comorbidities

EP1.16-19 EXPECTED YEARS OF LIFE LOSS AND SURVIVAL OUTCOME IN NON-SMALL CELL LUNG CANCER PATIENTS IN RAJAVITHI HOSPITAL

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Background: To determine expected years of life loss (EYLL) that was the burden of disease parameter of all stages non-small cell lung cancer (NSCLC) patients, survival outcomes in advanced NSCLC patients and association between clinical prognostic factors and survival outcomes in advanced diseases. **Method:** This retrospective cohort study was conducted by reviewing 305 eligible all stages NSCLC patients treated at Oncology Unit, Department of Medicine, Rajavithi hospital from 2011 to 2015. The iSQoL statistical package was used to evaluate EYLL compared to the reference Thai population. For advanced NSCLC patients, univariate and multivariate analysis were used to determine prognostic factors associated with survival

outcomes. **Result:** Total 305 patients were included for EYLL analysis. From survival extrapolation, corresponding EYLL of stage I, II, III, and IV NSCLC patients were 9.20, 15.61, 18.03, 20.23 years, respectively. Male patients had EYLL less than female patients (18.81 years vs 20.70 years). In advanced NSCLC, 261 patients were included in survival and prognostic factors analysis. The median overall survival was 6.08 months. The clinical parameters associated with poor survival outcomes in multivariate analysis were male gender (HR 1.71; p = 0.017), presentation with cough or hemoptysis (HR 1.81; p < 0.001), significant weight loss (HR 1.80; p < 0.001), SVC obstruction (HR 1.98; p = 0.019), pathological fracture (HR 2.16; p = 0.002), symptomatic brain metastasis (HR 2.05; p = 0.005), pericardial metastasis (HR 1.88; p = 0.015), adrenal metastasis (HR 1.58; p = 0.011), and not received palliative chemotherapy (HR 6.18; p < 0.001).

Figure: Expected years of life loss (EYLL) of non-small cell lung cancer patients by different staging. The difference of life expectancy between non-small cell lung cancer patients and the sex- and age-matched referents were represented in the shadowed area

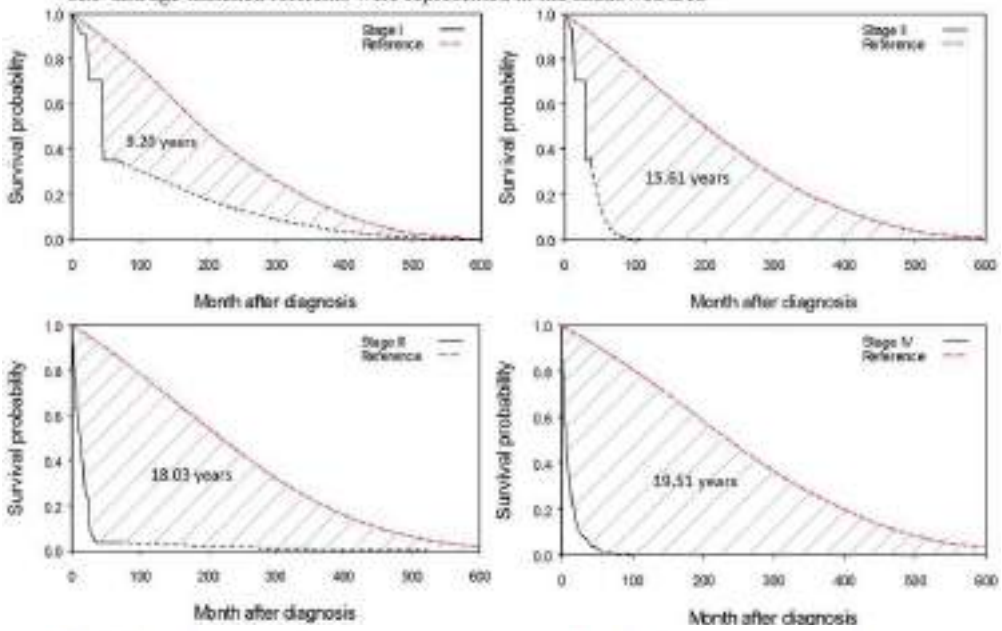

Table: Multivariate analysis of factors related to overall survival outcome in advanced non-small cell lung cancer patients

Variables		Crude HR			Adjusted HR		
		HR	95% CI	p-value	HR	95% CI	p-value
Sex							
Male		1.68	1.28 – 2.22	< 0.001	1.71	1.10 – 2.66	**0.017***
Female		1.0	reference		1.0	reference	
ECOG PS							
0		1.0	reference	< 0.001	1.0	reference	0.064
1		1.26	0.74 – 2.15	0.382	1.66	0.96 – 2.89	0.069
2		1.95	1.13 – 3.39	0.017	1.22	0.67 – 2.22	0.496
> 2		5.24	2.94 – 9.32	< 0.001	1.80	0.93 – 3.48	0.079
Smoking (pack-year)							
None		1.0	reference	0.021	1.0	reference	0.510
1 – 10		1.34	0.87 – 2.06	0.178	0.98	0.58 – 1.66	0.951
11 – 20		1.04	0.69 – 1.55	0.847	0.70	0.41 – 1.18	0.182
> 20		1.55	1.15 – 2.08	0.004	0.83	0.51 – 1.34	0.452
Clinical presentation							
- Cough or hemoptysis:	Yes	1.33	1.02 – 1.73	0.034	1.81	1.34 – 2.46	**< 0.001***
	No	1.0	reference		1.0	reference	
- Significant weight loss[a]:	Yes	1.48	1.13 – 1.93	0.004	1.80	1.34 – 2.42	**< 0.001***
	No	1.0	reference		1.0	reference	
- SVC syndrome:	Yes	2.21	1.28 – 3.82	0.004	1.98	1.12 – 3.52	**0.019***
	No	1.0	reference		1.0	reference	
- Pericardial effusion:	Yes	2.54	1.12 – 5.73	0.025	1.78	0.65 – 4.83	0.257
	No	1.0	reference		1.0	reference	
- Pathological fracture:	Yes	2.47	1.62 – 3.77	< 0.001	2.16	1.32 – 3.53	**0.002***
	No	1.0	reference		1.0	reference	
-Symptomatic brain metastasis:	Yes	2.52	1.64 – 3.86	< 0.001	2.05	1.24 – 3.39	**0.005***
	No	1.0	reference		1.0	reference	
Metastatic sites							
- Pericardial metastasis:	Yes	1.58	1.03 – 2.42	0.034	1.88	1.13 – 3.14	**0.015***
	No	1.0	reference		1.0	reference	
- Adrenal metastasis:	Yes	1.70	1.21 – 2.37	0.002	1.58	1.11 – 2.25	**0.011***
	No	1.0	reference		1.0	reference	
Ability to receive palliative CMT							
Yes		1	reference		1.0	reference	
No		4.44	3.38 – 5.82	< 0.001	6.18	4.16 – 9.18	**< 0.001***

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; SVC syndrome, superior vena cava syndrome; CMT, chemotherapy.
[a] Weight loss ≥ 5% in 6 months.

Conclusion: Diagnosis and treating patients with NSCLC as early as possible would be save more life-years from 18 – 20 years in advanced disease to 9 – 15 years in early stage disease. In advanced NSCLC patients, palliative chemotherapy was the most important factor related to better survival outcomes.

Keywords: Non-Small Cell Lung Cancer, Survival outcome, expected years of life loss

EPOSTERS

EP1.16-20 PEMBROLIZUMAB - SUBSEQUENT LINES IN NON-SMALL CELL LUNG CANCER: THE EXPERIENCE OF A TERTIARY HOSPITAL

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Background: Pembrolizumab is currently approved for the treatment of metastatic NSCLC, with PD-L1 expression ≥1% and with progressive disease during or after treatment with chemotherapy. **Method:** A retrospective study was conducted in patients with metastatic NSCLC with ≥ 1% of PD-L1 expression, proposed for subsequent therapeutic lines with pembrolizumab. Patients were recruited in our Thoracic Tumor Unit between June 2017 and December 2018. An epidemiology characterization of patients was performed and progression-free survival (PFS) was analyzed throw a Kaplan-Meier method. **Result:** Fourteen patients were included. The majority of patients were male (85.7%), with a mean age of 65±11 years, and 78.6% of them were smokers or former smokers. The observed PS was: PS0 in 7.1% and PS1 in 92.9%. The most prevalent histologies were adenocarcinoma (71.4%) and squamous cell carcinoma (28.6%), with the majority of patients in stage IV (78.6%) at the time of initiation of pembrolizumab. The median of PD-L1 expression was 60% (IQR 50). Mutations and translocations (KRAS and BRAF) were present in 38.5% of these patients. Partial disease remission was achieved in 28.6% of patients, stable disease in 50.0%, and 21.4% of patients progressed. The median PFS was 8.0 months. Adverse effects were documented in 28.6% of patients, namely hypothyroidism (28.6%) and hepatitis (7.1%). Only one patient developed grade 3 adverse effect that led to drug interruption. **Conclusion:** The PFS obtained in our study was twice as large as that described in the literature (3.9 months), although due to the small number of patients it was not possible to divide in subgroups of PD-L1 expression. However, the high median of PD-L1 expression in our study may explain in part the results obtained. The authors intend to show that pembrolizumab in 2nd line is an effective drug and should be considered in patients with high expression of PD-L1.

Keywords: Pembrolizumab, second line, advanced NSCLC

EP1.16-21 FREQUENCIES AND PROGNOSIS OF NON-SMALL CELL LUNG CANCERS COMPLICATED WITH SYNCHRONOUS/METACHRONOUS MULTIPLE PRIMARY CANCERS

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Background: Recently, opportunities to diagnose multiple primary cancers have been increasing due to the progress of diagnostic technology, resulting in the difficulty in treatment decisions. Therefore, we examined the frequencies, background, and prognosis of non-small cell lung cancers (NSCLC) complicated with synchronous/metachronous multiple primary cancers. **Method:** Between 2013 and 2017, we retrospectively examined the medical charts in patients with NSCLC who had never experienced cancers before. We classified such NSCLC patients into the following three groups: (1) single primary NSCLC group (SPN), showing no other cancers during the follow-up period, (2) synchronous NSCLC group (SN), showing other cancers diagnosed within 2 months from the first NSCLC diagnosis, and (3) metachronous NSCLC group (MN), showing other cancers diagnosed after 3 months or more from the first NSCLC diagnosis. **Result:** Among 1350 cases enrolled, the frequencies of SPN, SN, and MN groups were 88.6% (1196 cases), 8.3% (112 cases), and 3.1% (42 cases), respectively. Background factors such as age, sex, performance status, smoking history, clinical stage, EGFR mutation, EML4-ALK fusion gene, ROS-1 gene, PD-L1 expression, and the number of affected cancers were adjusted using Cox proportional hazards model analysis. In SN group, NSCLC (32 cases), colon cancer (20 cases), and gastric cancer (12 cases) were commonly observed. Similarly, in MN group, NSCLC (17 cases), colon cancer (4 cases), and gastric cancer (4 cases) were commonly observed. The median survival times of SPN, SN, and MN groups were 24.0 months, 42.1 months, and not reached, respectively ($p < 0.001$). Regarding the prognostic factors, the hazard ratios [HR] of SN and MN groups toward SPN group were 0.98 (95% confidence interval [CI]; 0.71 to 1.36, $p = 0.91$) and 0.38 (95% CI; 0.22 to 0.66, $p < 0.001$), respectively. The other prognostic factors were 75 years old or older (HR; 1.46, 95% CI; 1.24 to 1.72, $p < 0.001$), male (HR; 1.56, 95% CI; 1.26 to 1.94, $p < 0.001$), performance status 3-4 (HR; 3.88, 95% CI; 3.09-4.82, $p < 0.001$), smoking history (HR; 1.44, 95% CI; 1.12 to 1.84, $p = 0.01$), and clinical stage IIIB-IV NSCLC (HR; 4.37, 95% CI; 3.62 to 5.30, $p < 0.001$). **Conclusion:** In patients with NSCLC who had never experienced cancers before, synchronous/metachronous multiple primary cancers could be often observed. However, their coexistence might not adversely affect the prognosis of firstly diagnosed NSCLC.

Keywords: single primary lung cancer, synchronous cancer, metachronous cancer

EP1.16-22 PEMETREXED, PLATINUMIN COMBINATION WITH BEVACIZUMAB FOR CHINESE PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA CANCER: A REAL WORLD STUDY

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Background: Bevacizumab and platinum based chemotherapy have been standard treatment for advanced non-squamous non-small cell lung cancer. Otherwise, the chemotherapy protocol is often paclitaxel and carboplatin, and pemetrexed combination with platinum are also generally used in our clinical practice. Thus, the aim of this present study is to evaluate the efficacy and safety of cisplatin or carboplatin+pemetrexed combination with bevacizumab followed by maintenance pemetrexed and bevacizumab for Chinese chemotherapy-naïve patients with advanced lung adenocarcinoma cancer in real word. **Method:** A total of 44 chemotherapy-naïve patients with advanced lung adenocarcinoma cancer were administered pemetrexed (500 mg/m2), cisplatin(60mg/m2)/carboplatin (AUC, 5.0 mg/ml/min) and bevacizumab (7.5 mg/kg) intravenously every three weeks for up to six cycles. Maintenance PB was administered until disease progression or unacceptable toxicity. The endpoints were objective response rate (ORR), progression-free survival (PFS) and safety. **Result:** 44 advanced lung adenocarcinoma cancer patients were enrolled and median age was 61 years. 33 patients were males, 24 were never smokers, the ECOG performance status of 42 patients were 0 and 1. The status of epidermal growth factor receptor mutation, ALK and ROS1 fusion were all negative in 26 patients. EGFR mutation, ALK or ROS1 fusion positive and unkown were 10, 2 and 6 patients respectively. The median cycles of induction therapy and maintenance were 4.2 (95% confidence interval, 2-7) and 3.7 (95% confidence interval, 0-22).The median PFS was 7.4 months. The ORR, SD and DCR were 63%, 32 % and 95% respectively. The grade 3 or 4 toxicities were neutropenia (8%), anemia (1%), fatigue (1%). **Conclusion:** The combination of the bevacizumab, pemetrexed, and platinum demonstrated activity with acceptable toxicity in patients with advanced lung adenocarcinoma cancer regardless of drive gene status.

Keywords: Bevacizumab, pemetrexed, platinum, lung adenocarcinoma cancer

EP1.16-23 THE EFFICACY OF S-1 IN THE THIRD OR MORE THAN LINE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: S-1 as the third generation of fluorouracil derivate with well safety and low toxicity, presented some efficacy in lung cancer treatment. The aim of this study was to evaluate the efficacy of S-1 treatment in advanced non-small cell lung cancer (NSCLC) in a real world. **Method:** We explored the efficacy of S-1 in advanced NSCLC patients with previously treated from 2015 to 2018 in Jiangshan People's Hospital, Zhejiang Rongjun Hospital and Zhejiang Cancer Hospital. Platinum or the third-generation chemotherapy drugs could be combinedly used. Clinical response was assigned every cycle according to Response Evaluation Criteria in Solid Tumors

(RECIST) version 1.1. Survival analysis and univariate survival analysis were performed by the Kaplan-Meier method. **Result:** 158 patients were included in the research. These patients received S-1 treatment were as a third-line or more-line therapy, including 63 patients S-1 monotherapy, the other 95 patients combined regimens. All 158 NSCLC patients had therapeutic evaluation. Six patients were partial response (PR), and 51 patients were stable disease (SD), then an overall response rate (ORR) was 3.80% and a disease control rate (DCR) was 36.08%. Median progression-free survival (mPFS) was 1.94 months (95%CI 0.56-10.98), no difference between monotherapy and combined group (DCR 30.16% *vs* 40.00%, P>0.05), the liver metastasis showed poorer PFS (1.29 months *vs* 1.92 months, P<0.05). **Conclusion:** S-1 presented some activity in advanced NSCLC treated with more than third lines of treatment. The addition of other drugs cannot improve efficacy. S-1 monotherapy can be used as a choice for heavily-treated patients.

Keywords: non-small-cell lung cancer, S-1, Chemotherapy

EP1.16-24 OVERCOMING APPOINTMENT DELAY IN RADIOTHERAPY: A SINGLE INSTITUTION EXPERIENCE

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Background: Delay to access to radiation therapy in developing countries is challenging and compromising the cancer prognosis. In our department, we have one linear accelerator for a whole region in the country. We treated about 50 to 60 patient a day and appointments were for more than 3 months. The medical and psychological impact on patients was important. Our objective was to shorten this delay. **Method:** The radiotherapy treatment delivery was to treat 50 to 60 patients from Monday to Friday as the majority of radiation therapy departments. Treatments started at 8 AM to finish at about 7 to 8 PM. The idea was to treat more patients and quickly. Therefore, actions were taken on three main situations: 1st Before radiotherapy, we had to shorten the time from the first consultation to the first radiotherapy fraction. 2nd during radiation, we extended treatment period to above 8 PM.and 3rd concerns fractionation regimens. **Result:** The hospital executive decided to transform the oncology hospital to an emergency hospital with the possibility to treat 24/7. With this way, we could treat up to 100 patient a day or more. we also treat on weekends especially palliative patients. Concerning the patient workflow, patients were seen immediately when they arrive at the department, and if the medical file is complete and ready to radiation, CT scan simulation was done within a week, contouring, dosimetry, and validation with safety checks were done within 3 days. and finally, when possible, we chose hypo-fractionated regimens. The appointment time started to drop from more than 3 months to almost 2 weeks. **Conclusion:** In developing countries, access to radiotherapy is a real problem. The number of linear accelerators per capita is very low. Therefore delays are very long. This kind of approach, if sufficient human resources, could solve the problem while waiting for a second and maybe other machines.

Keywords: Delay - Radiotherapy - Emergency hospital

EP1.16-25 INVESTIGATING THE SYSTEM IMPACT OF REPORTING MULTIDISCIPLINARY CARE MEASURES FOR CANCER SERVICES IN NSW

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Background: Multidisciplinary cancer care to facilitate the provision of patient centred and evidence-based care is considered best practice internationally. The Cancer Institute New South Wales (the Institute), the government cancer control agency for the state of New South Wales (NSW) in Australia, has supported multidisciplinary care development and sustainability since 2006. In 2016, measures were developed and reported on by all local health districts across NSW to further understand the practices of different multidisciplinary team meetings (MDT). The measures focused on lung cancer and communication from the MDT to the general practitioner following the MDT meeting. The aim of this study was to identify system level changes and quality improvement activities initiated in the NSW cancer system as a result of reporting on these measures. **Method:** Focus group discussions were used to generate a synergy of ideas from stakeholder respondents regarding the way in which multidisciplinary care and multidisciplinary team meetings operated and how the measures were being used. The participants included NSW Cancer Registry Program Managers and Cancer System Innovation Managers. Content analysis was undertaken using Framework Analysis. **Result:** Two focus groups were held with a total of 17 participants. Five primary themes emerged: use of the oncology medical information system (OMIS); documentation in the MDT; awareness of the measures; relationships; and current and future measures. Some of the key findings included that reporting on the measures expedited the development of the OMIS and improved documentation directly into the OMIS during the MDT. Some challenges that emerged were implementing change in processes and documentation when the MDT sat outside of cancer services governance structures. **Conclusion:** This study has identified that the reporting of performance measures has expedited the development of electronic documentation and data extraction from the MDT, identified barriers and facilitators to MDT data collection and supported MDT improvement activities across NSW. The Institute will continue to work with the NSW cancer control system on the development of new measures to continue the development of multidisciplinary care through the use of MDTs state wide, to ensure all people with a cancer diagnosis in NSW have their care overseen by an MDT.

Keywords: multidisciplinary care, cancer system improvement, key performance indicators

EP1.16-26 PREHABILITATION FOR LUNG CANCER PATIENTS RECEIVING RADICAL RADIOTHERAPY

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Background: Radical radiotherapy with or without chemotherapy is recommended in patients with stage I to III lung cancer who are unsuitable for, or decline surgery. Treatment options are influenced by a patient's performance status, thoracic symptoms and co-morbidities. There is increasing evidence in other fields such as surgery, that prehabilitation has the potential to optimise patient's health prior to starting treatment, reduce treatment related toxicities and increase the opportunity for further treatment options. To investigate the therapeutic potential of prehabilitation, the Beatson West of Scotland Cancer Centre inititated a multidisciplinary prehabilitation clinic for patients with lung cancer embarking on radical radiotherapy. **Method:** Patients from the West of Scotland embarking on a radical dose of radiotherapy with or without chemotherapy were invited to attend the prehabilitation clinic 2 to 3 weeks prior to starting treatment. Their National Early Warning Score (NEWS), Malnutrition Universal Screening Tool (MUST) score, Karnofsky Status, Distress Themometer score, Godin Leisure-Time Exercise Questionnaire (GLTEQ); 30 second chair to stand test (CST) and smoking status were measured at prehabilitation (time point 1) and again during the first week of radiotherapy (time point 2). **Result:** Between May 2019 and July 2019 49 patients were eligible to attend the prehabilitation clinic. 78% attended clinic, 8% were not invited, 6% could not attend due to hospital admission and 8% declined. The range of dose and fractionation schedules varied but included 40 Gy in 15 fractions (N=9), 45 Gy in 30 fractions (N= 1), 55 Gy in 20 fractions (N=17) or 54 Gy in 36 fractions (N=11). 34% of patients received their radiotherapy concurrent with chemotherapy. Twenty-two patients (58%) were current smokers, 15 (68%) of whom engaged with smoking cessation. 13 current smokers (59%) remained smoke free during treatment, with 2 continuing to smoke. MUST, NEWS, Karnofsky Status and Distress scores were available for 15 patients who had commenced treatment. No statistically significant changes were noted in these measurements between time point 1 and two 2 (P = 0.49, 0.27, 1 and 1.53 respectively). However, significant improvements in the GLTEQ (p = 0.008) and CST (p = 0.008) between the two time points were observed for the 8 patients who completed these tests. **Conclusion:** Due to the small sample size conclusions cannot be drawn about the impact of this prehabilitation service as yet. The uptake of smoking cessation and physical activity are encouraging. Over time, data will be available from the Common Toxicity Criteria and the FACT-L to measure its effectiveness.

Keywords: Prehabiliation, radical radiotherapy, Multidisciplinary team working

EP1.16-27 OBSERVATIONAL STUDY TO INVESTIGATE THE IMPLEMENTATION RATE OF RE-BIOPSY IN EGFR-TKI-RESISTANT PATIENTS (NLCTG1602)

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Background: In EGFR-TKI treatment, cannot perform re-biopsy in all cases for recurrent style and involvement. In the case that only cytodiagnosis can gather, we cannot perform an examination for T790M by the Cobas method even if we can obtain a specimen.The examination of plasma is useful, but the case which cannot but provide the next treatment as we cannot confirm a resistant mechanism may often occur by the true clinic because we cannot detect all resistance. **Method:** Examine the rate of use of re-biopsy in the EGFR-TKI-resistant case of the EGFR mutation in the gene-positive progress non-small cell lung cancer and histological diagnosis and rate of agreement of the T790M mutation detection by the Cobas method of the cytodiagnosis prospectively. <subjects>Treated by EGFR-TKI, and do the case that an effect was able to continue with primary registration, and do it with the second registration when treatment was resistant, and do the laboratory procedure and results with registration when there are a recurrence point, PS, use or nonuse of re-biosy. We added up the liquid as re-biosy after July, 2017. **Result:** Start registration of this study in February, 2017, and 197 primary registration, second registration completion become 127 cases as of January, 2019.We conducted the interim analysis in 80 second registration in October, 2018. The Re-biopsy rate of use was 74/80 = 92.5%.The re-biopsy success rate was the whole, and 79.7%, the T790M positive rate were 41.9%.By the specimen distinction, the histological diagnosis, the cytodiagnosis, the re-biopsy success rate and the T790M positive rate by the examination of plasma were 92.3% /56.4%, 83.3%/8.3%, 56.5%/34 .8%, respectively. It is during data cleaning work and is going to report end results now at the general meeting. **Conclusion:** Section not applicable

Keywords: EGFR-TKI, Re-biopsy, Real world date

EP1.16-28 ALK TRANSLOCATED PATIENTS: SURVIVAL IN AN UNSELECTED POPULATION

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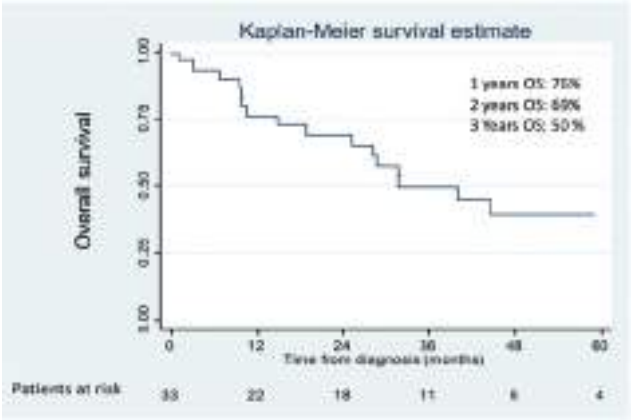
Background: Lung cancer is the leading cause of death from cancer in our environment. About 5% have ALK translocation, which is more frequent in young, Asian women and non-smoking patients. In the last years, multiple treatments have been developed for patients with ALK translocation, improving prognosis and reaching overall survivals (OS) of more than two years. **Method:** A cohort of 34 patients diagnosed of non-small cell lung cancer with ALK translocation were retrospectively analyzed in our center between 2008-2018. Baseline demographics characteristics were described. OS was calculated as the main objective. **Result:** Patients were followed a median of 47 months (IQR 30-203). Median age was 59 years (IQR 36-83), being 47% male and 53% female. 44% were never smokers and 58% had any comorbidities. At diagnosis, 83% were symptomatic and the most frequent metastases were bone ones (32%). Complete baseline characteristics are shown in Table 1. Median OS was 32 months (IQR 15-78). 1-year, 2-year and 3- year survival was 75%, 69% 49.9% respectively. Kaplan-Meier curve is shown in Figure 1. **Conclusion:** The ALK translocation and targeted treatments have led to a dramatic improvement in overall survival in clinical trials confirmed in our series.

Keywords: OS, NSCLC, ALK mutation

BASELINE CHARACTERISTICS	PATIENTS (N = 34)	
Gender	16 (47%) male, 18 (53%) female	
Age at diagnosis	59 years (IQR 33-83)	
Smoking habit	15 (44%) never smokers 19(59%) smokers (15 (44%) former and 4(12%) current)	
Smoking Pack year	16 (RIQ 10-39)	
Symptoms at diagnosis	6 (17%) → asymptomatic. Cough→12 (35%) Pain →5 (15%) Others→ 1 (2%) headache, dysphonia, low back pain, asthenia)	Weight loss →5 (15%) Dysnea→ 4 (12%)
Comorbidities	11(32%) → no comorbidities HTA → 9 (26%) Heart disease. →3 (9%) DM → 2 (6%)	DL 8 (24%) COPD → 2 (6%) Vasculopathy→ 2 (6%)
Metastases at diagnosis	Bone → 11 (32%) Pleural metastases → 7 (21%) Lymphangitis→2 (8%)	Lung →7 (21%) Brain →5 (15%) Hepatic metastases → 2 (8%)



EPOSTERS

EP1.16-29 CLINICAL CHARACTERISTICS AND OUTCOMES OF POSTOPERATIVE EMPYEMA FOLLOWING LUNG SURGERY

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Background: Postoperative empyema prolongs hospital-stay durations and may lead to mortality. However, clinical risk factors for postoperative empyema have been insufficiently investigated. This study explored the relevant characteristics and outcomes of postoperative empyema after lung surgery. **Method:** A retrospective study of 16 cases of postoperative empyema after lung surgery between April 2008 and December 2018 was conducted. The inclusion criteria were patients who had fever and bacterial pleural effusion confirmed by culture within the first 30 postoperative days. Preoperative patient characteristics, operative findings, and postoperative course were evaluated. **Result:** There were eight cases of empyema with fistula (six with pulmonary fistula and two with bronchopleural fistula) and eight without fistula. Patients included 15 men and one woman. Median (range) age, body mass index, and Brinkman index were 68 (20-84) years, 22.9 (14.5-27) kg/m2, and 650 (0-2320), respectively. Nine patients were operatively diagnosed with primary lung cancer (p-stage I, three cases; p-stage ≥II, six), six with metastatic lung cancer, and one with pneumothorax. Co-morbidities included chronic obstructive pulmonary disease (COPD) (eight cases; incidence, 50%); diabetes mellitus (five cases; 31%), and history of preoperative chemotherapy (seven cases; 44%). Operative procedures were as follows: two pneumonectomies, five lobectomies, two segmentectomies, six wedge resections, and one bulla suturing. Surgical approaches included 12 thoracoscopic surgeries and four open thoracotomies. Median (range) operative time and bleeding volume was 219 (92-739) minutes and 21 (0-1400) g, respectively. Surgery-to-empyema-onset duration was 12 (4-30) days. Before empyema onset, postoperative complications developed in 14 cases (88%) as follows: four, surgical-site infection; four, prolonged pulmonary air leak; two, pneumonia; two, bronchopleural fistula; one, both prolonged pulmonary air leak and surgical-site infection; and one, both pneumonia and surgical-site infection. Organisms cultured from empyema cases included *Staphylococcus aureus* (12 cases; MRSA, one), oral resident bacteria (three), and others (one). Postoperatively, five cases required treatment with antibiotics only; five, both antibiotics and chest drainage; and six, surgery with the aforementioned treatments. Surgical procedures for empyema included thoracoscopic debridement and/or pleural irrigation (four cases) and fenestration (two cases). The hospital-stay duration after first surgery was 30 (12-99) days. There were no postoperative mortalities. **Conclusion:** Diabetes mellitus, preoperative chemotherapy, and COPD could be significant risk factors for postoperative empyema. Infecting organisms associated with postoperative empyema were related to preceding postoperative complications. Therefore, emphasis on controlling factors that contribute to pulmonary and surgical-site infection and pulmonary air leak is important to prevent postoperative empyema.

Keywords: postoperative empyema, Postoperative complication, lung surgery

EP1.16-30 BENIGN EMPTYING OF THE POST-PNEUMONECTOMY SPACE

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Background: Whenever a sudden drop in intrapleural effusion occurs after a major pulmonary resection, a bronchopleural fistula is suspected. It often presents with a productive cough due to oral expulsion of pleural fluid as the fistula allows direct communication between the thoracic space and bronchus. An empyema usually follows due to contamination of bacterial flora from the bronchus into the aseptic pleural space. Still, rarely a sudden drop in the pleural fluid occurs in a stable patient, usually with a benign evolution. **Method:** Section not applicable **Result:** A 67 year old man with an adenocarcinoma of the left upper lobe, cT2,N2,Mx, was submitted to a left pneumonectomy due to invasion of the lower lobe and proximity to the hilum. The patient made an uneventful recovery, but on the 13th postoperative day, presented respiratory failure with need for invasive ventilation, but hemodynamically stable. CT-scan showed a pneumonia spanning the entire right upper and lower lobes. On 15th day, Chest X-ray showed a sudden drop on the normal pleural effusion level, with no worsening of the ventilatory or hemodynamic status and no visible loses. No fistula of the bronchial stump was identified on bronchoscopy, and CT-scan showed an empty left pleural cavity. The patient's condition worsened and he died on the 63rd day. **Conclusion:** This rare entity was first described in 2011 by Merritt et al. in a subset of patients who presented inconsistently with a sudden drop in the pleural fluid level following pneumonectomy and coined the term benign emptying of the post-pneumonectomy space (BEPS). These same authors presented the largest series of confirmed BEPS, with seven cases, with, to the best of our knowledge, no more than 20 cases described. Several mechanisms were proposed to explain this entity. Kanakis et al. theorise the existence of a transient bronchopleural fistula that closes spontaneously. This causes the negative pleural pressure to equalize that of the atmosphere, the hydrostatic balance to be reversed and fluid to be absorbed through the parietal pleura. Another possible explanation is a defect in the diaphragm, either congenital, a porous diaphragm syndrome, or created at the time of the surgery, being more likely when an extrapleural pneumonectomy is performed. Similarly, a less-than-watertight chest wall closure, would allow the fluid to enter the soft tissues of the chest wall. Finally, Gervez-Zapata et al. described a case of a drop in air–fluid level likely due to severe dehydration. Given the case of a septic patient with a sudden drop in the intrapleural effusion level, and even in the setting of a contralateral pneumonia, the hypothesis of a bronchopleural fistula could not be warded of. Still, upon review, the patient was stable, ventilating well and had had no vomits. Bronchoscopy and CT scan showed no fistula, and the surgical team had not seen or caused any diaphragmatic lesion. The question that should be asked is at what point is a wait and watch approach valid? The authors believe that even though BEPS is a diagnosis of exclusion, this point is just before a surgical reexploration.

Keywords: Pleural effusion, BEPS, Postpneumonectomy

EP1.16-31 DISENFRANCHISED GRIEF TOOLS USED IN THE TREATMENT OF BEREAVEMENT, ARE USED IN THE THERAPY OF CANCER PATIENTS

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Background: In the last decade, treatment for bereavement evolved. Jorst (1988) said that mourning occurs when we grieve for the death of our beloved people, but similarly we can mourn the end of a marriage, termination from work, disability, illness, premature delivery, etc. The bereavement experience is characterized by tremendous emotional difficulty, deep sorrow, pain, helplessness, lack of control, disappointment, anger frustration, etc. (Robin, Malkinson, and Witztom 2016), which can lead to depression, and even major dysfunction. People who are dealing with cancer, experience a great sense of loss i.e: loss of self-perception, loss of dreams and expectations, and loss of control in their life. These personal emotional experiences often are not fully spoken about, and there is a large gap between the patient's inner feelings and the perception of their family and friends The reaction of the family and friends is normally encouraging, strengthening, and providing hope for the cancer patient. It is for this reason, there is great difficulty for the family to perceive negative reactions such as deep sorrow, depression, lack of appetite, dysfunction, anger, helplessness from the patient. These reactions stimulate severe responses in both the family and the therapist, especially when there is a major gap between the physical condition of the patient and their emotional response. (For example, the patient has been informed that he is ill, but he has no symptoms, and yet he is currently dysfunctional due to his personal bereavement). The goal of the intervention is to help the patient and his family by the understanding that the patient is dealing with a real loss. This understanding enables emotional processing, as well as reducing the gap between the patient and his family **Method:** During therapy, we use the same tools that are used in the field of bereavement, for example, the use of the 'Two Track Model of Bereavement ', the four truths of the Buddha, the acquisition of the concept of "self-compassion" and techniques for distraction and relaxation. These tools enable normalization, acceptance of the situation, and a discussion of existential questions that arise. **Result:** In families where these tools of bereavement were used, a

reduction was seen, in the gap between the patient and his family. The family became more empathetic, the patient became calmer in the understanding of himself. Thus, the patient was more willing to participate in social functions vs social isolation. **Conclusion:** Treating cancer patients and families, as those who deal with real loss, enables them to better manage and understand their situation appropriately, and enables us (therapists) to be more empathic and target precisely the appropriate treatment for them.

Keywords: Grief - Bereavement therapy - emotional response oncology

EP1.16-32 PERCENTAGE OF ALK REARRANGEMENT AS A RESPONSE PREDICTOR IN NON-SMALL CELL LUNG CANCER TREATMENT

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Background: The presence of the Anaplastic Lymphoma Kinase (ALK) fusion oncogene defines a subgroup of non-small cell lung cancer (NSCLC) with clinical and pathological characteristics. It is estimated that 4 to 7% of patients have this rearrangement and it may be detected in the tumour using fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), and reverse transcription polymerase chain reaction of cDNA. As we walk to a more personalised treatment in NSCLC, we need to search every day for more predictors of response to our newer therapies, such as ALK inhibitors. Our study aimed to correlate the percentage of ALK rearrangement found as a predictor of response in NSCLC ALK-positive treatment. **Method:** Designed a retrospective study with NSCLC ALK rearrangement patients in a peripheral Hospital from the last six years. Collected demographic data, histology, disease stage, the percentage of ALK rearrangement detected by FISH, lines of treatment, the response rate (RR) evaluated by RECIST 1.1 criteria, the progression-free survival (PFS) and the overall survival (OS) in patients under ALK inhibitors. Results are presented as medians and range for non-normally distributed continuous variables and as number/total for categorical data. Statistical analysis was performed using U-Mann-Whitney test, considering a significance level of 5%. **Result:** Eight patients diagnosed with NSCLC ALK-positive, male (4/8), aged 64 (28-85) years, most common histology pattern was adenocarcinoma (6/8), followed by adenosquamous (2/8), mainly in stage IV (6/8) and 2 in stage IIIB, where the most frequent distant metastasis was pleural (4/6), followed by bone (2/6) and pulmonary (1/6), none of the patients had brain metastasis. All ALK-positive with % of rearrangement 68 (18-100), PD-L1 positive, but under 50%, in 1/8 patients with no other mutation found. First line therapy was mainly platinum-based chemotherapy (6/8), followed by ALK inhibitor Crizotinib (2/8). As second-line therapy, all used ALK inhibitors, mainly Crizotinib (5/7) and then Ceritinib (2/7). In third line therapy, there was only one patient with Ceritinib. RR of the patients to the first line therapy was progression disease (5/8), partial response (2/8) and stable disease (1/8). RR in the second line therapy was progression disease (4/6), stable disease (1/6) and partial response (1/6). RR in the third line was progression disease. PFS was 5,5 (2-31) months, and when we used ALK inhibitors as first line, the PFS improved to 19 months. OS was 17 (5-53) months, and with ALK inhibitors as first line was 25 months. We found that there is no statistical correlation between the percentage of ALK rearrangement and the PFS, OS or the response rate in our patients, whatever the line of therapy. Nevertheless, there is an improvement in RR, PFS and consequently in OS among patients with ALK inhibitors in first line. **Conclusion:** Besides our negative results with the the percentage of ALK rearrangement, we found in our sample an improvement in the RR, PFS and OS in patients that made in first line, ALK inhibitors rather than platinum-based chemotherapy, which is compatible with the literature and the use of ALK inhibitors in first line in NSCLC ALK-positive patients.

Keywords: Non-Small Cell Lung Cancer, ALK rearrangement, Response predictor

EP1.16-33 QT PROLONGATION IN AN EGFR 19 DELETION LUNG ADENOCARCINOMA PATIENT FROM ICOTINIB TREATMENT

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Background: An increasing number of tyrosine kinase inhibitors (TKIs) are available for the treatment of non-small cell lung cancer (NSCLC). QT prolongation is one of the known, but relatively rare, adverse events of several TKIs (e.g. osimertinib, crizotinib). Screening for QT prolongation in (high risk) patients is advised for these TKIs. When a QT prolongation develops, the physician is challenged with the question whether to (permanently) discontinue the TKI. **Method:** In this perspective, we report on a patient who developed a QT prolongation during icotinib (a first-generation epidermal growth factor receptor [*EGFR*]-TKI) treatment. **Result:** On discontinuation of icotinib, he developed a symptomatic disease flare, not responding to subsequent systemic treatment. The main aim of this perspective is to describe the management of QT prolongation in stage IV *EGFR* 19 deletion mutation NSCLC patients. We also discuss the ethical question of how to weigh the risk of a disease flare due to therapy cessation against the risk of sudden cardiac death. A family history of sudden death and a prolonged QT interval might indicate a familiar long QT syndrome. **Conclusion:** We have summarised the current monitoring advice for TKIs used in the treatment of lung cancer and the most common druge TKI interactions to consider and to optimise TKI treatment in *EGFR* mutation patients.

Keywords: QT prolongation, lung adenocarcinoma, icotinib

EP1.16-34 SURVIVAL ANALYSIS OF ICOTINIB FOR BRAIN METASTASES IN EGFR MUTATED NON-SMALL CELL LUNG CANCER

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Background: Survival and treatment options are limited for patients with brain metastases arising from non-small cell lung cancer (NSCLC). The aim of this study is to investigate the efficacy and survival analysis icotinib treatment for brain metastasis in non-small cell lung cancer patients with *EGFR* mutation. **Method:** We retrospectively reviewed NSCLC patients with brain metastases who were treated with icotinib, and the survival rate was calculated by Kaplan-Meier method and log-rank test was used to compare the survival rates. Univariate and multivariate factors for survival were analyzed by COX proportional hazards regression model. **Result:** 116 cases of rain metastases in *EGFR* mutated non-small cell lung cancer were female, less than 60 years old and non-smoking patients predominant; COX multivariate analysis found that histologic subtype and EGFR gene subtype were independent prognostic factors for these patients. **Conclusion:** Icotinib showed promising efficacy in NSCLC patients with brain metastases. PFS and OS was longer in patients with adenocarcinoma than in those with a non-adenocarcinoma subtype. PFSand OS was longer in patients with *EGFR* common mutations than *EGFR* uncommon mutations.

Keywords: Non-Small Cell Lung Cancer, brain metastasis, icotinib

EP1.16-35 SURVIVAL OF PATIENTS WITH SMALL CELL LUNG CANCER AT A CANCER HOSPITAL IN THAILAND, 2007-2016

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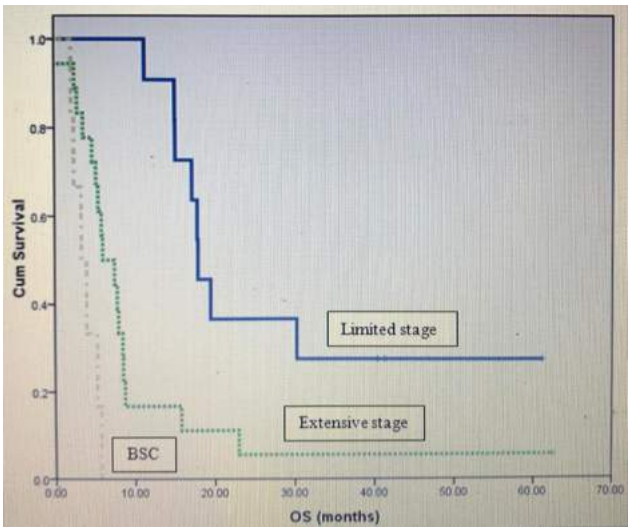
Background: To determine survival of small cell lung cancer (SCLC) patients treated at Chonburi Cancer Hospital (CCH), Thailand. **Method:** The researcher conducted this retrospective study by review medical records of SCLC patients treated at CCH from Jan, 2007-Dec, 2016 and follow up until Dec, 2018. **Result:** This study enrolled 35 patients with median follow up time 7.9 months. The median age of patients was 61.0. Patient characteristics were male (82.9%), history of smoking (91.4%), clinical SVC obstruction at initial treatment (28.6%), ECOG 0-1 (57.1%), ECOG 2-4 and no record ECOG (42.9%).

Treatment		Concurrent chemo +definitive TRT	Sequential chemo +definitive TRT	Sequential chemo +palliative TRT	Palliative chemo.	BSC +/- TRT	Total N=35
Stage	Limited	4	4	3	0	1	12
	Extensive	1	3	3	11	5	23

BSC; best supportive care, Chemo; chemotherapy, TRT; thoracic radiotherapy

Treatment modality was shown in the table. The first two most common chemotherapy as first-line regimen was cisplatin/etoposide (n=18) and carboplatin/etoposide (n=10). Treatment response was CR 10.3%, PR 44.9%, SD 10.3%, PD 3.4 % and NA 31%. Prophylaxis cranial irradiation (PCI) was done in one patient. Overall survival (OS) of the patient received systemic chemotherapy and/or radiotherapy with limited and extensive stage was 17.77 (95%CI;15.22-20.32)(n=11) and 5.94 (95%CI; 2.60-9.23) (n=18) months, respectively, and those of patient received supportive care was 3.28 (95%CI;1.43-5.13) (n=6) months.



Conclusion: The OS of the limited stage SCLC patients at our hospital was comparable to landmark studies. Nevertheless, the small number of the patient received PCI and most received treatment as sequential chemo-radiation.

Keywords: Survival, small cell lung cancer, real world

EP1.16-36 A GOOD INTESTINAL BACTERIAL ENVIRONMENT CAN REDUCE THE SIDE EFFECTS OF TYROSINE KINASE INHIBITORS AND ENHANCE THEIR ANTI-CANCER EFFECTS

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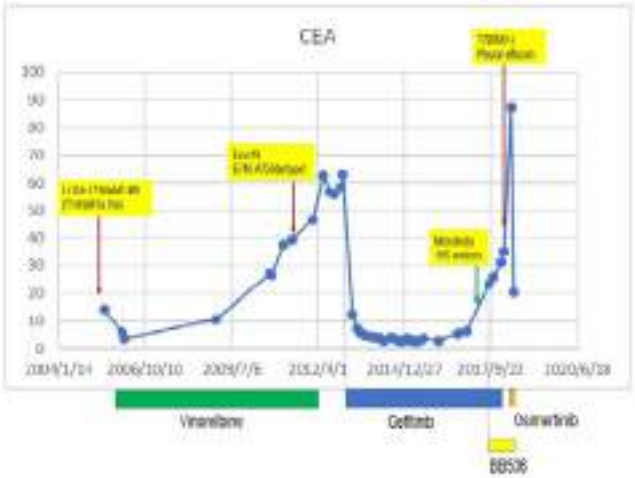
Background: We live in symbiosis with a huge number of microorganisms. Recently, analysis of intestinal bacterial layer has been analyzed in detail in the clinical field by the development of 16S next-generation sequencer. Furthermore, in the lung cancer

region, various tyrosine kinase inhibitors are being administered based on gene mutations of EGF receptor of lung cancer. In this case, an elderly female patient with EGFR gene mutation who was p-stage IVa at the time of surgery was appropriately treated with anticancer agents after surgery and a long-term survival of 14 years after surgery was obtained with a good intestinal bacterial environment. **Method:** The case was a 78-year-old woman at the first treatment in 2004. There was a tumor in the left S4, pleural effusion was positive, and numerous pleural disseminations were observed during surgery (stage Iva). She was treated with vinorelbine alone, taking into consideration her age. The treatment was successful with caution for hematopoietic disorders. She was treated at home, but in October 2011, she observed an increase in CEA and confirmed that the focal gene mutation was the exon 19 deletion E746-A750 deletion type 1. Then, she had multiple systemic metastasis when CEA rose to 63.0ng/mL, gefitinib was introduced in January 2013. Gefitinib responded dramatically, then CEA dropped to 2.8ng/mL and metastases also became CR with dermatitis as an adverse effect. Although she had paronychia in her extremities, she had no gastrointestinal symptoms such as diarrhea and constipation, and her appetite was good. Since there were no digestive tract symptoms at all, analysis of the intestinal flora was analyzed by the next-generation sequencer. **Result:**



The next-generation sequencer has detected no microbiota-disturbing bacteria and balance-regulating bacteria such as Ficarra, fragilis, bifidobacterial, lactic acid bacteria, and equal-producing bacteria. Respiratory distress appeared in November 2017 and a large pleural effusion was noted in the left thoracic cavity. At the same time, CEA rose to 25.9 ng/mL. After genetic mutation check of the pleural effusion, the T790M mutation was confirmed. At this point CEA had risen to 87.4 ng/mL. At this time, Osimertinib was administered, and CEA decreased to about 1/4 to 20.3 ng/mL in two weeks. There were no digestive tract symptoms such as diarrhea and vomiting constipation, and the appetite was also a normal amount. **Conclusion:** A good intestinal bacterial environment can reduce the side effects of tyrosine kinase inhibitors and enhance their anti-cancer effects.

Keywords: Microbiota, tyrosine kinase inhibitor, Bifidobacterium

EP1.16-37 CORRELATION OF SERUM ALBUMIN AND CRP LEVELS WITH CHEMOTHERAPY TOXICITY IN PATIENTS OF METASTATIC LUNG CANCER

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Background:significant proportion of patients of lung cancer present with metastatic disease. Chemotherapy is often offered as first line treatment if patients does not have driver mutations in a specific targetable oncologic pathway and is fit to receive systemic therapy. Systemic inflammation associated with advanced cancer is often regarded as one of the factors for poor prognosis in lung cancer patients. High level of CRP and low levels of albumin are regarded as markers of systemic inflammation and prior studies have shown poor survival in such patients. It has also been shown that systemic inflammation alters the metabolism of chemotherapeutic agents resulting in either treatment failure or increased toxicity, both of which can lead to poor outcomes. This study aims to identify if increased systemic inflammatory response leads to enhanced toxicity with chemotherapeutic agents used in palliative setting in patients of metastatic lung cancer, and in turn poorer survival. **Method:** Trial design Objectives • Primary objective – Correlating chemotherapy toxicity with patients' baseline albumin and CRP levels • Secondary objective - Correlating CRP and Albumin levels with PFS and OS Materials and Method: • Study Design - Patients with a tissue diagnosis of lung cancer will be prospectively enrolled in the study after informed consent. All clinically relevant details will be entered in a clinical proforma. • Site and duration of study - Kidwai Cancer Institute; June 2018 to Dec 2019 • Sample size – All patients meeting the inclusion criteria between the study time period will be included Inclusion Criteria: • Patients of Metastatic Biopsy Proven Lung Cancer • Age 18 – 80 • Planned for chemotherapy with a platin Doublet • Albumin > 2.0 Exclusion Criteria • Presence of targettable driver mutations • Any other Synchronous / Metachronous cancer • Any other uncontrolled medical comorbidities **Result:** Statistical Analysis The Mann-Whitney U test and the $\chi 2$ test will be used to determine statistically significant differences *1/10/2019 #337: Correlation of Serum Albumin and CRP Levels with Chemotherapy Toxicity in Patients of Metastatic..* https://cpaper.ctimeetingtech.com/elcc2019/submission/preview/print?publication_id=337 2/2 Kaplan-Meier method will be used to assess survival curves; Log-rank test to evaluate the statistical

significance of differences and Cox proportional hazards model for multivariate analysis of the effect of clinicopathological factors on survival. **Conclusion:** This study aims to identify if increased systemic inflammatory response leads to enhanced toxicity with chemotherapeutic agents used in palliative setting in patients of metastatic lung cancer, and in turn poorer survival.

Keywords: chemotherapy toxicity, CRP, Serum Albumin

EP1.16-38 PULMONARY INFILTRATES IN PATIENTS TREATED WITH ANTI-PROGRAMMED DEATH-1/PROGRAMMED DEATH LIGAND 1 THERAPY

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Background: Interstitial lung disease (ILD) is one of the fatal toxicities of anti-programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) monoclonal antibodies (mAbs). Some possible risk factors are indicated like male, smoker, and previous history of interstitial pneumonia, but clinical, and radiologic features are not well known. **Method:** Patients who received anti-PD-1/PD-L1 monotherapy were identified at our hospital from March 2016 to October 2018. We identified the patients who developed pulmonary infiltrates after PD-1/PD-L1 therapy, cases with confirmed malignant lung infiltration were excluded. We retrospectively analyzed their clinical and radiological features. **Result:** Of 77 patients who received anti-PD-1/PD-L1 mAbs, pulmonary infiltrates developed in 10. The clinical and radiologic features are shown in Table 1,2.

Table.1 Baseline characteristics of 10 patients with pulmonary infiltrates related to immune checkpoint inhibitors.

Pt	Sex	Age	Histology	Smoking status	Smoking (pack-years)	Stage	Primary site	Performance status	Prior chemotherapy	Radiation history to the Chest	TPS (22c3)	Agents
1	M	73	Adeno	Former	45	IV	Right upper lobe	0	None	None	100	Pembrolizumab
2	M	74	Adeno	Former	80	Recurrent	Right lower lobe	1	None	None	95	Pembrolizumab
3	M	71	Squamous	Current	85.5	IV	Right lower lobe	1	None	None	70	Pembrolizumab
4	M	84	Adeno	Current	48	IIIC	Left lower lobe	1	None	None	65	Pembrolizumab
5	M	71	Squamous	Former	46	IV	Right upper lobe	1	Carboplatin/nab-Paclitaxel Docetaxel	None	30	Pembrolizumab
6	M	70	Squamous	Former	80	IV	Left upper lobe	0	Carboplatin/nab-Paclitaxel Carboplatin/S1	None	NA	Nivolumab
7	M	61	Adeno	Former	28	IIIB	Left upper lobe	1	Carboplatin/Paclitaxel Docetaxel Carboplatin/Pemetrexed Carboplatin/nab-Paclitaxel	60Gy	NA	Nivolumab
8	M	61	Adeno	Former	37	IV	Right pleural	0	Carboplatin/Paclitaxel Carboplatin/Pemetrexed Docetaxel Carboplatin/S-1	None	NA	Nivolumab
9	M	58	Squamous	Former	54	IV	Left upper lobe	2	Carboplatin/Paclitaxel	70Gy	NA	Nivolumab
10	M	81	Squamous	Former	59	IV	Right upper lobe	2	Docetaxel Carboplatin/S-1 nab-Paclitaxel	None	NA	Nivolumab

Table.2 Occurrence with pulmonary infiltrates related to immune checkpoint inhibitors.

Pt	Radio-graphic patterm	Grade	Distribution	Time to event onset, days	KL-6, U/ml		CRP at onset, mg/dl	Treatment	Time from treatment to resolution/ resolving, days	Outcome
					at Base-line	at Event onset				
1	DAD	4	Bilateral/ Diffuse	151	493	4348	25.2	Steroid pulse therapy Antibiotics	64	Resolving
2	OP	5	Bilateral/ Diffuse	9	368	948	25.2	Steroid pulse therapy Antibiotics	Not resolved	Not resolved
3	OP	2	Bilateral/ Focal	63	340	1591	1.1	Oral ste-roids Antibiotics	9	Resolved
4	NSIP	2	Bilateral/ Diffuse	71	407	489	12.2	Antibiotics →Oral steroids	60	Resolved
5	NSIP	3	Bilateral/ Diffuse	17	724	1266	9.9	Steroid pulse therapy	7	Resolved
6	OP	3	Bilateral/ Diffuse	291	254	1182	0.3	Steroid pulse therapy	Not resolved	Not resolved
7	NSIP	1	Unilateral/ Focal	251	256	189	0.2	None	24	Resolved
8	OP	2	Unilateral/ Diffuse	70	N/A	300	2.3	Steroid pulse therapy	69	Resolved
9	NSIP	3	Bilateral/ Diffuse	402	N/A	N/A	7.3	Steroid pulse therapy Oxygen therapy Antibiotics	18	Resolving
10	OP	1	Unilateral/ Focal	56	1078	1257	1.0	None	31	Resolved

Conclusion: Pulmonary infiltrates associated with anti-PD-1/PD-L1 mAbs showed variable onset and clinical, and radiologic appearances. Sometimes it is difficult to identify whether it is ILD or infection. Most ILD cases were successfully treated with corticosteroids, but rarely, ILD worsened despite treatment. Thus, careful monitoring including imaging examinations is important to preventing the worsening of ILD.

Keywords: pd-1/pd-l1, pulmonary infiltrates, ILD

EP1.16-39 PROSPECTIVE EPIDEMIOLOGICAL STUDY OF METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) IN LATIN AMERICA – LATINO LUNG (LACOG 0116)

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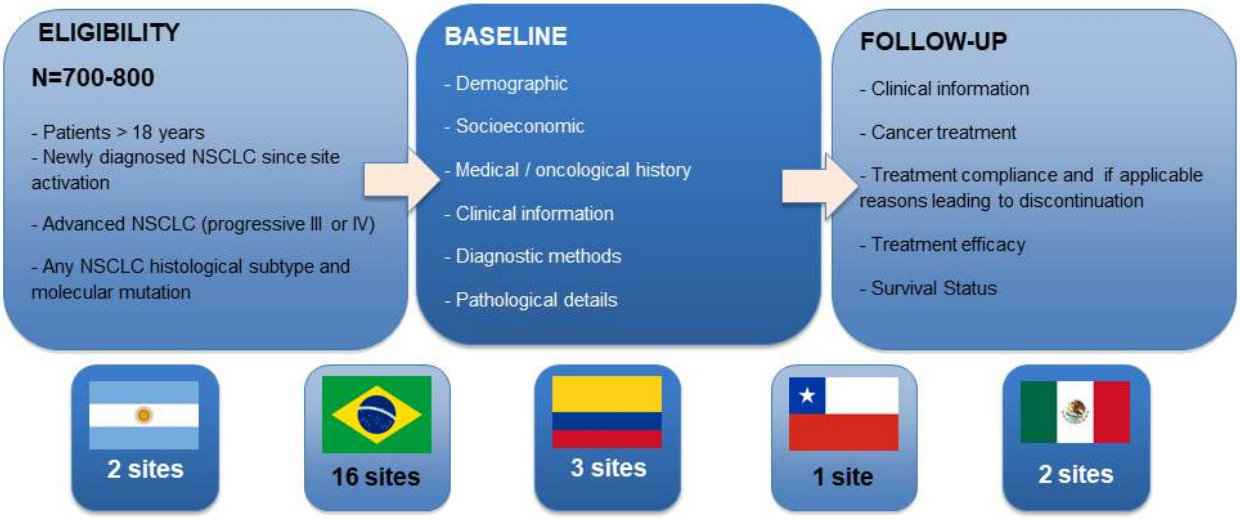
Background: Non-small cell lung carcinoma (NSCLC) is the main cause of cancer-related death in Latin America. Nonetheless, there is insufficient information regarding its epidemiology, treatment and outcomes in the region. The goals of this study are to describe disease characteristics, treatment patterns and survival for advanced NSCLC in Latin America. **Method:** LACOG 0116 LATINO Lung is a prospective cohort study aiming to include approximately 800 patients with advanced stage NSCLC (stage III/IV at diagnosis or distant relapse of early-stage disease) from 24 sites in Brazil, Argentina, Mexico, Colombia and Chile. All consecutive newly diagnosed patients seen at each site will be invited to participate. Data on socioeconomic and demographic characteristics, medical/ oncologic history and clinical-pathological characteristics will be collected at baseline. Thereafter, patients will be followed every 6 months for 3 years in order to gather information regarding treatment patterns and sequencing, reasons for treatment discontinuation, response to treatment, disease progression and overall survival. Data will be collected during medical visits or telephone calls and by medical charts review. Primary endpoint is to estimate the overall survival. Descriptive analysis of treatments and outcomes are planned. Multivariable regression methods will be applied to assess possible independent prognostic or predictive factors. **Result:** As of April 3rd, 2019, 107 patients have been included, all of them within 16 sites in Brazil. Currently, there are 2 sites from Argentina, 2 from Mexico, 3 from Colombia and 1 from Chile awaiting regulatory approval to begin enrollment. Recruitment is planned to last until December 2019, when the estimated sample size will be achieved.



Conclusion: LACOG 0116 LATINO Lung is the first Latin American lung cancer prospective cohort study that will generate real-world data on NSCLC. The study may identify gaps and inequities in a diverse population of NSCLC in Latin America and consequently raise the need for improvement and individualized approach of lung cancer care in the region.

Keywords: Non-Small Cell Lung Cancer, epidemiology, Latin America

EP1.16-40 COMMUNICATING WITH LUNG CANCER PATIENTS IN EASTERN EUROPEAN COUNTRY: TOPICS OF INTEREST

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Background: Sincere and open communication about comprehensive lung cancer (LC) care is often avoided both by physicians and patients. Knowing the patients' points of interest is of great importance for better provision of treatment and further planning of care. Aim of this pilot study was to assess the importance of selected topics for LC patients in order to provide a pathway for improvement of communication with patients. **Method:** This prospective pilot study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Serbia within a one Month period. Consecutive patients with advanced lung cancer in ECOG performance status 0-1 were included in this study regardless of lung cancer type and therapy regimen. Patients filled a questionnaire with 50 selected topics of interest and grading them based on importance using a on 5 point Likert scale. Topics were divided into following sections: diagnosis and prognosis, therapeutic options, care, rehabilitation, supportive and palliative care, psycho-oncology and spirituality. In the last question patients were asked to decide on length or quality of life (QoL). **Result:** The total number of subjects included in this prospective study was 78. Out of total, 66.7% were male and 33.3% female. Average age of subjects was 64 (46-78). Section with topics about diagnosis and prognosis was rated with highest and the one about supportive and palliative care with lowest scores. We observed that topics of highest interest were the goal of therapy, effects of therapy and whether the cancer is curable. Among others most subjects in this study were willing to know more about duration of life when on therapy, how therapy will be applied and should they (and how) change life habits. Least important topics were ones about influence of therapy on sexual life, supportive and palliative care and accommodation in the nursing homes and palliative care units. Out of total, 53.8% of subjects chose quality over duration of life, 15.4% gave priority to life length and the rest (30.8%) could not decide. There were no differences between gender and age. **Conclusion:** Advance communication skills should be equal with other (technical) medical skills. Comprehensive cancer care of LC patients starting from the diagnosis, promoting supportive and palliative care through open communication should be of great importance for all involved parties: patients and their family members and medical staff. Acknowledging important topics and introducing topics of interests for advanced cancer care planning can improve the QoL of LC patients.

Keywords: Communication, Lung cancer, Palliative medicine

EP1.16-41 LUNG LOBECTOMY FOR ELDERLY PATIENTS OVER 85 YEARS OLD IS A RISK OF A COMPLICATION AND LONG-TERM HOSPITALIZATION COMPARED WITH SUBLOBAR RESECTION

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Background: The increased number of elderly patients with non-small lung cancer underwent lung resection, though the clinical outcome has remained unclear. In this study, we reviewed the postoperative complications and clinical outcome after lung resection in elderly patients over 85 years old with lung cancer, defied as "very elderly patients". **Method:** Among patients who underwent lung surgery for non-small cell lung cancer (NSCLC from 2012 to 2019 in our institute, a total 24 patients were enrolled for this retrospective study. **Result:** During the study period, 24 elderly patients (mean age, 87.3) underwent lung resection, consisting of 14 female and 11 male, 19 adenocarcinomas and 5 non-adenocarcinomas, and 19 c-Stage 0: 1, IA: 16, IB: 3, IIA: 2, IIB: 1, IIIA:1[KS1] (based on UICC 7th edition), and 12 sublobar surgery (6 wedge resections and 6 segmentectomies) and 12 lobectomy. Perioperative complications were observed in 8 patients, and the average hospitalization days are 23.4 days. Next, patients were Stratified by the surgical procedure. The clinical stage is, in limited resection group,cStage 0: 1, 1A: 8, 1B: 3, otherwise in lobectomy group, cStage1A: 8, 1B: 0, 2A: 2, 2B: 1, 3A:1[KS2]. The procedures underwent complete video assisted thoracic surgery are 6 in sublobar resection, 3 in lobectomy. Average operation time is 168 minutes in limited resection, 207 minutes in lobectomy, and blood loss is 48.8 ml and 67.5 ml, respectively. No perioperative mortality was observed within 30 days after surgery. There are more complications in lobectomy group than in limited resection group (50.0%, 25.0%), although the p value was not significant (p = 0.22). [KS3] The patients need HOT after surgery is one in limited resection, two in lobectomy. Especially the frequency of onset of arrhythmia requiring treatment is high, 33.3%, in lobectomy group and one case needs implanting a pacemaker. On the other a patient in lobectomy group onsets appendicitis after thoracic surgery and the patient is proceeded appendectomy. The average hospitalization days in lobectomy group, 32.5 days, are longer than in limited resection group, 14.3 days.(p = 0.20) **Conclusion:** Lung lobectomy in very elderly patients is associated with postoperative complications and prolonged hospitalization compared with sublobar surgery.

Keywords: very elderly patients, Elderly patients, complication

EP1.16-42 PHARMACEUTICAL FOLLOW-UP PROGRAM FOR PATIENTS WITH DRIVER MUTATION IN NON-SMALL CELLS LUNG CANCER

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Background: Lung cancer has faced important changes in its recent history. With the improvement of main genetic mutations and its discovery evidences, the target-therapy oriented to specific molecular groups have revolutionized that kind of tumour. Those recent discoveries made possible oral drugs administration procedures at anti-lung cancer treatment. Compared to intravenous therapy, the oral medicine administration brought several benefits, which include the treatment in the comfort of patient's home. However, its use can be frequently associated with some concerns as: treatment adherence, medical conciliation, collateral effects and drug cost. The purpose of this paper is to describe the best practices of follow-up lung cancer patient service model while making use of oral drugs in the household environment. **Method:** This article presents a multidisciplinary team's expertise acting in an oral chemotherapy program, managed by pharmacists between april of 2016 and march of 2019. All patients had driver mutations at non-small lung cancer cells and were being treated at a private medical clinic. **Result:** We developed a service program named as *Projeto Droga Oral (Oral Drug Project)* (Figure 1), in order to contribute to the better management of interdisciplinary team while handling the above mentioned patients. A total number of 77 persons where identified and 9 different drugs where applied: Afatinib, Alectinib, Brigatinib, Ceritinib, Crizotinib, Erlotinib, Gefitinib, Lorlatinib and Osimertinib.

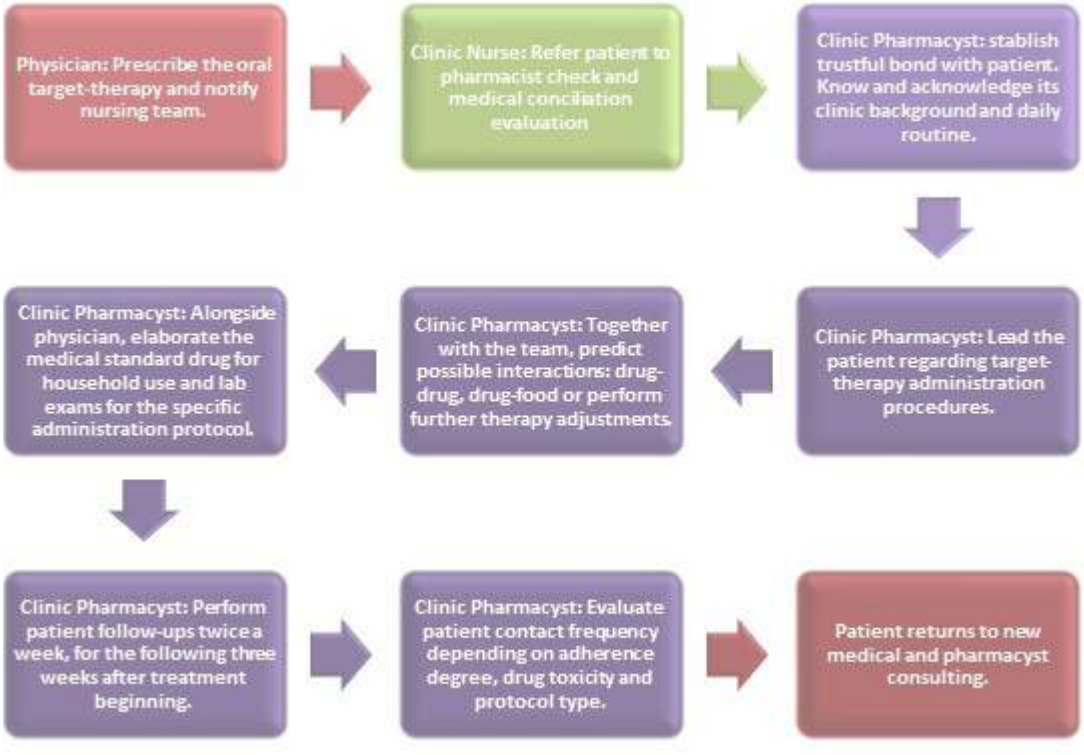

Figure 1: Service flowchart for *Oral Drug Project* Of the mentioned patients, 53% presented drug-drug and 43% drug-food interactions. 95% of all interventions where accepted by multidisciplinary team. No hospitalizations due to drug intoxication were registered and only 2% needed to suspend treatment definitely due to 3rd degree of non-manageable toxicity. 56% presented 1st or 2nd degree of toxicity and prematurely managed. All toxicities were identified and there were no patient abandonment during treatment. **Conclusion:** The *Oral Drug Program* is a key factor to guarantee patient correct follow-ups and treatment success. The development of a support program for the patient and caregiver during the administration of target-therapy at household environment granted the main benefits: quality of life improvement, better therapeutic control, better patient adherence and caregiving management, early problem identification related to the drug use, reduction of hospitalization costs and collateral effects. To ensure the project implementation success, institutional protocol and conduct standardization is mandatory as well as qualified workforce participation and correct patient education about his or her treatment plan.

Keywords: multidisciplinary team, target-therapy, Pharmaceutical follow-up

EPOSTERS

EP1.16-43 COMBINED PROGNOSTIC VALUE OF CYFRA 21-1 AND CEA IN OVERALL SURVIVAL OF PATIENTS WITH III-IV CLINICAL STAGE NSCLC

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Background: Despite great advances in diagnostics and treatment, lung cancer still represents a fatal disease worldwide. Most biomarkers that have been described are not reliable neither applicable in clinical practice, however higher mortality has historically been associated to disease burden and blood biomarkers as CYFRA21-1 and CEA. Our aim was to evaluate the combined prognostic value of two known biomarkers (CEA and CYFRA21-1) among patients with III-IV clinical stage NSCLC in a private Peruvian institution (Oncosalud - AUNA). **Method:** We analyzed data of 117 patients with III-IV clinical stage NSCLC, treated at Oncosalud-AUNA between 2011-2014 (Lima - Peru). The clinical-pathological data were collected from digital medical records. Tumor biomarkers (CYFRA 21.1 and CEA) were collected from blood routine test. Optimal cutoff value of CYFRA 21.1 (<3.3 and >3.3) and CEA (<9 and >9) were calculated using the maximally selected rank statistics. OS was determinate using Kaplan-Meier method and survival curves comparison were performed using log-rank or Breslow test. Cox model was used for multivariate analysis. **Result:** The median age was 67 years (range: 40-84) and 49% of patients were women. The 22.4% had ≥2 ECOG scale, and 74.4% were CS IV, and the most frequent site of metastasis was bone (36%) and brain (22%), and adenocarcinoma (82.9%) was the most common histology. The 90.6% of patients received chemotherapy with or without radiotherapy and 9.4% have TKI as front-line of treatment. The median follow-up was 60 months (95%CI: 4.8-5.1), median survival was 1.4 months (95%CI: 1.1 - 1.7), and two and 5 years survival rate were 37% and 18.6%, respectively. The median survival for monotherapy -based treatment was 5.7 months and 17.2 months for combined treatment. In univariate analysis, ≥2 ECOG scale (p = 0.004), IV CS (p = 0.023), NLR >3.6 (p = 0.003), CYFRA 21.1 >3.3 ng/mL (p < 0.001) and CEA > 9 ng/mL (0.045) were associated with poor survival. Age, sex and LMR do not show significant effect. In the Cox model, high values of NLR (HR: 1.6, 95%CI: 1.1 - 2.5), CYFRA 21.1 (HR: 2.4, 95%CI: 1.4 - 4.1) and CEA (HR: 1.9, 95%CI: 1.1- 2.6) was associated with poor prognosis. The high values of CYFRA 21.1 or CEA increment the risk of death by 4 times more than in those with low values (HR: 4.3, 95%CI: 2.1-9.0). **Conclusion:** Patients with combined values of CYFRA 21.1>3.3 and CEA > 9 were associated to high risk of death in our cohort, combined treatments were associated to longer survival.

Keywords: Advanced NSCLC, CYFRA 21.1, CEA, Overall Survival

EP1.16-44 SURVIVAL AND PROGNOSTIC ASSOCIATION OF NON-SMALL CELL LUNG CANCER WITH BRAIN METASTASES AFTER WBRT: A MULTICENTRE STUDY

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Background: Forty percent of intracranial tumors are metastatic, arising most commonly from lung. To our knowledge, no data is available on prognosis factors of the survival of non-small cell lung cancer (NSCLC) patients with brain metastases in Bangladesh. This study aims to determine overall survival (OS) and identify prognosis factors in NSCLC patients with brain metastases after whole brain radiation therapy (WBRT). **Method:** The study retrospectively investigated histologically proven NSCLC patients with brain metastases at two tertiary hospitals in Bangladesh from January, 2013 to April, 2018. A total of 62 patients were eligible who received 30 Gy (3 Gy per fraction) of WBRT. The primary end point was OS and the secondary endpoint was prognostic association with various factors including patient age and gender, tumor histology, Karnofsky performance status, pleural effusion, primary not controlled, extracranial metastases, the number of brain metastases, surgical resection and diagnosed initially with brain metastases or developed brain metastases later. RTOG Recursive Partitioning Analysis (RPA) was used to categorize the patients. Survival was calculated by Kaplan-Meier method and compared by Log-rank test. Prognostic association was evaluated with Cox proportional hazards model analysis. **Result:** Mean survival of the entire cohort was 5.76 months (95% CI: 4.69 – 6.84 months). Patients with brain metastases at diagnosis or developed brain metastases later during disease progression had a statistically similar mean survival (6.18 months vs. 5.49 months; P = 0.422). Among the 62 patients, 16.1%, 30.6% and 53.2% were RPA Class I, II and III respectively. Mean survival differed significantly among the three classes (Class I: 9.10 months, Class II: 6.68 months, Class III: 3.64 months; P = 0.00). Individual prognostic factors were not found to be associated with survival difference except, single vs. multiple brain metastases (P = 0.042) and primary controlled or not (P = 0.026). **Conclusion:** The study reported survival time of NSCLC patients with brain metastases undergo WBRT, and indicated that higher RPA classes, primary not controlled and greater numbers of brain metastatic lesions are the three prognostic factors of poor survival for this cohort. Our results may help clinicians in patient counseling, treatment selection and designing future clinical trials.

Keywords: Non small cell lung cancer, Prognostic factor, Brain metastases

EP1.16-45 THE USE OF PROPENSITY SCORE MATCHING TO ANALYZE THE EFFECTIVENESS OF MEDICAL PROCEDURES ON THE EXAMPLE OF SURVIVAL OF PATIENTS WITH LUNG TUMORS

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Background: Cancer diseases are among the most common causes of mortality in Poland, with the highest mortality caused by cancers of the trachea, bronchi and lungs (C33 and C34). Simple comparison of the appropriate median survival rates for groups of patients receiving different treatments would require the assumption of high similarity of the characteristics of the patients, what usually cannot be assumed. The Propensity Score Matching method used among others to assess the effects of treatment addresses this problem. The propensity score vector is defined as the probability of being treated. **Method:** Using the Propensity Score Matching method, the impact of the disease stage was estimated as a conditioning variable on the survival of patients undergoing surgery due to squamous cell lung tumors, registered in the database of the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland. The resulting variable in the study is the change in survival calculated in days for two surgical procedures, that is thoracotomy and VATS. In order to ensure comparability of results obtained for both procedures, the analysis included patients with tumors smaller than 55 mm. 10803 patients who have undergone thoracotomy and 1167 patients who have undergone VATS were identified in the database. Only those stages for which number of observations was at least 1000 were analyzed. The calculations were made using the Matching package in R Software. **Result:** In the case of thoracotomy, stages IIA, IB, IIB were associated with prolonged survival (325, 63 and 124 days respectively), whereas patients in stages IVA, IIIA and IIIB survived accordingly 340, 217 and 453 days shorter. For VATS, only patients in stage IIIA survived for considerably different time than other patients – 329 days shorter. **Conclusion:** Propensity Score Matching method confirmed findings from simple comparisons of the appropriate median survival rates.

Keywords: propensity score matching, survival, squamous cell lung tumors

EP1.17 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE

EP1.17-01 SURGICAL RESECTION OF SYNCHRONOUS QUADRUPLE PRIMARY LUNG TUMORS PRESENT AS THREE-DIFFERENT CANCERS AND ONE BENIGN MASS

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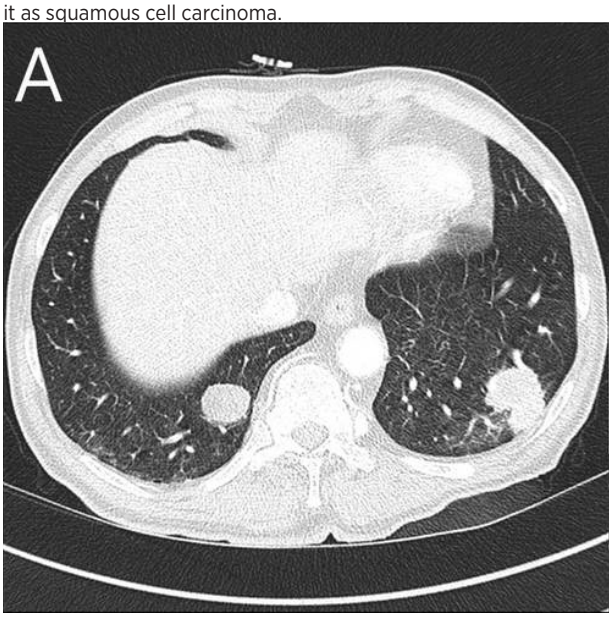
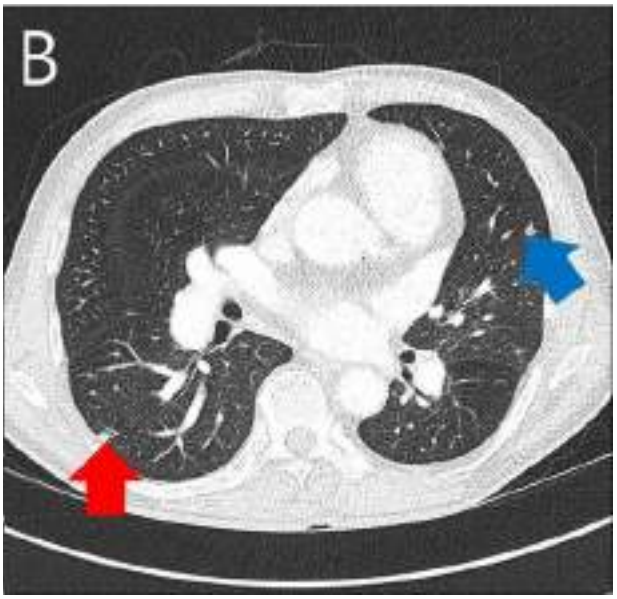
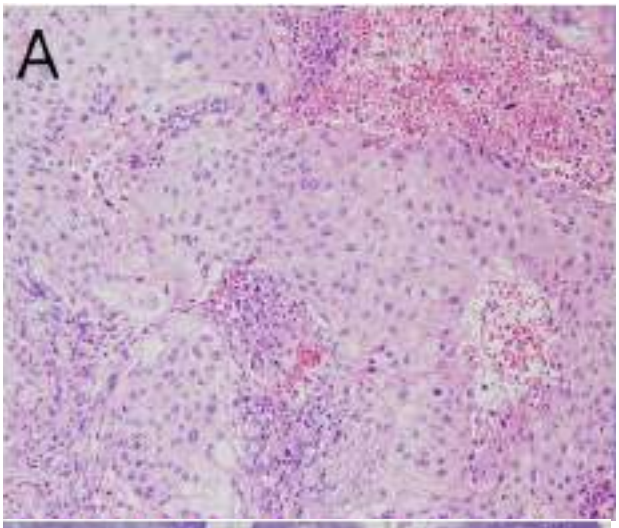
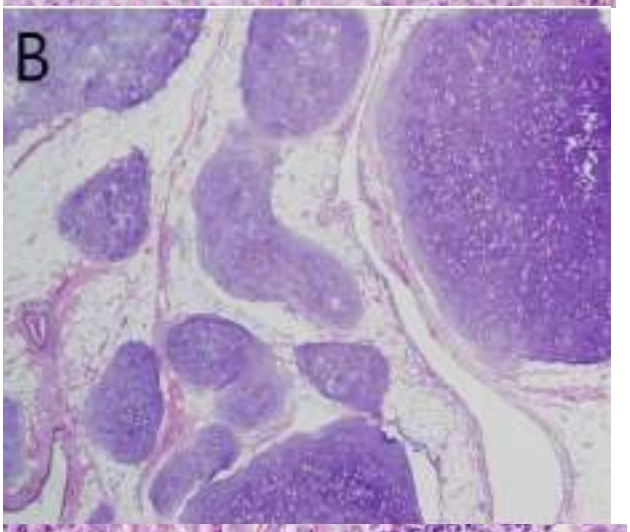
Background: Synchronous triple lung cancer is uncommon and little is known, making it difficult to establish proper guidelines or treatment strategies. In this report, we describe a 70-year-old male with three synchronous independent and histologically different primary cancers and one benign hamartoma. **Method:** Chest CT showed a 30 mm-sized lobulated lung mass in posterior basal segment of the left lower lobe (tumor 1) (Figure 1A). In addition, there were another 26 mm-sized well defined solid nodule in the right lower lobe (tumor 2) (Figure 1A). Two sub-centimeter nodules were also presented in superior segment of the right lower lobe (tumor 3) (Figure 1B) and the lingular segment of the left upper lobe (tumor 4) (Figure 1B). A transthoracic percutaneous needle aspiration biopsy performed on the 30 mm-sized nodule in the left lower lobe revealed it as squamous cell carcinoma.

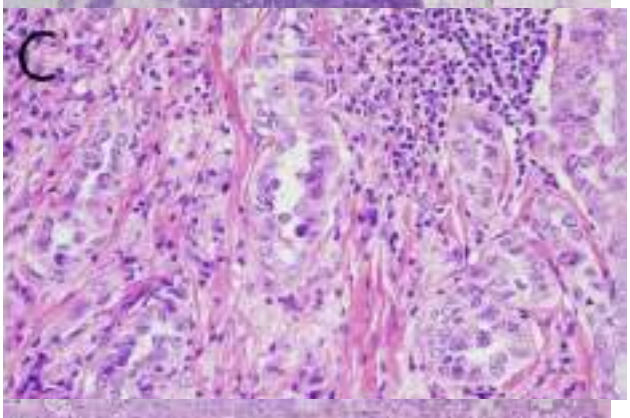


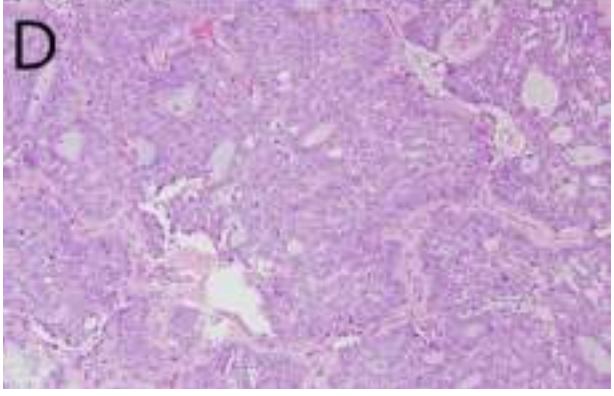


Result: During the right side surgery, intraoperative frozen biopsy of tumor 2 and tumor 4 were reported as chondroid hamartoma and adenocarcinoma, respectively. As we already knew that the left side tumor was squamous cell carcinoma, we decided to continue left side surgery with mediastinal lymph node dissection. The final results of the pathological examination of tumor 1 showed squamous cell carcinoma of pT2bN1M0 (Figure 2A), stage IIB. Tumor 2 was diagnosed as chondroid hamartoma (Figure 2B). Small nodules located in the right lower lobe (tumor 3) and left upper lobe (tumor 4) were 6 mm-sized adenocarcinoma with visceral pleural invasion (pT2aNx) (Figure 2C) and 7 mm-sized adenoid cystic carcinoma (pT1aN0) (Figure 2D), respectively. There was no recurrence during the 3-year follow-up period.









EPOSTERS

Conclusion: Appropriate preoperative staging work up including HRCT and percutaneous needle aspiration biopsy can allow timely detection of synchronous multiple lung cancer, offer proper surgical strategy, and give the possibility of implementing potentially curative treatment for patients conventionally misdiagnosed or considered as metastasized.

Keywords: synchronous tumor, lung cancer, chondroid hamartoma

EP1.17-02 ARTIFICIAL INTELLIGENCE IN THE QUALITATIVE STUDY OF PULMONARY NODULES BY ANALYZING THE GENETIC MAP AND IMAGING DATA OF LUNG ADENOCARCINOMA

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Background: Artificial intelligence is the most influential technology for the future and the hottest research and technology at present. Lung cancer is the most common malignant tumor with the highest morbidity and mortality. By analyzing the genetic characteristics and imaging of patients with lung adenocarcinoma, this study aims to analyze the pulmonary nodules in the susceptible population to find the most characteristic. Gansu province is an economically backward province in northwest China, with a poor environment, poor living conditions, low level of medical and health services, mainly rural population, per capita income less than 5,000 yuan, and a high incidence and mortality of lung cancer and esophageal cancer. Most patients come to the hospital for treatment are in the middle and late stage of lung cancer, and often miss the best time for treatment. Even if they come to the hospital for treatment, there is no good effect, and bring huge economic burden and family burden. The early diagnosis and treatment of lung cancer is particularly important. Artificial intelligence for lung cancer and population census is an economical, convenient and accurate technology, which will bring huge benefits to people's health. **Method:** In this study, the imaging data of diagnosed lung adenocarcinoma patients with pulmonary nodules and the gene sequencing and mutation point of pathological specimens were studied by artificial intelligence, and the lung cancer genes identified by NICC were compared with deep learning to produce relatively complete learning software. The software was used to select the selected sample population of people with high risk of lung cancer regions, and then the postoperative pathology of pulmonary nodules highly suspected of lung cancer was input into the database, and the preoperative diagnosis of AI was compared and studied to optimize the software. **Result:** It is hoped that this study can develop a set of artificial intelligence software with high accuracy and sensitivity, and then carry out early diagnosis and treatment of lung cancer in high-risk groups. Provide research basis for the genetics of lung adenocarcinoma and the early invasion characteristics of lung adenocarcinoma. **Conclusion:** This study could develop a set of artificial intelligence software with high accuracy and sensitivity, and then carry out early diagnosis and treatment of lung cancer in high-risk groups. Provide research basis for the genetics of lung adenocarcinoma and the early invasion characteristics of lung adenocarcinoma.

Keywords: Artificial Intelligence Pulmonary Nodules the Genetic Map adenocarcinoma

EP1.17-03 NEW APPROACH TO COMPLETE VIDEO-ASSISTED THORACOSCOPIC LOBECTOMY IN T2 AND T3 NON-SMALL CELL LUNG CANCER

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Background: The advantages of complete video assisted thoracoscopic surgery(c-VATS) include less postoperative pain and early cosmetic benefit because of the small incision recured. If large tumors can be successfully removed without need for a long thoracic incision or extensive costal rib resection, c-VATS may be performed in patients with stage II or III NSCLC. We herein repot our experience with a novel c-VATS technique that involves removal of resected lung tissu from an abdominal incision in patinets with T2 and T3 NSCLC. **Method:** Fifteen patients with T2 and T3 NSCLC who underwent surgical treatment. Five patients underwent c-VATS lobectomy, and 10 patients under went hybrid VATS(h-VATS), which is performed mainly by direct visualization using video assistance. The tumour large perpendicular was 60 to 140mm in the c-VATS group and 52mm to 82mm in the h-VATSgroup. **Result:** *Surgical procedure.* For lobectomy, the ports were placed in the 3rd, 5fh, and 7th intercostal spaces on the anterior axillary line for the operator and camera pole and in the 6th and 8th intercostal spaces on the infrascapular line for the assistant. An abdominal skin incision of <5cm was then created just below the xiphoid in Fig1. A forceps was inserted through this incision into the intrapleural cavity through the preperitoneal space to remove the resected lung tissu by grabbing the endocatch bag. the resected lung tissue was remoed with the forceps through this route.

Comparison between c-VATS and h-VATS groups. Significantly fewer patients in the c-VATS than h-VATS group developed severe pain in Table1. Fig.1

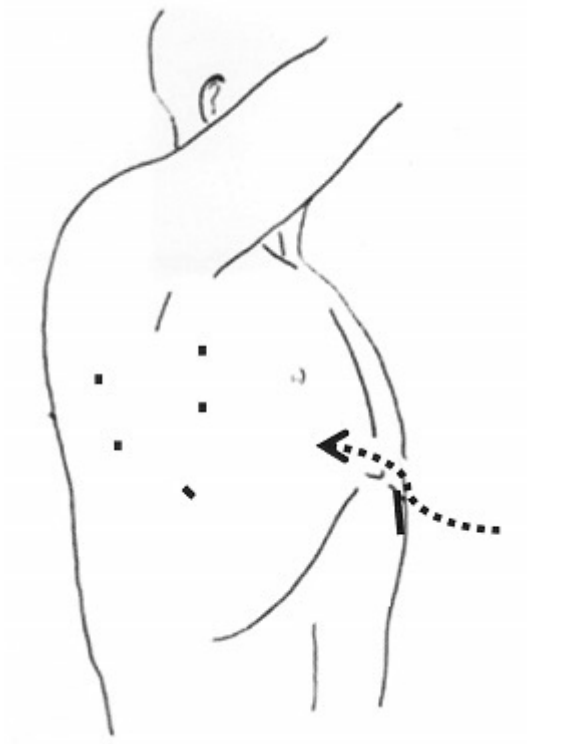

Table 1

	Pain control		
	Yes	No	Total
New procedure	1	4	5
Previous procedure	8	2	10
Total	9	6	15
p-Value	0.025*		

*Calculated by the Chi-squared test.

Conclusion: The present study suggests that the indications for c-VATS lobectomy in patients with T2 and T3 NSCLC can be expanded by implementation of our approach, which involves removal of the free lobe through an abdoninal incision.

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EP1.17-04 PNEUMONECTOMY SHOULD BE AVOIDED IN PATIENTS WHO DO NOT REACH THE DISTANCE OF 500 METERS IN 6-MINUTE WALKING TEST DUE TO HIGH EARLY MORTALITY

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Background: Pneumonectomy is required in less than 10% of patients operated for lung cancer. This type of surgery is performed ultimately because of its debilitating character, high morbidity, and mortality. Previously estimated values of the 6-minute walking test (6MWT) performed preoperatively helps to identify high risk of postoperative complications, increased early mortality and worse long term results in patients undergoing lobectomy for lung cancer. The aim of the study was to validate the value of 500 meters in 6MWT differentiating risk of complications in patients undergoing pneumonectomy. **Method:** Between January 2009 and January 2018 1618 patients were operated in the Thoracic Surgery Department. All of the patients were accepted for resection based on a standard evaluation protocol. Additionally, on the day before the surgery, patients performed 6MWT. 141 patients underwent pneumonectomy, but 16 patients did not undergo 6MWT due to different reasons. Finally, 125 patients entered the analysis. The cut-off value of 6MWT – 500 meters was defined in previously published papers in patients requiring lobectomy. This value was validated in the current study in patients who underwent pneumonectomy. **Result:** There were 93 men and 32 women with a mean age of 63 years. All patients underwent pneumonectomies due to primary lung cancer. The cut-off value of 500 meters identified patients with increased 90-day mortality [17.9% vs. 3.5% odds ratio (OR) 6.271 95% confidence interval (CI) 1.528-25.739 p=0.005], and first-year mortality (30.7% vs. 11.6% OR 3.378 95%CI 1.310-8.709 p=0.009), while 30-day mortality (10.3% vs. 2.3% OR 4.800 95%CI 0.840-27.418 p=0.055) fairly reached statistical significance. Patients who covered distance shorter than 500 meters had increased risk of atrial fibrillation (35.9% vs. 16.3% OR 2.880 95%CI 1.207-6.870 p=0.015) and cardiac complications (38.4% vs. 19.8% OR 2.537 95%CI 1.100-5.849 p=0.026). The rates of pulmonary complications, general complications, and duration of postoperative stay did not differ between the study populations. **Conclusion:** Patients who do not reach the distance of 500 meters in 6MWT have a high risk of cardiac complications and early postoperative death after pneumonectomy.

Keywords: mortality, pneumonectomy, Lung cancer

EP1.17-05 UNIPORTAL VIDEO-ASSISTED THORACOSCOPIC SURGERY LOBECTOMY AND SEGMENTECTOMY FOR EARLY STAGE LUNG CANCER

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Background: With the extensive application of imaging techniques such as HRCT in general and the potential adoption of low-dose spiral CT screening for high-risk former smokers. It is likely that a greater number of small lung cancers will be detected. Uniportal VATS lobectomy and segmentectomy for small-sized lung cancer has been accepted. **Method:** We retrospectively analyzed for 180 patients who underwent Uniportal VATS lobectomy and segmentectomy between January 2018 and December 2018 at our hospital.We reported our uniportal experience, the surgical technique, the extent of lymph node dissection and decision-making of uniportal VATS lobectomy and segmentectomy for small-sized lung cancer. **Result:** 180 patients of early stage lung cancer underwent intended uniportal VATS included 120 lobectomies and 60 segmental resections. The mean operation time was 120.2±40.5 minutes. Chest drain duration was 2.1±0.8 days. The total amount of lymph node stations sampled or dissected were 8.0±0.7. There were no deaths 30 days after surgery. **Conclusion:** Uniportal Video-assisted Thoracoscopic Surgery Lobectomy and Segmentectomy was safe and feasible for early stage lung cancer.

Keywords: Early Stage Lung Cancer, Video-assisted thoracoscopic surgery (VATS)

EP1.17-06 RETROSPECTIVE REVIEW OF INITIAL EXPERIENCE OF ROBOT-ASSISTED LEFT UPPER LOBECTOMY FOR LUNG CANCER IN AN ATTEMPT TO STANDARDIZE ITS PROCEDURE

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Background: Left upper lobectomy (LUL) is high risk because the incidence of pulmonary artery injury is the most frequent than the other lobes. In Japan, lobectomy by robot-assisted thoracoscopic surgery (RATS) has been accepted by the national insurance since April 2018, many institutes still avoid LUL by RATS. We retrospective reviewed our first 8 cases of RATS-LUL and the results were compared with LUL by video-assisted thoracoscopic surgery (VATS) in an attempt to standardize the procedure of RATS-LUL. **Method:** We have started RATS with da vinci Si since September 2018, and the system was switched to Xi in March 2019. Twenty-six RATS were performed until March 2019 including 23 lobectomies. Nine LUL were found but one was performed for benign disease, therefore 8 cases were included in this study as RATS-LUL group. Twenty-eight LUL by VATS were performed from April 2015 to March 2019, were also included in this study as VATS-LUL group. Two groups were compared statistically and the procedure of RATS-LUL in 9 cases was retrospectively reviewed by the videoin an attempt to standardize its procedure. **Result:** No significant difference was found in sex, age, clinical and pathological stages, nodal dissection between the groups. The average operative time (min), console time (min, RATS only), bleeding (g) in RATS-LUL and VATS-LUL were, 142 (127-226), 102 (58-171), 36 (0-165), and 116 (57-166), not available, 74 (0-391), respectively. The operative time was significantly longer in RATS-LUL (p=0.0156). The duration of chest drainage was significantly shorter (p=0.0294) in RATS-LUL (median 1 day) than in VATS-LUL (median 2 days). By the video review, A3 was transected before bronchial transection in VATS-LUL, however, in all cases of RATS-LUL, A3 was transected after bronchial transection. **Conclusion:** RATS-LUL took longer operative time than VATS-LUL but its extension time was only 26 min. RATS-LUL also showed a shorter duration of drainage than VATS-LUL. In our institute, bronchial transection before A3 transection was the de facto standard.

Keywords: robot-assisted thoracic surgery, robot-assisted thoracoscopic surgery, video-assisted thoracoscopic surgery

EP1.17-07 PARTIAL ANOMALOUS PULMONARY VENOUS CONNECTION FOUND DURING A LOBECTOMY FOR LUNG CANCER

F. Yokote, Y. Yamauchi, T. Sakai, Y. Saito, H. Uehara, Y. Sakao, M. Kawamura

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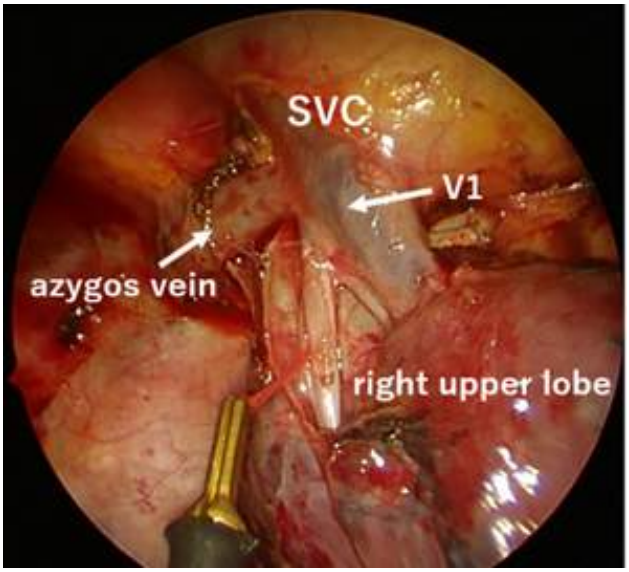
Background: Partial anomalous pulmonary venous connection (PAPVC) is an uncommon congenital anomaly and asymptomatic in most cases. According to previous reports, PAPVC found during a lobectomy for lung cancer is rare. **Method:** A 76-year-old man who was asymptomatic, was referred to our hospital for an abnormal shadow found in the right upper lobe of the lung on computed tomography (CT) scan. A preoperative thoracic plane CT showed a small nodule in the right lobe. The contrast-enhanced CT for evaluating vascular system was not tested due to his renal dysfunction. **Result:** Right upper lobectomy and mediastinal node dissection was performed without any surgical complications. An irregular vascular access was found intraoperatively that the one of superior pulmonary vein (V1) didn't drain into the left atrium but the superior vena cava. The pathological diagnosis of the right lung tumor was adenocarcinoma, pT1bN0M0 stgeIA-2. The postoperative course was uneventful and echocardiography after surgery showed normal cardiovascular activity.



Conclusion: It is possible that PAPVC of a single anomalous pulmonary vein with an intact atrial septum may not be clinically important. However, when the PAPVC is located in a different lobe, major lung resection (especially pneumonectomy) for lung cancer can result in fatal acute right heart failure due to increased shunting through the PAPVC. Therefore, the preoperative discovery of asymptomatic PAPVC may be very important for patients with planned lung resection. We must carefully interpret the findings of the existing architectural structure, including pulmonary artery, vein, or bronchus, as well as a lung tumor on the CT.

Keywords: Partial anomalous pulmonary venous connection, PAPVC

EP1.17-08 GOOD SURVIVAL IN FEMALES UNDERGOING SURGERY WITHOUT ADJUVANT CHEMOTHERAPY FOR STAGE THREE LUNG CANCER: A REVIEW OF OUR 12-YEAR EXPERIENCE

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Background: Lung cancer is a major disease in Singapore. Anatomical surgical resection is the treatment of choice for early lung cancer. No study on outcome of surgery on early lung cancer has been reported in a mixed Asian population. We aim to review the outcome of patients with early lung cancer who underwent surgery in our tertiary centre. **Method:** We performed a retrospective cross-sectional study on all patients who underwent lung resection between 1st January 2006 and 31st December 2017. Information collected included patient's age, gender, race, stage of disease and outcome data. Those with a diagnosis of primary lung cancer were included whilst those whose surgery was not for curative intent were excluded. **Result:** 404 patients are included in our study. The mean age is 62.9 years with the modal age group between 60 and 69 years old. Females are significantly younger than males (mean 61.6 years vs 64.0 years, p = 0.019). 76.6% (n = 310) are early disease (Stage 1 or Stage 2) and 20.0% (n = 81) are late disease (Stage 3). Overall survival is significantly higher in early than late disease and in females than males. In female patients with Stage 3 disease, there is no significant difference in 1-year survival between early (97.3%) and late (89.7%) (p = 0.177) disease. Those aged between 70 and 79 years has a significantly higher mortality at 3 years (27.3%, odds ratio 3.73 (1.0 – 13.5, CI 95%)). There is no significant difference in 3 year mortality between early and late disease in females younger than 60 years old (87.5% vs 77.8%, p = 0.303). T3/T4 disease patients have better survival rates than N2 disease patients. All female patients with T3/T4 disease are still alive at 5 years even in those without adjuvant chemotherapy. In females with N2 disease, 3 and 5-year survival is also higher in patients with partial or no adjuvant chemotherapy but this is not statistically significant. The use of adjuvant chemotherapy is also associated with a significant higher rate of recurrence (53.5% vs 16.1%, p = 0.001) in all patients with Stage 3 disease, especially in female patients (68.2% vs 18.2%, p = 0.009). In females with N2 disease, the recurrence rate is significantly higher in those who had adjuvant chemotherapy (68.4% vs 25.0%, p = 0.049). For those with T3/T4 disease, there is no recurrence in patients who did not have any adjuvant chemotherapy but this is not statistically significant. **Conclusion:** Our study demonstrate that female patients with early lung cancer present earlier and have significant higher survival rates than males. Even in patients with stage 3 disease, there is good survival benefit up to 3 years post-surgery for patients aged 60 years old and below. Three and five year survival are better in female patients with N2 disease who did not have or did not complete their adjuvant chemotherapy than those who did. The use of adjuvant chemotherapy is also associated with a higher rate of recurrence, especially in females with N2 disease.

Keywords: lung cancer surgery, Stage 3 disease, Women health

EP1.17-09 SURVIVAL ANALYSIS OF 911 PATIENTS WITH SURGICALLY RESECTED LUNG CANCERS

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Background: To summarize the treatment results of surgically resected lung cancers. **Method:** Survival analysis was conducted in 911 cases of lung cancers surgically resected during the period of April 2000 to July 2010; 577 (63.3%) were male, 334 (36.7%) female; aged 16 to 85 years-old (middle 60); 455 (49.9%) were smokers. **Result:** Lobectomy and lymph node dissection were undergone. The1, 3, 5, 10-years survival rate for this group of resected lung cancers was 81%, 62%, 53% and 43%, respectively; the middle survival time was 85.5 months. Univariate analysis revealed that gender, smoking status, histology and pathological stages (pTNM stages), tumor size (T factor), lymph nodes' metastasis (N factor), and postoperative adjuvant chemo-radiation therapy were important prognostic factors affecting the postoperative survival significantly (P<0.05). The1, 3, 5, 10-year survival rate for this group of resected stage I (336 cases) lung cancers was 94%, 79%, 75% and 62%, respectively, the middle survival time 132 months; stage II (234 cases): 78%, 60%, 48% and 32%, respectively, the middle survival time 64 months; stage III (242 cases): 69%, 45%, 33% and 24%, respectively, the middle survival time 33 months (P=0.000). The1, 3, 5, 10-years survival rate for resected adenocarcinoma (491 cases) was 85%, 65%, 53% and 39%, respectively, the middle survival time 84 months; squamous cell carcinoma (315 cases): 79%, 60%, 53% and 45%, respectively, the middle survival time 91 months; adenosuamous carcinoma (17 cases): 82%, 58%, 58%, and none, respectively, the middle survival time 78 months; small cell lung cancer (43 cases): 64%, 44%, 33% and none, respectively, the middle survival time 32 months (P=0.011). The1, 3, 5, 10-years survival rate for those who received adjuvant chemo or chemo-radiation therapy (319 cases) was 87%, 73%, 67% and 64%, respectively, the middle survival time 132 months; who did not receive adjuvant chemo or chemo-radiation therapy (592 cases): 78%, 57%, 46% and 36%, respectively, the middle survival time 57 months (P=0.000). **Conclusion:** Pathological stages and postoperative chemo-radiation therapy are independent prognostic factors for surgically resected lung cancers. Surgically resected early stage lung cancers have much better prognosis; postoperative adjuvant chemo-radiation could improve prognosis of surgically resected lung cancers. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05, 17-230-9-71)

Keywords: lobectomy, Lung neoplasms, Survival analysis

EP1.17-10 FIRST RESULTS OF THE BRONCHIAL CANCER REGISTRY OF THE THORACIC ONCOLOGY INTERGROUP (IGOT) OF CASABLANCA, MOROCCO

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Background: Primary bronchial cancer is the leading cause of cancer deathwith an estimated incidence of 1.6 million new cases per year and a mortality rate of 1.4 million per year. In Morocco, according to the Casablanca Cancer Registry, itaccounts for 22.1% of all cancers. The objective of this work is to describe the epidemiological, clinical, pathological and therapeutic characteristics of patients diagnosed with primary bronchial cancer. **Method:** This is a descriptive

retrospective study of a series of 74 cases, conducted by the Thoracic Oncology Intergroup (IGOT) of the Ibn Rochd University Hospital Center in Casablanca from January 2016 to October 2018 and which met the inclusion criteria. All records of patients diagnosed with primary bronchial cancer were retained based on histopathological examination of operative specimens. **Result:** The majority of patients were diagnosed in the later stages of the disease:stage I and II :9,3%, stage III:16% and the stage IV:73,7%. We were able to operate only 6.3% of the 9.3% resecable which is 74 patients. There were 56 men (76%) and 18 women (24%) with a sex ratio calculated at 3.11. The average age was 58.5 years, with age extremes ranging from 24 to 82 years. 35% of our patients had histological confirmation at the time of the diagnosis carried out by the flexible bronchoscopy or the scanno-guided biopsy puncture. Occupational exposure was not noted in our patients. 65% of our patients were smokers. The medical pathological antecedents were tuberculosis in 10% of cases, arterial hypertension in 10% of cases, diabetes in 8% of cases and chronic obstructive pulmonary disease in 4% of cases. Neoplastic antecedents were lung cancer in 4% of cases, digestive cancer in 4% of cases, breast cancer in 3% of cases, cancer of the Otorhinolaryngology sphere in 6% of cases. The average consultation time exceeded three months in 80% of cases. The symptomun derlying the consultation was chest pain in 46% of cases. The radiological lesions were preferentially located at the level of the right lower lobe. The PET-Scan was performed in 65% of the cases and the respiratory functional exploration in 93% of the cases. Neoadjuvant chemotherapy was necessary in 32% of cases and neoadjuvan tradiotherapy in 19% of cases. The treatment was surgical. Surgical approache was postero lateral thoracotomy in 21 cases (28%) and video-assistedt horacic surgery (VATS) in 53 cases (72%). Conversion to thoracotomy was necessary in 9 cases. The interventions performed were 63 lobectomy (85%) and 11 pneumonectomy (15%).The average size of the tumor was 5.5 cm (0.5-12 cm). The predominant histological type was adenocarcinoma in 64% of cases. On the evolutionary level, in the short term, the operative follow-up was simple in 80% of the cases. The other cases had various complications. The main complication recorded was prolonged bubbling in 3.2% of cases. **Conclusion:** The very low level of stage I and II at the time of diagnosis requires sensitization on the interest of screening and early diagnosis so that patients can benefit from endoscopic treatment.

Keywords: VATS, thoracotomy, bronchial cancer

EP1.17-11 NON-SMALL CELL LUNG CANCER SURVIVAL: GENDER INEQUALITY AFTER LUNG RESECTION?

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Background: Gender has been reported as a predictor factor for non-small cell lung cancer survival. Economical status has also been associated with poor prognosis. The objective of this study was to evaluate weather gender or public versus private healthcare assistance is prognostic variables after lung anatomical resection. **Method:** Retrospective analysis of patients with non-small cell lung cancer (NSCLC) surgically resected between January 2008 and December 2013 in a single institution. Gender and type of healthcare system used were evaluated for five-year survival analysis using Kaplan-Meier and log-rank test, as well as by means of Cox proportional hazards regression, adjusted and non adjusted for propensity scores. **Result:** In our study, 300 patients underwent lung anatomical resection for NSCLC, 141 (47%) were women, mean age 63.8 years (10.43), 195 (65%) were from public healthcare system, 254 (84.7) had lobectomy, 145 (48.3%) had adenocarcinoma. Five-year survival for women was 56.1% and men 42,4% (log-rank p=0.003). Five-year survival for public healthcare was 46.0% and private 54.4% (log-rank p=0.133). Female gender was a prognostic factor predicting better survival. However, that was not confirmed after adjusting for propensity scores: HR 1.28 (95%CI 0.91-1.81) for 60-month survival. Public healthcare assistance had no survival difference with patients with private healthcare, HR 1.15 (95% CI 0.80-1.66). **Conclusion:** After adjusting, female gender is not an independent prognostic factor predicting better survival for lung cancer. Patients with lower economic status (public healthcare) treated within the same institution and group of surgeons had no difference in five-year survival compared to patient with access to private healthcare.

Keywords: Gender, Survival, Lung cancer

EP1.17-12 MULTIMODAL AGGRESSIVE MANAGMENT FOR ASKIN' TUMOR: RESULTS AND PROGNOSIS ABOUT 3 CASES

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Background: Peripheral primitive neuroectodermal tumor (pPNET) is a highly aggressive small round cell tumor belonging to PNET/Ewing sarcoma family. Askin's tumor is a rare entity of neuroectodermal pathology that starts from the soft parts of the chest wall. It is observed with predilection in the young subject. Herein; We discuss follow up of three cases after multimodal therapy. **Method:** We report the case of three patients aged respectively 18; 20; 60 years; whose main symptom in consultation is the appearance of a thoracic parietal mass gradually increasing in size and painful. The general condition was completely preserved in all three patients; and the clinical examination is without abnormalities apart from clubbing in the person aged on a past of smoking. Imaging revealed the presence of a thoracic parietal tumor, the largest of which was 15 X 10X 6 cm without signs of locoregional or distant extension with weak contrast. The histological diagnosis was made on a transparietal mass biopsy with a conclusive immuohistochemical study in favor of a PNET tumor (Askin'tumor) **Result:** Management was multimodal with 6 aggressive chemotherapy cycles, followed by extensive carcinologic resection surgery and radiation therapy on the tumor bed. We deplore the loss of a patient after distant recurrence in 8th month; the other two patients remain alive after 25 and 36 months of progression without recurrence. **Conclusion:** Askin's tumor is a bone or extra-bone tumor that is histologically similar to Ewing's sarcoma and PNET, which is characterized by its thoracic location. These three tumors appear to represent different forms of the same entity. They present the same specific chromosomal translocation (11q24-22q12) and, in immunohistochemistry, the same expression of the MIC2 oncogene (CD99) and of the translocation-related FLI-1 protein. The diagnosis is often made at the late stage of locoregional or remote invasion. The treatment is mainly based on surgery and radiotherapy and postoperative chemotherapy to reduce recurrence. The prognosis is unfavorable with a survival at 2 years not exceeding 40% after treatment. Pulmonary metastases are frequently observed even a few years after surgery.

EP1.17-13 OPERATED STAGES I-IIIB NSCLC AMONG YOUNG INDIAN COHORTS - CLINICAL PROFILE AND OUTCOMES

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Background: Lung cancer is the third highest cause of mortality in India. Young lung cancers are on a rise and the characteristics of operable NSCLC among these group needs evaluation. We aim to compare the differential risk factors of Indian young NSCLC patients compared to the older group who underwent resection. **Method:** A retrospective analysis of NSCLC patients operated from May 2012 to December 2018 at DR.BRAIRCH, All India Institute of Medical Sciences, New Delhi, India. Patients were divided into two groups, group (Gp)-YON includes young patients (defined as age 50 years or less) and Gp-OLD includes those older than 50 years. Factors analysed were demographics, histology, stage, disease free survival(DFS) and overall survival(OS) rates. **Result:** A total of 143 patients of NSCLC underwent resection (including those post neoadjuvant chemotherapy). Gp-YON includes 37 (26%) and Gp-OLD 106 (74%) patients. Significant differences were observed between Gp-YON vs GP-OLD among non-smokers 40% vs 26% (p=0.025). Young females were higher in number 27% vs 18% but was insignificant (p=0.229). Other factors between the two groups like performance status(ECOG-2) 5% vs 4% (p=0.297), histologic subtypes(p>0.05)-squamous cell carcinoma(49% vs 55%), adenocarcinoma(38% vs 43%) and NSCLC(not otherwise specified) (2% vs 4%) did not reach statistical significance. The distribution of cases in various stages

were stage IA(13% vs 18%), IIA (24% vs 17%), IIB (18% vs 16%), IIIA 35% vs 36%) and IIIB (10% vs 13%). Stage for stage evaluation was insignificant(p>0.05). Family history, FEV1, intraoperative blood loss, postoperative complications, chest tube drainage and postoperative hospital stay were also insignificant (p>0.05). Distant metastases was lesser in Gp-YON (27% vs 16%, p=0.046). Median follow up was 40.7 months (95%CI 29.7-47.2).The median DFS in Gp-YON (23.3 months, 95% CI: 17.1-28.5) was higher than Gp-OLD (13.6 months, 95% CI: 10.1-15.3). Median OS in Gp-YON (38months, 95% CI: 32-45) was also higher than Gp-OLD (24months, 95% CI: 19-27). Only independent adverse prognostic factor was NACT(neoadjuvant chemotherapy) (HR,2.254, CI:0.98-5.15,p=0.050). **Conclusion:** The number of young operable lung cancer is increasing in India (26%). Non-smokers contribution is significant. Incidence among young females is slightly higher. Patients receiving NACT has an adverse prognosis. Histologic type has no predilection to young age. No survival difference among young compared to old with respect to TNM substages. Distant metastases is lesser in young. Short-term follow up shows that overall young patients have a better DFS and OS as observed from our study.

Keywords: NSCLC, young, India

EP1.17-14 LESS IS MORE: AN UNUSUAL CASE OF BENIGN EMPTYING OF THE POST - PNEUMONECTOMY SPACE

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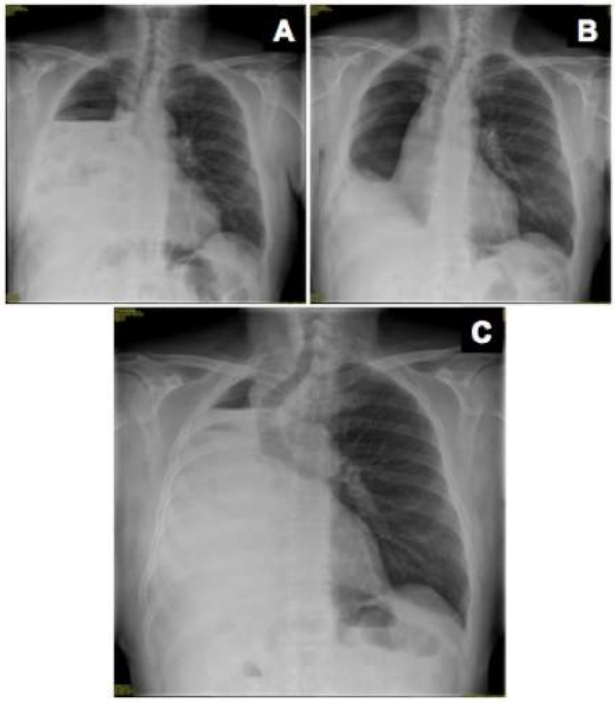
Background: To describe an unusual case of benign emptying of the post-pneumonectomy space. **Method:** A 68-years-old man presented to our clinic with a large swelling located on the previous thoracotomy increasing at Valsalva maneuvers. One month before he underwent right pneumonectomy for lung adenocarcinoma. He was discharged on the seventh post-operative day uneventfully. Patient denied any history of chest trauma, fever, neither productive cough nor vomica. Chest X-Ray showed a drop of the air-fluid level within the post-pneumonectomy space. Suspecting of a broncho-pleural fistula (BPF), patient underwent a flexible fiberoptic bronchoscopy which showed a regular bronchial stump. A chest CT-scan revealed an empty right hemithorax associated with an air collection in the subcutaneous tissues. No pleural puncture was performed, in order to avoid any contaminations of the pleural cavity. A BPF was ruled out; a watchful waiting approach without surgical intervention or antimicrobial therapy was decided. A roentgenogram 10 weeks later showed the almost refill of the pleural cavity and at physical examination the swelling was dramatically decreased. At chest CT-scan 3 months later the post-pneumonectomy space was completely filled by fluid associated with an overexpansion of the residual lung. After one year the patient is healthy and disease-free. **Result:** Patient's presentation meets the clinical and laboratory criteria of Benign Emptying of the Postpneumonectomy Space (BEPS) (afebrile, normal WBC, no fluid expectoration, negative bronchoscopy, negative pleural culture if performed). Among the hypotheses about the pathogenesis of BEPS we advocated the valve-like mechanisms of "occult bronchopleural fistula", which was large enough to let enter only air into the postpneumonectomy space although arresting the passage of pleural effusion to the airways. A spontaneous healing of the micro-fistula was maybe the underlying mechanisms of the refilling of the thoracic cavity. BEPS seldom occurred after pneumonectomy although it should be considered during differential diagnosis of a sudden drop of the pleural fluid especially in asymptomatic patients, in order to avoid unnecessary invasive procedures.



Conclusion: Benign emptying of the postpneumonectomy space should be considered when facing with a sudden drop of the pleural fluid in asymptomatic patients in order to avoid unnecessary invasive procedures.

Keywords: pneumonectomy, Lung cancer, bronchopleural fistula

EP1.17-15 COMPARISON OF LONG-TERM OUTCOME OF WEDGE RESECTION, ANATOMICAL SEGMENTECTOMY AND LOBECTOMY IN STAGE I-II NON-SMALL CELL LUNG CANCER

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Background: In patients with early stage non-small cell lung cancer (NSCLC) lobectomy is still considered the treatment of choice, whereas sublobar resection is more frequently performed in patients with reduced lung function and high perioperative risk. We investigated long term outcome of patients undergoing either lobectomy or anatomical segmentectomy or wedge resection for early stage NSCLC. **Method:** In this retrospective cohort study patients with early stage NSCLC who underwent either lobectomy or anatomical segmentectomy or wedge resection at our center between 2006 and 2018 were analyzed. Primary endpoint was overall survival (OS) and disease-free survival (DFS). **Result:** 383 patients with peripherally located stage I or II NSCLC (TNM 8) who underwent curative intent surgery were identified. Patients undergoing neoadjuvant or adjuvant treatment or with centrally located tumors were excluded. 325 patients (84.8%) received lobectomy, 26 patients (6.8%) anatomical segmentectomy and 32 patients (8.4%) wedge resection. Pathological stage was IA 221 (57.7%), IB 93 (24.3%), IIA 48 (12.5%), IIB (3.9%). Histology revealed adenocarcinoma in 285 (74.4%), squamous cell lung cancer 98 (25.6%). There was no significant difference regarding OS and DFS between all three groups. Interestingly, in patients with tumors larger than 2cm there was also no significant difference in OS and DFS between all groups. **Conclusion:** The relevance of sublobar resection in early stage NSCLC patients is still controversial. In our cohort study the long-term outcome of anatomical segmentectomy and wedge resection was comparable to outcome after lobectomy. However, well-designed prospective randomized studies are necessary to confirm the value of sublobar resections for stage I and II NSCLC.

Keywords: segmentectomy, Wedge, Sublobar

EP1.17-16 ULTRA-SMALL LUNG CANCER (≤0.5CM) IS FACING DILEMMA SITUATION OF OVER-RESECTION

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Background: Lung cancer is increasing rapidly in China. More and more ground-glass opacity (GGO) nodules, micro-small pulmonary nodules (micro-SPN, ≤1.0cm), and ultra-small pulmonary nodules (ultra-SPN, ≤0.5cm) are being detected, most are not malignant, some are atypical adenomatous hyperplasia (AAH), but some are indeed early stage lung cancer, either adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA). Limited resection is reasonable for these micro-small lung cancer (micro-SLC, ≤1.0cm), and ultra-small lung cancer (ultra-SLC, ≤0.5cm), but we always face the dilemma situation that the patients prefer to ask for lobectomy instead of limited resection, no matter what the postoperative pathology will be, a MIA, AIS or just an AAH. For some patients, especially those with family cancer history suffer more mental pressure than others. On the other hand, we face the dilemma situation that when surgery performed at early stage, ultra-SPN stage, the result will be ultra-SLC, AIS, or AAH; when follow-up finds GGO nodules growing up, emerging with malignant signs, it will enter into micro-SPN stage, we may need to cut more lung tissues, the result will become micro-SLC, MIA; when enter into SPN (≤2.0cm) stage, it may become SLC (≤2.0cm), invasive lung adenocarcinomas (ILA). **Method:** Video-assisted thoracoscopic surgery (VATS) and minimally invasive small incision, muscle- and rib-sparing thoracotomy (miMRST) were performed. Case 1: male, aged 60 in 2015, a peripheral ultra-SPN, GGO nodule, 0.3X0.3cm in right upper lobe; it became 0.5X0.3cm in Jan 2018, *VATS* wedge resection was performed. Case 2: female, aged 59 in 2013, an ultra-SPN, GGO nodules, 0.5X0.3cm in right middle lobe; the patient omitted it until it became 0.8X0.6cm in Nov 2016, VATS wedge resection was performed. Case 3: male, aged 55 in 2016, an ultra-SPN, GGO nodules, 0.5X0.4cm in lingular segment, segmentomy was advised; the patient refused; it became 1.0X0.8cm in Jan 2019, lingular segmentomy with lymph node sampling was advised, but the patient insisted on asking for lobectomy, instead of limited resection (both his brothers suffered from lung cancer). miMRST was performed for case 3. **Result:** The patients recovered quickly from mini-invasive surgery. The final pathology was AIS, or MIA. Case 1: the frozen pathology was AAH; the postoperative pathology was AIS. Case 2: the frozen pathology was AAH; the postoperative pathology was MIA. Case 3: the frozen pathology was AAH; the postoperative pathology was MIA. No adjuvant treatment needed. Follow-up shows no recurrence and metastasis. **Conclusion:** Certain GGO nodules progress rapidly, surgery should be performed at much earlier stage, ultra-SPN stage, ultra-SLC stage might be of first choice. For Case 1: if the surgery was done earlier, the final result might be AAH, instead of AIS. For Case 2, 3: if the surgery was done earlier, especially at ultra-SPN stage, the postoperative pathology should be AAH, AIS, instead of MIA. To perform surgery at much earlier stage could help save much more lung tissues, to achieve a much better prognosis for micro-SLC and ultra-SLC patients. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05, 17-230-9-71).

Keywords: Ultra-small lung cancer, over-resection, minimally invasive small incision, muscle- and rib-sparing thoracotomy

EP1.17-17 FEASIBILITY STUDY ON THE CENTRAL OF MASSIVE LESION IN NON-SMALL CELL LUNG CANCER WITH HIGH-DOSE RADIOTHERAPY

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Background: Radiotherapy of the massive lesion in Non-small cell lung cancer remains a great challenge because of the dose limitation due to the normal tissue damage. This study aims to explore the potential feasibility, adding high dose for the central of massive lesion in NSCLC and the surface of massive lesion is conventional dose. **Method:** Patients with massive lesion in NSCLC (tumor volume>500cm^3) who required radiotherapy were enrolled in this study. In the first course of radiotherapy ,the Dose of tumor is divided into 3 parts, PTV of tumor was received 200cGy/F×10 times, the surface of tumor was received 250cGy/F×10 times, The central of massive lesion(delineated by reducing a 3D margin of 1-2 cm from surface of tumor) was received 400cGy/F×10 times. In the second course, GTV should be decreased when tumor shrinked and PTV was received 200cGy/F×15-20 times. The dose did not gived to th surface and central of massive lesion. **Result:** 7 patients with massive lesion in lung cancer was treated with intensity-modulated radiotherapy (IMRT). In the first course, the tumor volume in 6 patients was reduced. After second course, 7 patients were PR. The significant reduction in GTV of one patient (1560cm^3 to 565.25cm^3) .No obvious treatment-related complications occurred during the treatment. **Conclusion:** There was significant reduction in tumor volume and no obvious treatment-related complications by adding high dose for the central of massive lesion in NSCLC. This method is worth to further study.

Keywords: radiotherapy, massive lesion, Non-Small Cell Lung Cancer

EP1.17-18 NEUTROPHIL COUNT IS NON-PROGNOSTIC IN EARLY STAGE LUNG CANCER TREATED WITH SABR: RETROSPECTIVE ANALYSIS FROM A SINGLE UK CENTRE COHORT

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Background: Stereotactic body radiotherapy (SABR) has become the non-surgical treatment of choice for stage I and II lung cancer patients. The small number of treatment fractions required and the favourable toxicity profile means SABR is being utilised in frailer population groups, who are more likely to have other life-limiting conditions. Elevated neutrophil count has previously been shown to associated with poorer overall survival across all lung cancer stages. However, there is a relative paucity of evidence for this relationship for in early, opposed to locally advanced, disease. We aimed to determine if neutrophil count was associated with poorer outcome in our SABR cohort. **Method:** A database was kept of all patients undergoing lung SABR at the Edinburgh Cancer Centre between 2013-2015. Neutrophil counts from up to three months prior to first radiotherapy fraction were obtained from the Scottish Clinical Information Store. Patient outcome data was extracted from the electronic patient records. Statistical analysis was undertaken using Microsoft Excel and SPSS v25.0 (IBM). **Result:** One hundred and forty-eight patients were included in the sample. Eight-one patients (54.7%) were female, mean age 74.1 years (s.d. 8.6, range 52-93). Patients were followed-up for a mean of 1.36 years (range 0.17-4.07 years). Full blood counts were available for ninety-six patients. There was no significant difference in neutrophil count between patients who were alive or dead at the end of follow-up: median (interquartile range) 5.40 (3.40-6.40) *vs.* 6.35 (3.85-8.85), $p = 0.657$. Neutrophil count was also not associated with progression-free survival: median (interquartile range) 5.41 (4.41-6.41) *vs.* 5.86 (3.86-7.86), $p = 0.835$. **Conclusion:** Our findings suggest that pre-treatment neutrophil count is non-prognostic in early stage lung cancer treated with SABR. This contrasts with findings from two other single centre series. Our findings may be attributable to the small tumour size in our cohort.

Keywords: SABR, neutrophils, prognosis

EP1.17-19 ROBOTIC-ASSISTED THORACIC SURGERY FOR EARLY STAGE LUNG CANCER: TEN YEARS' SINGLE INSTITUTION EXPERIENCE

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Background: Less invasive surgical resection for early stage lung cancer is gaining popularity. We analyzed the short- and long-term outcomes of robotic-assisted thoracic surgery (RATS) for early stage non-small cell lung cancer (NSCLC). **Method:** We retrospectively reviewed 339 patients who underwent RATS for clinical stages I ($n = 318$) or II ($n = 21$) NSCLC from November 2006 to December 2016 and we analyzed long-term survival by Kaplan-Meier method. **Result:** Twenty-nine patients underwent segmentectomy, 307 lobectomy,

and 3 pneumonectomy. Conversion occurred in 22 patients (6.5%): 15 (4.4%) due to technical issues, 4 (1.2%) for oncological reasons, and 3 (0.9%) for bleeding. The median number of N1 and N2 stations resected was 2 and 3, respectively, and the median number of N1 and N2 lymph nodes resected was 9 and 6, respectively. Median operative time was 192 minutes for lobectomy, 172 minutes for segmentectomy, and 275 minutes for pneumonectomy. Median length of hospital stay was 5 days (2-191). The most common postoperative complication was prolonged air leak (12.1%). Major complications occurred in eight patients (2.4%). The 30-day and 90-day operative mortality was 0% and 0.3%, respectively. Two and 5-year cancer-specific survival rate was 96.1% and 91.5%, respectively. Five-year survival rate was 96.2% for patients who underwent segmentectomy, and 89.1% for lobectomy. All three patients who underwent pneumonectomy were alive at 5 years with no disease. **Conclusion:** Besides the well-known short-term outcomes showing very low morbidity and mortality rates, mediastinal lymph node dissection during RATS adequately assesses lymph node stations detecting occult lymph node metastasis and leading to excellent oncologic results. However, these results await longer follow-up studies.

Keywords: Early lung cancer, robotic

EP1.17-20 INFLUENCE OF INSURANCE STATUS ON SURVIVAL OF PATIENTS WITH NON-SMALL CELL LUNG CANCER UNDERWENT SURGICAL TREATMENT

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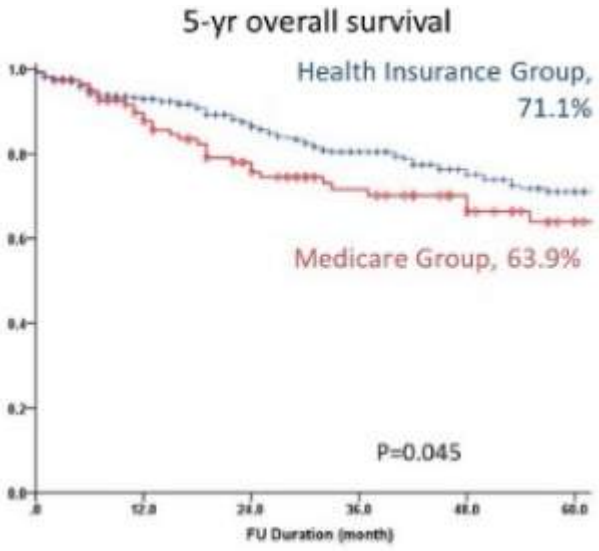
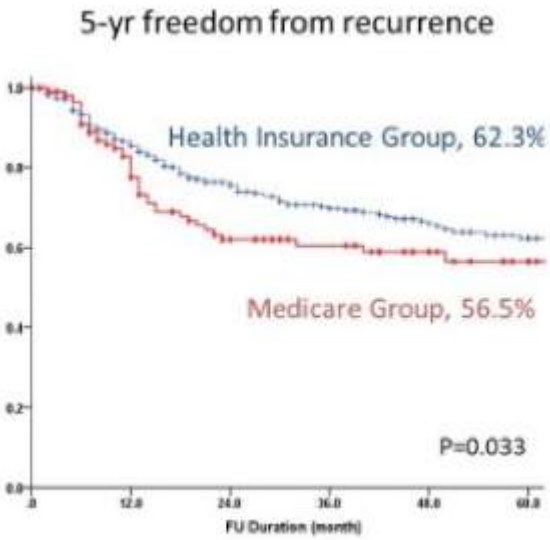
Background: Insurance coverage was an important determinant of access to care and was on potential cause of disparities in lung cancer care outcomes. The aim of the study was to clarify the association between National Health Insurance Status (Health insurance vs Medicare) and survival of patients with non-small cell lung cancer (NSCLC) who underwent surgical treatment. **Method:** Among 544 patients who underwent surgical resection for primary NSCLC from January 1997 to July 2017, 116 patients (21.3%) were in the Medicare Group. Data were analyzed to identify the clinical manifestation and to compare the postoperative and oncologic outcomes between two groups. **Result:** There was no significant different in distribution of pathologic stage (p=0.89). The rates of squamous cell carcinoma were significantly higher in the Medicare group (43.9% vs 30.9%, p=0.03). Minimally invasive surgical approach was performed more in the Health insurance group (67.3% vs 56.9%, p=0.04). In the Healthy insurance group, the median length of hospital stay was significantly shorter (8 days vs 11 days, p=0.01). Although postoperative mortality rates were not different between two groups (1.7% vs 2.1%, p=0.79), the incidence of postoperative complications was non-significantly higher in the Medicare group (35.1% vs 29.8%, P=0.29). The 5-year overall survival and freedom from recurrence were significantly lower in the Medicare group (63.9% vs 71.1%, p=0.045, 56.5% vs 62.3%, p=0.033, respectively). (Figure. 1)





Conclusion: Socioeconomic status based on National Health Insurance service could have a bad influence on overall survival in patients with surgical treated lung cancer.

Keywords: Survival, Lung cancer, Health insurance

EP1.17-21 EARLY STAGE NSCLC (ES-NSCLC) 5-FRACTION STEREOTACTIC BODY RADIATION THERAPY (SBRT) 3-YEAR PATTERNS OF FAILURE

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Background: SBRT is an effective treatment for ES-NSCLC. Five fraction approaches have been advocated to limit treatment induced toxicity. In this report, we evaluate 3-year patterns of failure for an institutional 5 fraction protocol. **Method:** Medically inoperable patients were treated with frameless robotic SBRT. PET/CT was completed for staging and at 6 month follow up intervals. A tumor was considered central if it was located within 2 cm of the proximal bronchial tree (PBT). **Result:** From December 2010 to December 2015, 50 patients with biopsy proven ES-NSCLC (stage I - 31; stage II – 19) with median age of 75 were treated to 50 Gy in 5 fractions. Thirty-nine tumors were peripheral and 11 were centrally located. The majority of peripheral tumors were adenocarcinoma (73%) and the majority of central tumors were squamous cell carcinoma (73%). At median follow up of 36 months, local control, regional control, distant metastasis free survival (DMFS) and overall survival (OS) were 88%, 92%, 83% and 52% for all patients. Local control for peripheral tumors was significantly better than central tumors (94% vs. 60% p-value=0.018). Squamous tumors constituted 60% of local failures despite making up 40% of the entire cohort. Conversely, 12% of peripheral adenocarcinoma failed regionally comprising the only regional failures in this series. DMFS (88% vs. 81% p-value=0.445) and OS (46% vs. 54% P=0.421) were not different for central and peripheral tumors. **Conclusion:** Acceptable outcomes are achievable for central and peripheral inoperable ES-NSCLC patients treated with 5-fraction SBRT alone. However, future trials should consider the addition of systemic therapy to reduce the risk of locoregional and distant failures.

EP1.17-22 IN STAGE I NON-SMALL CELL LUNG CANCER, ABUTTING ADJACENT STRUCTURES IS A POSSIBLE PROGNOSTIC FACTOR

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Background: In TNM staging system, tumor which invades directly adjacent lobe does not change its T status. But there are some papers that emphasize, adjacent lobe invasion should be classified as T3. Here, we report our analysis of clinical characteristics and prognosis of abutting stage I non-small cell lung cancer (NSCLC). **Method:** Non-small-cell lung cancer (NSCLC) which does not exceed three centimeters was enrolled. All patients underwent curative surgical resection from October 2008 to April 2017. We divided the patients into two groups. Abutting group comprised of tumors, which abutted adjacent structures (interlobar fissure, parietal pleura, mediastinal pleura, pericardium, and diaphragm) and non-abutting group was not. We compared patient demographics, surgical procedures, pathologic status, and recurrence rate. Finally, we compared overall survival using Kaplan Meier survival curves. **Result:** Non-small-cell lung cancer (NSCLC) which does not exceed three centimeters was enrolled. All patients underwent curative surgical resection from October 2008 to April 2017. We divided the patients into two groups. Abutting group comprised of tumors, which abutted adjacent structures (interlobar fissure, parietal pleura, mediastinal pleura, pericardium, and diaphragm) and non-abutting group was not. We compared patient demographics, surgical procedures, pathologic status, and recurrence rate. Finally, we compared overall survival using Kaplan Meier survival curves.

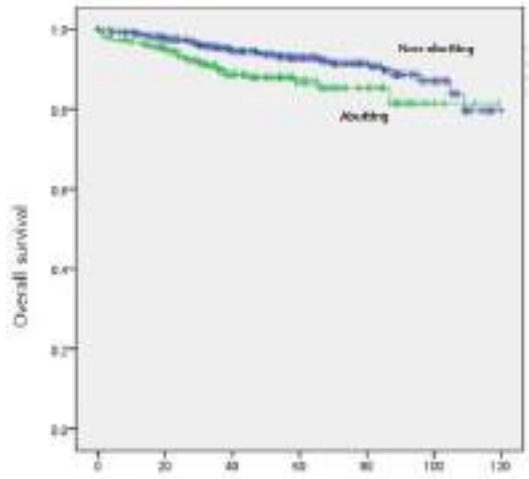

Figure 1. Kaplan-Meier survival curves for overall survival (p<0.01)

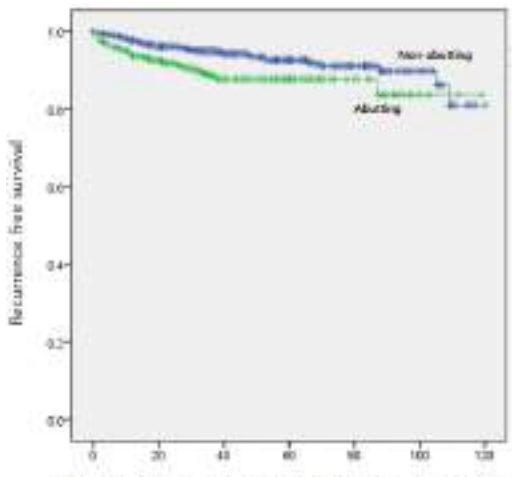

Figure 2. Kaplan-Meier survival curves for recurrence free survival(p<0.01)

Conclusion: In stage I NSCLC which does not exceed three centimeters, abutting to the adjacent structures could be an unfavorable factor in prognosis after curative surgical resection. Further study should be conducted.

Keywords: Lung cancer, Abutting, surgical resection

EP1.17-23 OMENTOPEXY FOR POST-PNEUMONECTOMY BRONCHOPLEURAL FISTULA IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AFTER SALVAGE RADIOTHERAPY

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Background: Preoperative chemotherapy or radiotherapy could affect bronchial mucosa blood flow and also the normal healing process of bronchial stump after surgical resection. Otherwise, bronchopleural fistula (BPF) is the worst and time consuming complication in lung cancer surgery. Pneumonectomy is reported as a high risk surgery of BPF. Here, we report our successful treatment experience of BPF using omentum after salvage radiotherapy in NSCLC patient. **Method:** Retrospective medical chart review **Result:** A sixty-four years old male patient who had a history of chronic obstructive pulmonary disease diagnosed as squamous carcinoma in left upper lobe, clinical stage of T2aN1M0. Because interlobar artery invasion was suspicious, the patient was treated with radical radiotherapy. After 6600cGy of radiotherapy, the lesion showed marked response. Thus we decided to perform curative surgical resection, pneumonectomy. The patient had discharged in postoperative day 11 and the pathologic report was ypT1aN0M0. But after 1 week from discharge, the patient readmitted and complained of dyspnea and profound sputum. In bronchoscopy, fistula was seen. We performed the second operation. Due to hard fibrosis, direct closure of bronchial stump was not possible. Thus, we covered the stump site with omental flap in multilayers. The patient discharged uneventfully and now in disease free status almost after 2 years from initial operation.

Figure1. CT shows bronchial wall disruption and air fluid level in left hemi-thorax. Bronchoscopy shows small fistula hole in bronchial stump.

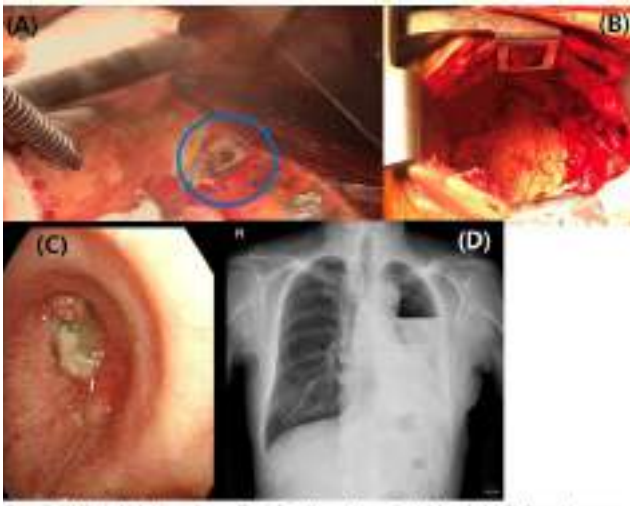

Figure2. (A) Bronchial stump shows disruption(Bronchotomy view), blue circle. (B) Omentum was sutured to peri-stump tissues, double layered. (C) Previous opening has closed with omentum. (D) Uneventful postoperative chest x-ray.

Conclusion: Neoadjuvant radiation therapy and pneumonectomy are risk factors for post-operative BPF. Direct closure with buttressing biocompatible flap is the treatment of choice. But if direct closure is not possible, double-layered omentopexy could be an alternative treatment strategy.

Keywords: Omentopexy, Bronchopleural fistula(BPF), Lung cancer

EPOSTERS

EP1.17-24 BIOLOGICALLY EFFECTIVE DOSE WAS ASSOCIATED WITH OVERALL SURVIVAL IN STEREOTACTIC BODY RADIOTHERAPY FOR LUNG TUMORS

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Background: To evaluate factors associated with overall survival (OS) in inoperable lung cancer cases treated with stereotactic body radiotherapy (SBRT). SBRT delivers precise concentric radiation to a tumor. It is well established that local control depends on the biologically effective dose (BED) delivered, with BED10 of ≥100 as a significant predictor of local control. **Method:** From 2013 to 2016, 22 patients with inoperable lung cancer treated with SBRT who could be followed up until their time of death were retrospectively enrolled. Data on Sex, age, dose (Gy), number of fractions, BED (α/β = 10), pathology, tumor location, performance status, and background lung disease were collected. The median total dose at the isocenter was 50 Gy, and median BED was 120 Gy. We compared OS in groups with BED of ≥120 Gy ("high-BED"; n = 14) and BED of <120 Gy ("low-BED," n = 8). **Result:** Overall, 1-year OS was 48%. In the univariate analysis, the number of fractions, BED, and pathology were significantly associated with OS. The high-BED group showed better OS, with 1- and 2-year OS of 64% and 21%, respectively, compared with 25% and 0% for the low-BED group (p = 0.04). No adverse event of grade 3 or higher occurred. **Conclusion:** For these inoperable lung cancer cases treated with SBRT, BED was significantly associated with OS. The poor of OS rate in our series might be associated with that all the tumors were inoperable.

Keywords: stereotactic body radiotherapy, Lung cancer, inoperable

EP1.17-25 RADIO-GUIDED LOCALIZATION OF SMALL LUNG NODULES

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Background: The widespread use of computed tomography and the obligation of early diagnosis and treatment of small lung nodules have increased in recent years. There are few localization techniques, ROLL seems one of the safest and most effective. The purpose of this study is to report our experience. **Method:** We have retrospectively reviewed all patients with undetermined lung nodule that underwent radio-guided localization. The aim of the study was to evaluate the efficacy of the ROLL for the diagnosis and treatment of small lung nodules. The morning of the surgery, Tc99 macroaggregated albumin was injected guided by computer tomography. Afterwards a SPECT-CT was performed to check the correct localization of the tracer and the patient was brought into the operating room. During the surgery a gamma probe connected to a gamma ray was introduced and the lung surface scanned. After detecting the higher value area, a lung resection was performed and the lung is rescanned to check the residual activity (less than 10%). **Result:** Between November 2011 and February 2019, 30 patients (22 male and 8 female) underwent radiotracer injection followed by lung resection surgery in our institute. Mean age was 66,3 years (range 52 to 76 years). The main complication was pneumothorax (9 patients, 30%), but no patient required chest drainage. There was one non-complicated aortic puncture. There were no other complications. The mean nodule size was 9,07mm +/- 4,35mm and the mean visceral pleural distance was 19,6mm +/-16,27mm. By radiology characteristics, 16 were ground glass opacities, 10 solid nodules and 4 partially solid nodules. The lesions were well detected in 100% cases. They were resected by wedge resection in all the cases. The final pathologic diagnosis confirmed 12 lung adenocarcinoma (6 lepidic growth adenocarcinoma, 3 adenocarcinoma in situ, 2 solid adenocarcinomas, 1 minimally invasive adenocarcinoma), 12 lung metastasis, 2 atypical adenomatous hyperplasia, 2 inflammatory nodules, 1 squamous carcinoma and 1 hamartoma. Clean margins were obtained in 28 patients (93,3%). There were not intraoperative and postoperative complications secondary to the procedure. **Conclusion:** The radio-guided localization is a simple, easy and safe procedure for the diagnosis and treatment of small lung nodules. There were not problems of radiotracer lung diffusion and misplacement.

Keywords: Lung cancer, surgery, Radio-guided

EP1.17-26 SPONTANEOUS RIGHT CONTRALATERAL TOTAL PNEUMOTHORAX IN BULLOUS LUNG AFTER LEFT PNEUMONECTOMY FOR LUNG CANCER

F. Gradica[1], L. Lisha[1], D. Argjiri[1], A. Cani[1], F. Kokici[1], S. Gradica[2], A. Lala[2], K. Gradica[2], L. Shpataraku[1], G. Quadir[3]

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Background: Introduction: The spontaneous contralateral pneumothorax after pneumonectomy is very rare and with a high death rate. Objective: To introduce a patient with spontaneous total pneumothorax in the right hemithorachal post-pneumonectomy with dg.:cancer bronchial. The treatment alternatives are controversial. **Method:** Involved a 52-year-old man with non-small-cell lung cancer (NSCLC) who underwent left pneumonectomy after induction chemoradiotherapy on 2015.One year after surgery 2016 he had total right pneumothorax was treated by pleural drainage. Two(2) years after surgery 2018, he had recureent pneumothorax and was treated with chest tube drainage and pleurodesis with autolog blood. He was discharged and no pneumothorax recurrence occurred for one year. **Result:** After one year he had total pneumothorax right side and severe respiratory insuficience .He came to our hospital 3 hour after right Pneumothorax was started.O2SAT 60 %.Imediatly was treated with right chest tube drainage and airlack was stoped but for safety reason was discharged with Heimlich valvul after pleurodesis with povidion jod(BETADINE) .Heimlich valvul was get out after 10 days.The clinical status of patient is good. **Conclusion:** Although management of pneumothorax after pneumonectomy is challenging, surgical intervention may be useful and necessary especially when there is high risk of recurrent pneumothorax.

Keywords: Contralateral total pneumothorax; After pneumonectomy; Pleurorodese; Heimlich valvul

EP1.17-27 DEVELOPMENT OF TITANIUM ALLOY VASCULAR MIRROR FORCEPS FOR UNIPORTAL VATS

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Background: During lung surgery after the elderly or chemotherapy, blood vessel walls of blood vessels, including pulmonary arteries and micro vessels of soft tissues become fragile. For this reason, it may lead to bleeding during peeling operation with forceps. In order to reduce tissue damages in manipulation at the time of tissue detachment, we have developed a "Mirror ™" forceps with OFFSET of the groove position at the tip in industry and university co-creation and launched it in Japan in 2016. However, when an electric scalpel is used in the distal end portion, minute roughness occurs on the surface of the forceps. In order to solve this problem, we began developing technology to make Uniportal VATS forceps by Electropolishing as a titanium alloy. **Method:** A steel material with a diameter of 5 mm of a titanium alloy material used for the tip of a forceps was cut out and physically polished with # 600 to 1200 diaphragm as a pretreatment for electrolytic polishing. As an electrolytic polishing condition, a comparative test was carried out by using an electrolytic bath of 50% ethylene glycol water with sodium chloride, voltage of 10, 25 and 35 V intermittently applied voltage and time of 3 minutes 10 minutes.

Result: Polishing at 25 V for 3 minutes caused less pitting corrosion (roughening of metal surface) on the surface of the titanium alloys. **Conclusion:** By adopting state-of-the-art Electropolishing at the "last 1 mm" part where the surgical instrument contacts, the patient, it has improved the precision of the surface finishing work.

Keywords: Mirror forceps, Uniportal VATS, Electrolytic polishing

EP1.17-28 ELECTROMAGNETIC NAVIGATION-GUIDED PREOPERATIVE LOCALIZATION FOR SMALL MALIGNANT PULMONARY TUMORS

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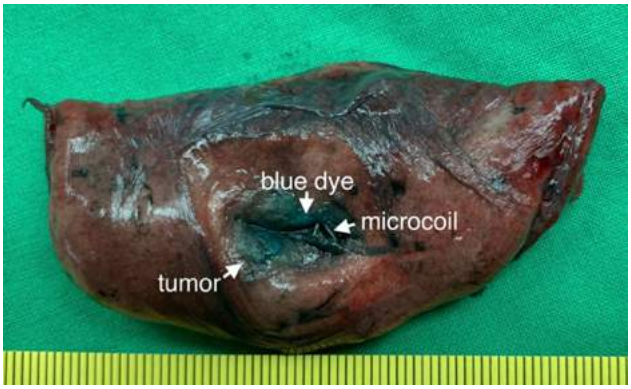
Taipei Veterans General Hospital, Taipei/Taiwan

Background: Surgical removal of non-visible, non-palpable small pulmonary nodules is sometimes challenging during video-assisted thoracoscopic surgery (VATS) and preoperative nodule localization is of paramount importance for precise resection. We reported our experience of preoperative localization using the SPiN thoracic electromagnetic navigation system. **Method:** The inclusion criteria include: 1. Patients with highly suspicious malignant pulmonary nodules according to persistent or progressive nature on follow-up CT scans, or history of extrathoracic malignancy. 2. Target nodule size less than two centimeters. 3. Presumed to be non-visible and non-palpable during VATS according to surgeon`s judgement. 4. Patients who received electromagnetic navigation for preoperative localization. As the SPiN system allows for both transbronchial (endobronchial) and transthoracic (percutaneous) routes, the optimal approach was decided according to the location of target nodule.The preoperative localization and thoracoscopic resection were performed in the same operation room by the same team. The successful localization was defined as successful identification of target tumors during VATS procedure without palpation. **Result:** From Jun 2018 to March 2019, a total of 30 patients with 35 nodules were included. Thirty-one percutaneous and five endobronchial approaches were performed. One patient received both approaches for the same tumor. Three patients received both percutaneous and endobronchial approaches for multiple targets localization. The mean nodule size was 9.6 ±3.5 mm. The materials used for marking included dye (n = 18), micorcoil (n = 4), indocyanine green (ICG, n = 2), microcoil + dye (n = 8), and microcoil + ICG (n = 3). There was no localization-related adverse event. Successful localization was achieved in 27 of 30 (90.0%) patients and 32 of 33 35 (91.4%) nodules. In three patients, localization failed as dye extravasation in the pleural cavity without any stains in the subpleural parenchyma. The pathological diagnosis included metastatic tumors (n = 6), primary pulmonary squamous cell carcinoma (n = 2), and primary pulmonary adenocarcinoma (invasive adenocarcinoma, n = 9; minimally invasive adenocarcinoma, n = 12; adenocarcinoma in situ, n = 6).



Conclusion: We reported our experience of electromagnetic navigation-guided transbronchial and transthoracicpreoperative localization for small malignant pulmonary tumors. Lessons from failed cases were learned and localization techniques were modified to improve successful localization rate.

Keywords: electromagnetic navigation, localization, VATS

EP1.17-29 EVALUATION OF THE INFLUENCE OF REMOVED LYMPH NODES DURING VATS-LOBECTOMY IN THE GROUP OF PATIENTS WITH EARLY STAGE OF NSCLC ON LONG-TERM RESULTS

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National Institute of Chest Diseases, Warsaw, Poland, Warsaw/Poland

Background: Numerous controversies are caused by the smaller number of acquired lymph nodes (LN) during VATS-lobectomy (VATS-L) compared to the classic thoracotomy (TORA-L) and the potential impact on long-term results of treatment in the oncological aspect. The aim of the study was to determine the number of LN removed during VATS-L and compare it to TORA-L in the group of patients with pT1N0 stage and to determine distant experiences in both groups. **Method:** The study was based on data from the National Registry of Lung Cancer. In the first stage, the number of removed nodes in the whole group was analyzed with the cN0 feature including 18199 TORA-L and 2685 VATS-L in stages I and II. In the next stage, in the group of patients in the pN0 stage (9864-TORA-L and 2001-VATS-L), the differences in the number of removed nodes in particular types of lobectomy were determined using the Mann-Whitney test and correlated with the survival curves using the log-rang test **Result:** In the entire examined group, the median of removed nodes was higher in the TORA-L 13 group compared to VATS-L-10 (p <0.0001). In the TORA-L group, the change in grade from N0 to N1 and N2 was found in 11.1% and 7.7% of patients respectively, and in the VATS-L group in 8.8% and 5.7% (p <0.001). In the group of patients with pT1N0, the median of removed nodes for TORA-L and VATS-L were respectively 11 and 9 (p <0.001). The biggest differences concerned the nodes of the groups: 2L, 3, 4L, 7 and 8. In the division into individual lobectomy types, the differences of the removed LN were related to the groups: LDL-2L, 5,6,7,8; LDP-3, LGL-2L, 4L, 8.9; LGP-3, 4R, 7,8,12. 3- and 5-year survivors in the VATS-L group were 84% and 77%, respectively, and were significantly better in comparison to TORA-L: 76% and 67% (p <0.001). **Conclusion:** The long-term results in the early-stage NSCLC in the group of patients treated with VATS are significantly better than in the group treated classically despite the smaller number of removed lymph nodes during the operation. In the absence of the possibility to clearly determine the required number of lymph nodes, lymphadenectomy during VATS-lobectomy should meet the same criteria as for thoracotomy.

Keywords: Early lung cancer, VATS-lobectomy, Limphadenectomy

EP1.17-30 EXPERIENCE OF UNIPORTAL VIDEO-ASSISTED THORACOSCOPIC SURGERY IN A JAPANESE GENERAL HOSPITAL

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Background: The role of multiport video-assisted thoracoscopic surgery (M-VATS) is widely recognized for performing major pulmonary resections. Alternatively, uniportal VATS (U-VATS) is a novel upcoming approach and several institutions around the world have been reported its beneficial effects. We have been performing U-VATS since November 2018. The aim of this study is to evaluate the effectiveness, safety and analyzing short-term results of U-VATS compared with M-VATS. **Method:** A total of 76 patients underwent anatomical pulmonary resection via U-VATS or M-VATS procedures in our institution between June 2018 and March 2019. The general clinical data and perioperative data were retrospectively compared and analyzed between the two groups. **Result:** The two groups were similar in terms of clinicopathological features. Thirty-seven patients underwent U-VATS anatomical pulmonary resections (29 lobectomies and 8 segmentectomies) between November 2018 and March 2019. And 39 patients underwent M-VATS anatomical pulmonary resections (31 lobectomies and 8 segmentectomies) between June 2018 and October 2018. The mean wound length was 4.2cm in U-VATS group. U-VATS showed shorter operative time (124 vs. 152 min, P<0.01) and less postoperative pain at 24 hours (Numerical Rating Scale 0 vs. 1, P<0.01) than those with M-VATS approach. There was no statistical difference in the blood loss (5 vs. 5 g, P=0.07), duration of chest drainage (2 vs. 2 days, P=0.09), total number of dissected lymph nodes (6.3±3.9 vs. 5.6±4.6, P=0.63) and postoperative complications (4 vs. 6, P=0.48) in U-VATS vs. M-VATS. Prolonged air leak was the most common complications in both

groups. In U-VATS group, 1 case was converted to two port VATS due to the failure for stapler pass across the superior pulmonary vein. There was no intraoperative and thirty-day mortality. **Conclusion:** U-VATS is feasible and safe approach, and may be a less invasiveness alternative to M-VATS because of its effectiveness reducing operative time and postoperative pain.

Keywords: lung major resections, Uniportal, video-assisted thoracic surgery (VATS)

EP1.17-31 30 DAYS MAJOR MORBIDITY AND MORTALITY AFTER LUNG CANCER SURGERY. OUTCOMES OF FIVE YEARS IN A SINGLE CENTER EXPERIENCE

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Background: Lung cancer is the leading cause of cancer-related death in the world. Surgery offers the best potential cure, but as in any surgery there are some complications that will be minimized with the improvement of surgical practice and treatment protocols. The aim of this study was to clarify the level of service we are providing in order to improve it and to add more information in the global database on the Thoracic Morbidity and Mortality classification system for patients undergoing lung resection. **Method:** This is a retrospective study that included all patients who underwent lung resection in our department from January 2011 to January 2015. The parameters examined were postoperative mortality thirty days and postoperative complications. Both patients were evaluated prior to surgery according to the Karnofsky score and the intervention was performed by postero-lateral thoracotomy. **Result:** There were 216 patients who were operated on for lung cancer in which 37 (17%) of them underwent pneumonectomy meanwhile the rest lobectomies, bilobectomies and anatomical segmentectomies. The average age was 62.4 years (± 12SD). 12% of patients were women and 88% males. 79% were smokers and 21% non-smokers. According to TNM classification, 10.2% of cases were in the first stage, 44% in the second stage, 21.3% in the third stage and 5.6% in the fourth stage. 40.4% of cases had another illness (cardiovascular disease 24.2%, COPD 11.8%, diabetes mellitus 3.7% and other diseases 0.6%). 17% of patients had complications 30 days after surgery and only 2.3% died. As for pneumonectomy, the complication rate was 24% and the mortality rate was 8%. The main complications that have been observed were 19 cases of empyema, 4 cases of broncho-pleural fistula, 4 cases of pneumonia, 3 cases of prolonged air loss, 3 cases of heart attack and in 4 cases different complications were observed. 2 of mortality occurred due to a heart attack, in 2 cases occurred due to severe pneumonia and in one case a vascular accident occurred during the operation. Hospital stay was 8.5±3 days. **Conclusion:** In our specialty, the complication rate following a surgical operation is a parameter very often used to check the quality level provided by health professionals. Our results show average mortality and morbidity after lung cancer surgery. However, patients with reduced lung capacity and undergoing pneumonectomy should be treated with the utmost care, since they run a considerable risk of major complications or death during the first 30 days after surgery.

Keywords: Lung cancer, lung sresections, morbidity

EP1.17-32 LONG-TERM OUTCOMES OF PULMONARY RESECTION FOR LUNG CANCER PATIENTS WITH CHRONIC KIDNEY DISEASE

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Background: The increasing prevalence of chronic kidney disease (CKD) may hinder the perioperative management and postoperative follow-up of lung cancer. To our knowledge, this study is the first to evaluate the surgical outcomes of surgery for non-small cell lung cancer (NSCLC) in patients with CKD as a preoperative comorbidity. **Method:** Among 671 patients who underwent surgery for NSCLC between 2007 and 2014 at our hospital, 55 (8%) had CKD and we retrospectively analyzed the surgical outcomes of these patients. **Result:** Most patients with CKD were elderly and male. Patients with CKD had a higher frequency of smoking habit, cardiovascular disease, and pulmonary diseases, and a notably lower pulmonary function, resulting in receiving limited pulmonary resection. There were no marked differences in the frequency of surgical complications between patients with and without CKD (p = 0.16). Squamous cell carcinoma was more frequently diagnosed in patients with CKD than in those without it. The 5-year disease-free survival rates in patients with and without CKD were 60.0% and 69.7% (p = 0.06), respectively, and the 5-year overall survival rates were 68.9% and 80.0%, respectively, showing significant differences (p = 0.01). The rate of receiving supportive care was higher in patients with CKD when recurrence observed. **Conclusion:** CKD is associated with a poorer overall survival in patients who undergo lung cancer resection for recurrent disease. As patients with CKD tend to have a poor respiratory function, thoracic surgeons should carefully select the resection type to balance the therapeutic benefit and invasiveness.

Keywords: Lung cancer, surgery, chronic kidney disease

EP1.17-33 PREDICTORS OF AIR-RELATED COMPLICATION AND RE-INTERVENTION AFTER PLEURAL DRAINAGE TUBE REMOVAL IN DIGITAL THORACIC DRAINAGE SYSTEM USE

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Background: After digital drainage system coming onto the market, a number of its advantages have been reported. The objective of this paper is to review the patient's outcome and illustrate the risk factor of postoperative complications and potential of re-intervention needed after pleural drainage tube removal. **Method:** The study population included patients with pre-operative pulmonary function test within 3 months underwent video assisted thoracoscopic or open lung resection surgery and were subsequent managed with digital chest drainage system in our institution between March 2016 and July 2018. **Result:** A total of 497 patients were included, 182 (36.6%) had air-related complications (subcutaneous emphysema, pneumothorax or prolonged air leak) and 23 patients (4.6%) required reintervention because of progression of complications, including re-drainage (n=16) and re-operation (n=7). Patients have higher complication rates in male (56% versus 41.3% years; p=0.001), older age (61.2 versus 57.8 years; p=0.017), with previous smoking history (38.5% versus 18.1%; p<0.001) and chest surgery history (19.2% versus 12.4%; p=0.039), lower FEV1 value (91.47% versus 96.03%; p=0.01), presence of initial air leak (42.3% versus 23.5%; p<0.001) and longer duration of drainage tube placement (6.8 versus 3.9 days; p<0.001), especially prolonged air leak (95%CI: 5.91–19.12; OR: 10.63, p < 0.001). Within above, patients have higher potential of re-intervention due to air-related complication in presence of male (69.6% versus 45.6% years; p=0.024), previous smoking history (52.2% versus 24.3%; p=0.003), initial air leak (78.3% versus 28.1%; p<0.001) and longer drainage tube remaining day (10.4 versus 4.7 days; p=0.002). **Conclusion:** This study demonstrates higher risk of air-related complication after thoracic surgery and subsequently managed with digital chest drainage system, including male sex, old age, previous smoking and chest surgical history, lower forced expiratory volume (FEV1%), initial air leak noted at recovery room and higher proportions of remaining day. Higher potential risk of re-intervention after drainage tube removal are male, previous smoking history, intial air leak and longer tube day. Especially, prolonged air leak had the highest risk with the occurrence of air-related complications and longer tube duration day is significantly associated with higher risk of re-intervention after drainage tube removal, especially over 5 days.

Keywords: digital thoracic drainage system, Post-operative complication

EP1.17-34 ASSOCIATION BETWEEN THE NUMBER OF RESECTED LYMPH NODES AND LONG-TERM SURVIVAL IN N0 NON-SMALL CELL LUNG CANCER: DATA FROM A CHINESE LARGE COHORT

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Background: We aim to investigate the impact of the numbers of resected total lymph nodes (TLNs) and mediastinal lymph nodes (MLNs) on long-term survival in patients with node-negative (N0) non–small cell lung cancer (NSCLC) using a large cohort. **Method:** Patients with N0 NSCLC who underwent R0 resection between 2001 and 2014 were included. Scatter plots of hazard ratios (HRs) from Cox proportional hazards model against the numbers of resected TLNs and MLNs were depicted and curves were fit using a LOWESS smoother. Cut-off points for the optimal numbers of resected lymph nodes were further determined by Chow test. Kaplan–Meier method was used to compare the overall survival (OS) between groups divided by the cut-off points. **Result:** A total of 2,444 patients were included in this study and adenocarcinoma accounted for most of the cases (adenocarcinoma: 1,522/2,444, 62.3%; squamous-cell carcinoma: 784/2,444, 32.1%; others: 138/2,444, 5.6%). Mean numbers of resected TLNs and MLNs were 19.4 ± 11.0 (median: 17) and 12.1 ± 8.6 (median: 10). Cox regression analysis suggested that the increasing numbers of resected TLNs/MLNs were independent factors favoring OS in adenocarcinoma (TLNs: HR = 0.983, 95% confidence interval [95% CI] 0.971 to 0.996, $P < 0.01$; MLNs: HR = 0.983, 95% CI 0.968 to 0.999, $P = 0.034$). Curves of HRs against resected numbers of TLNs/MLNs with Chow test suggested that 17 resected TLNs and 12 resected MLNs were optimal cut-off points for prolonged OS in adenocarcinoma. Furthermore, both the cut-off points were confirmed by OS comparison (5-year OS: 84.2% [≥17 TLNs] vs. 77.9% [<17 TLNs], $P = 0.02$; 84.4% [≥12 MLNs] vs. 78.9% [<12 MLNs], $P = 0.04$) and Cox regression model (TLNs: univariate HR = 0.754, 95% CI 0.593 to 0.959, $P = 0.021$, multivariate HR = 0.712, 95% CI 0.556 to 0.914, $P < 0.01$; MLNs: univariate HR = 0.769, 95% CI 0.598 to 0.988, $P = 0.040$, multivariate HR = 0.730, 95% CI 0.560 to 0.952, $P = 0.020$). However, the numbers of resected TLNs/MLNs were not associated with OS in non-adenocarcinoma (TLNs: HR = 0.998, 95% CI 0.987 to 1.009, $P = 0.756$; MLNs: HR = 1.000, 95% CI 0.986 to 1.015, $P = 0.988$). **Conclusion:** The number of resected lymph nodes associated with OS in N0 lung adenocarcinoma patients. At least 17 TLNs and 12 MLNs are required to be resected to warrant the long-term survival in these patients.

Keywords: Survival outcome, Non–small cell lung cancer, Number of resected lymph nodes

EP1.17-35 CBCT RADIOMICS MAY PREDICT SHORT-TERM SBRT EFFECT IN EARLY STAGE LUNG CANCER PATIENTS

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Background: This study aimed to determine whether radiomics features can be obtained from cone-beam CT (CBCT) through the linac based onboard-imaging systems. **Method:** Thirty consecutive patients with early stage lung cancer treated with stereotactic body radiation therapy (SBRT) (Total dose:50-60Gy, Fraction:5-8) were included. CBCT scan were performed before delivery of each SBRT treatment. Diagnostic CT scan before Radiation Therapy (diagnostic CT) and follow-up CT at one month after radiotherapy (follow-up CT) were analyzed. Primary tumors were delineated manually and modified on diagnostic CT, CBCT and follow-up CT. Tumor size on diagnostic CT and follow-up CT were used to calculate the reduction rate. The primary endpoint was average daily tumor reduction rate. Radiomics features were extracted from first fraction CBCT (CBCT first), last fraction CBCT (CBCT last) and diagnostic CT by Imaging Biomarker Explorer (IBEX) software. Radiomic features were selected using correlation coefficient and LASSO dimensionality reduction based on R. **Result:** A total of 222 radiomics features were obtained from CBCT first, CBCT last and diagnostic CT of each patient. Based on correlation coefficients>0.70 and with LASSO dimensionality reduction, 5, 4 and 5 features were selected in diagnostic CT, CBCT first and CBCT last, respectively. Comparing the features in three CT subsets, two features were same between diagnostic CT and CBCT first, three features were the same between diagnostic CT and CBCT last. Two features are common in all three CT imaging sets. (Table 1)

Table 1 Different characteristic values of different CT radiomics be predicted SBRT reduction rate.

Images	diagnostic CT	CBCT first	CBCT last
Feature	Inverse Variance	Inverse Variance	Inverse Variance
	Percentile	Percentile	Percentile
	Complexity	Cluster Shade	Cluster Shade
	Correlation	Max3D Diameter	Correlation
	Inverse Diff Moment Norm		Information MeasureCorr1

Conclusion: A few radiomics features may be robust to the noise in daily CBCT images which are often considered of poor quality. Study with larger sample size are needed to verify this interesting finding.

Keywords: Radiomics, Cone-beam CT (CBCT), Stereotactic body radiation therapy (SBRT)

EP1.18 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC

EP1.18-01 EFFECTIVENESS OF VIDEO-ASSISTED SURGERY AND PRE-OPERATIVE MULTI-DISCIPLINARY SUPPORT FOR PRESERVING RESPIRATORY FUNCTION

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Background: Evaluation of post-operative respiratory function after lung resection is very important because it greatly affects the quality of life (QOL). **Method:** The predicted post-operative lung VC was calculated according to the number of 42 sub-segments of the lung. The % predicted post-operative VC (%PR) was defined as (number of resected segments)/42 × 100. The % real reduction (%RR) was defined as (pre-operative VC- post-operative VC)/ (pre-operative VC) ×100. Furthermore, we defined %PR-%RR as the index of post-operative reduction of respiratory function (RI).Using RI, we investigated the differences in respiratory function between 22 cases of open-thoracic surgery and 96 cases of thoracoscopic surgery and among 3 different pre-operative support groups, namely, no preoperative support (Non; 39 cases), pre-operative rehabilitation support (Reha; 20 cases), and multi-disciplinary support (Multi; 59 cases). Pre-operative rehabilitation support is coaching for respiratory rehabilitation provided to patients by the rehabilitation physicians and physical therapists at our outpatient clinic. In addition to rehabilitation support, multi-disciplinary support was provided by a multi-disciplinary team consisted of an anesthesiologist, a nutritionist, a pharmacist, a medical social worker, and a nurse. **Result:** The %PR for lobectomy was 9.31 and that of segmentectomy was 2.48; there was a significant difference between them (*p = 0.0151*). The average RI for open-thoracotomy and video-assisted thoracotomy was -0.80 and 9.16, respectively. Pulmonary function was significantly preserved in patients with thoracoscopic surgery compared with that in patients with open-thoracic surgery (*p = 0.00221*). With respect to pre-operative support, the average RI for the Non, Reha, and Multi groups was 5.31, 8.79, and 11.61, respectively. There were significant differences among the three groups (*p = 0.00991*). **Conclusion:** It is difficult to evaluate the respiratory function after lung resection, because the resected lung volume and pre-operative respiratory function may vary among patients. To reduce the fluctuation according to the resected lung volume in each case, the ratio of predicted % reduction and real % reduction (RI) was used to compare the preserved degree of respiratory function for each classified group. The comparison of RI, calculated from the pre-operative and 1-year post-operative VC, proved the preservation of respiratory function by thoracoscopic surgery and pre-operative support.

Keywords: lung resection, evaluation of respiratory functional loss, multi-disciplinary support

EP1.18-02 PATTERN OF POSTOPERATIVE RECURRENCE AND CLINICAL VALUE OF ADJUVANT RADIOTHERAPY IN COMPLETELY RESECTED STAGE III/N2 EGFR-MUTANT NSCLC

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Background: The pattern of postoperative recurrence among patients with stage III/N2 EGFR-mutant non-small cell lung cancer (NSCLC) is seldom reported. Moreover, the clinical value and optimal candidate of postoperative radiotherapy (PORT) for stage III/N2 NSCLC is still controversial. **Method:** Consecutive patients who underwent curative resection and were pathologically confirmed EGFR-positive stage III/N2 NSCLC at Fudan University Shanghai Cancer Center from January 2007 to December 2017, were retrospectively enrolled. Serial imaging scans of each patient were intensively examined and the initial recurrence sites were categorized into five groups: thoracic recurrence, brain recurrence, neck recurrence, abdominal recurrence, and bone recurrence. Recurrence-free survival (RFS) were estimated by Kaplan-Meier curves. The Cox proportional hazards model was applied to estimate the association between RFS and clinic-pathological parameters (including age, sex, tumor size, TNM stage, tumor differentiation, tumor histology, lymphovascular invasion, visceral pleural invasion, and EGFR mutation subtypes), as well as a panel of routinely used immunohistochemical markers (including Her2, Ki67, TTF-1, CK20, CK7, CK5/6, p53, RRM1, NapsinA, p40, syn, Bcl-2, CDX2, ERCC1 and p63). **Result:** Ninety-one patients were identified, all of whom received adjuvant chemotherapy and 28 of whom received PORT. After a median follow up of 28 (range, 6-103) months, disease recurrence occurred in 62 patients. Thirty-six (58.1%) patients had thoracic recurrence, 15 (24.2%) had bone recurrence, 14 (22.6%) had brain recurrence, 9 (14.5%) had neck recurrence, and 8 (12.9%) had abdominal recurrence. Nineteen patients had multiple sites of initial recurrence. In terms of thoracic recurrence, initial relapse at the resection margin occurred in 1 patients and relapse in the mediastinal or ipsilateral hilar lymph nodes was observed in 11 patients. Ki67≥45% and positive expression of ERCC1 were identified as independent predictors of postoperative recurrence in multivariate analysis. Of note, PORT was not significantly associated with RFS in the whole population (p=0.877). However, among the 62 patients who had at least one of the independent predictors of postoperative recurrence (ie: Ki67≥45%, expression of ERCC1), PORT (n=22) significantly prolonged RFS (p=0.043). **Conclusion:** The majority of patients with stage III/N2 EGFR-mutant NSCLC developed their initial recurrence in the thorax. Patients with Ki67≥45% and/or positive expression of ERCC1 have a significant higher risk of postoperative recurrence, who may be the potential candidate for PORT.

Keywords: Non-Small Cell Lung Cancer, EGFR mutation, postoperative radiotherapy

EP1.18-03 OUTCOME OF SURGICAL RESECTION FOR INVASIVE MUCINOUS ADENOCARCINOMA: EXPERIENCE AT A SINGLE INSTITUTION

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Background: Invasive mucinous adenocarcinomas are new histological type which was determined by WHO classification 4thedition. The aim of this study was to investigate the outcome of surgical treatment for the patients with invasive mucinous adenocarcinoma who underwent surgery in our institution. **Method:** Between 2010 and 2013, We identified 68 patients with invasive mucinous adenocarcinoma who underwent surgical resection. We measured the distance of tumor cell size and mucinous size, and their clinical and pathological data were retrospectively reviewed. Overall survival (OS) rates were compared using a log-rank test and survival curves were plotted using the Kaplan–Meier method. **Result:** Participants comprised 31 men and 37 women, ranging in age from 46 to 83 years (median, 67 years). Median observation period in the survivors was 5.1 years. T classification of group oftumor cell size was T1/T2/T3,4=42/17/9 cases, and group of mucinous size was T1/T2/T3,4=38/17/13 cases. The 5-year overall survival rate for group oftumor cell sizewere T1/T2/T3,4=94.3/88.3/60.5%, and group of mucinous size were MS:T1/T2/T3,4=94.1/85.7/70.0%(5Y-OS tumor cell size / mucinous size:p=0.02/p=0.147, 5Y-RFS tumor cell size / mucinous size:p=0.04/p=0.237). **Conclusion:** Our result indicated that to determine T classification, we should measure the distance of tumor cell size instead of mucinous size.

Keywords: invasive mucinous adenocarcinoma, surgery

EP1.18-04 DO TUMOR-RELATED FACTORS PREDICT POSTOPERATIVE PULMONARY COMPLICATIONS IN PATIENTS UNDERGOING CURATIVE SURGERY FOR LUNG CANCER?

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Background: The purpose of the present study is to identify preoperative risk factors related to pulmonary complications with a focus on tumor-related factors. **Method:** The authors conducted a retrospective review of the clinical records of all patients operated at the thoracic department of the Lviv State Oncological Regional Treatment and Diagnostic Center in 2010-2011. Tumor-related factors (histological type of lung cancer, tumor localization, TNM classification, past medical history of different cancer types) were analyzed. Postoperative pulmonary morbidity was defined as: respiratory failure, atelectasis, air leak more than 7 days, prolonged intubation (>72hours), pleural effusion, pleural empyema, chylothorax, and pneumothorax. The study included patients meeting the following criteria: age under 70, absence of neoadjuvant chemo- and/or radiotherapy, benign lung lesions, lung metastases, and non-curative lung resection. Logistic regression was performed using IBM SPSS Statistics 22 program. The result was considered statistically significant when p<0.05. **Result:** 144 patients underwent surgery for primary lung cancer at our institution. Lobectomy was performed in 36.1%, pneumonectomy – in 59%, lung resection – in 4.9% of patients. Histological examination showed that 84 patients had squamous cell carcinoma, 31 patients – adenocarcinoma, 6 patients – large cell carcinoma, 6 patients – small cell carcinoma, 8 patients – NET and 9 patients – other histological types. 12 (8.3%) patients had a medical history of a different type of cancer. The 30-day postoperative mortality rate was 3.47%, postoperative morbidity was 36.8%. The analysis showed that presence of a different type of cancer in past medical history (p<0.05) remained a significant risk factor for respiratory morbidity after lung cancer surgery while the presence of NET reduces the risk of postoperative pulmonary complications (p<0.05). **Conclusion:** Presence of a different type of cancer in past medical history constitutes a significant risk factor for respiratory postoperative morbidity in lung cancer patients. Patients with NET have a lower risk of postoperative pulmonary complications. We suggest that this result requires confirmation by further research

Keywords: lung cancer, postoperative pulmonary complication, risk factors

EP1.18-05 DO WE HAVE BETTER CHOICE FOR INOPERABLE LUNG CANCER PATIENTS WITH GOOD PERFORMANCE STATUS? CONCURRENT VERSUS SEQUENTIAL CHEMO-RADIOTHERAPY

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Background: Lung cancer has hitherto been the commonly life-threatening disease, adjuvant treatment regimens are being explored when tumors are beyond the indication of surgery. Concurrent chemo-radiotherapy is nowadays recommended when compared with sequential chemo-radiotherapy for overall survive benefits during treatment at the cost of increased acute esophageal toxicity. **Method:** Studies are searched from the public database (PubMed, EMBASE, Medline, Cochrane library. Data were analyzed by calculating pooled hazard ratio(HR) for survival and dichotomous variables with risk ratio(RR) for toxicities. Survival benefits (OS and PFS) was regarded as primary outcome, and toxicities was the second outcome. Data consolidation was reflected through forest plots with the bias were evaluated through the tools

of risks of bias. **Result:** 8 studies contained 1223 patients were finally included in this meta-analysis. There were no significant benefits in concurrent chemo-radiotherapy on the two groups' overall survival (HR,0.92; 95% CI, 0.81 to 1.04; p=0.18). Concurrent chemo-radiotherapy performed better in progression-free survival comparing with sequential chemo-radiotherapy (HR,0.83; 95% CI, 0.73 to 0.95; p=0.007). Concurrent chemo-radiotherapy increase the esophagitis and thrombocytopenia (grade 3-4), with (RR 4.49; 95% CI, 3.18 to 6.33; p<0.0001) and (RR 1.55; 95% CI,1.01 to 2.39; p=0.04), respectively. Whereas the two groups performed little significant difference in pulmonary toxicities (RR 0.83; 95% CI, 0.64 to 1.08; p=0.18). **Conclusion:** 8 studies contained 1223 patients were finally included in this meta-analysis. There were no significant benefits in concurrent chemo-radiotherapy on the two groups' overall survival (HR,0.92; 95% CI, 0.81 to 1.04; p=0.18). Concurrent chemo-radiotherapy performed better in progression-free survival comparing with sequential chemo-radiotherapy (HR,0.83; 95% CI, 0.73 to 0.95; p=0.007). Concurrent chemo-radiotherapy increase the esophagitis and thrombocytopenia (grade 3-4), with (RR 4.49; 95% CI, 3.18 to 6.33; p<0.0001) and (RR 1.55; 95% CI,1.01 to 2.39; p=0.04), respectively. Whereas the two groups performed little significant difference in pulmonary toxicities (RR 0.83; 95% CI, 0.64 to 1.08; p=0.18).

Keywords: concurrent chemo-radiotherapy, sequential chemo-radiothrapy, inoperable non-small cell lung cancer

EP1.18-06 RESULTS OF CYTOREDUCTIVE WEDGE RESECTION OF THE PRIMARY SITE IN MULTIDISCIPLINARY TREATMENT OF STAGE III NON-SMALL CELL LUNG CANCER

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Background: In patients with stage III non-small cell lung cancer (NSCLC), radical lung resection for curative intent sometimes can not be performed because of the highly local invasiveness of the tumor and/or the patient' poor general condition. In such cases, combination of radiation therapy, chemotherapy, and sometimes additional immunotherapy is considered. We have performed surgical excisional biopsy by wedge resection for primary site of the lung tumor not only with the diagnostic purose, but also with the intent of cytoreduction and sometimes narrowing the later irradiation range to reduce the risk of radiation pneumonitis (RP). The aim of this study was to determine the results of this cytoreductive wedge resection (CWR) retrospectively, exploring the risk of RP and progression-free survival (PFS). **Method:** We analyzed the medical records of 64 patients who were diagnosed clinical stage III NSCLC at our hospital between October 2012 and May 2018. The patients were divided into three groups according to the diagnostic method (42 patients were radical resection group, 10 patients were CWR group, and 12 patients were biopsy group that was including the patients diagnosed by surgical incisional biopsy and the primary tumor remained). The relationships between clinicopathological characteristics and the diagnostic method, and PFS among the three groups were investigated. **Result:** They were aged between 47 and 88 years (average 70.9), and 41 were men. Thirty-seven patients had adenocarcinoma, 19 had squamous cell carcinoma, and 8 had other. No significant difference was found in age, smoking index, performance status, adverse events in chemoradiotherapy among the 3 groups. In the biopsy group, men and squamous cell carcinoma were significantly more compared with the other 2 groups. PFS was not significantly different between the radical resection group and the CWR group but the biopsy group was significantly associated with shorter PFS (median 552 days, 533 days vs. 360 days, p = 0.01). The incidence of RP was 25% in the CWR group and 57% in the biopsy group (p = 0.20). **Conclusion:** The CWR group showed no inferiority upon PFS compared with the radical resection group. The CWR group showed more than a half rate of RP compared with the biopsy group however this was not statistically significant. It was suggested that the surgical removal of the primary tumor could reach the PFS that is not inferior to the radical resection, and also might reduce the risk of RP compared with the biopsy group.

Keywords: cytoreductive wedge resection, stage III non-small cell lung cancer, Radiation pneumonitis

EP1.18-07 EVALUATION OF PATIENT OUTCOMES USING HAEMATOLOGICAL BIO-MARKERS IN PATIENTS UNDERGOING CHEMORADIATION FOR NON SMALL CELL LUNG CANCER

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Background: Baseline haematological markers have potential to prognosticate the outcomes of patients undergoing chemoradiation for NSCLC (1)(2). We aimed to evaluate progression free survival (PFS) and overall survival (OS) from all patients with NSCLC receiving radical Cisplatin/Vinorelbine chemoradiation in 2017, based on absolute neutrophil count (ANC) and Neutrophil-Lymphocyte Ratio (NLR). **Method:** Patients identified by interrogating the local chemotherapy and radiotherapy prescribing databases. We included all patients whose intended treatment was radical radiotherapy (60Gy/30 fractions over 6 weeks), with 4 cycles of concurrent Cisplatin and Vinorelbine. We recorded patient and tumour characteristics alongside baseline ANC and NLR. Kaplan Meier Survival Analysis was used to compare Progression Free Survival (PFS) and Overall Survival (OS). Previous studies in locally advanced lung cancer has shown outcome differences comparing groups ANC of 8 and NLR of 5. We used a log rank test to differentiate between these cohorts with a pre-test p value of 0.05. **Result:** 50 patients were identified. Median age was 64 years old (range 42-78). 56% were male and 44% female. 11 patients (22%) were ECOG performance status (PS) 0, 38 patients (76%) PS 1 and 1 patient (2%) PS 2. No patients were PS 3 or 4. 10 patients(20%) had an ANC<8, 40(80%) had ANC >8 (Range 1.37-20.94). PFS (ANC<8 vs ANC>8, 115 weeks vs 34 weeks, p=0.005) and OS (130 weeks vs 34 weeks, p=0.047). 10 patients (20%) had a NLR>5, 40 (80%) had NLR<5 (Range 0.81-19.39). PFS (NLR <5 vs NLR >5, 101 weeks vs 32 weeks, p=0.053) and OS (130 weeks vs 59 weeks, p=0.132).

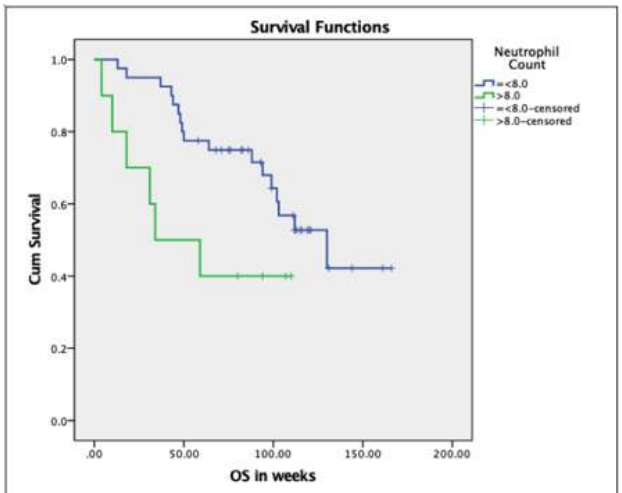

Figure 1: Kaplan Meier survival curve of patients with normal or high pre-treatment neutrophil count. Log Rank Significance = 0.047.
Median OS Neut =<8.0 = 130 weeks. (95% CI 86.904-173.096)
Median OS Neut >8.0 = 34 weeks. (95% CI 0.00 – 77.386)

Conclusion: The sample selected shows a statistically significant association between baseline neutrophil count and overall survival in patients receiving chemo-radiotherapy for NSCLC. This suggests that these haematological baseline characteristics can help risk stratify patients. Further understanding of NLR is required as the sample showed no statistical significance between the two groups although this may be in part due to relatively small sample size. References (1) Schernberg et al (2018). "Neutrophilia as prognostic biomarker in locally advanced stage III lung cancer." PLOS one. 13(10). (2) Scilla et al (2017). "NLR Is a Prognostic Marker in Patients with Locally Advanced Non-Small Cell Lung Cancer Treated with Combined Modality Therapy." The Oncologist. 22:737–742.

Keywords: Non small cell lung cancer, chemoradiation, biomarkers

EP1.18-08 PULMONARY LOBECTOMY AND COMPLETION PNEUMONECTOMY FOR IPSILATERAL LUNG CANCER AFTER RADICAL RESECTION

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Background: Ipsilateral reoperation such as lobectomy and completion pneumonectomy after radical resection of lung cancer is a high-risk operation. We evaluated outcomes after these operations in our hospital. **Method:** We retrospectively reviewed the records of 27 patients who underwent ipsilateral lobectomy or completion lobectomy for new primary lung cancer or recurrence after pulmonary lobectomy or bi-lobectomy between 1998 and 2017. **Result:** 9 patients underwent completion lobectomy, of which 4 were right and 5 were left, and 18 patients underwent lobectomy. Mean operative time was 308.7±27.4 minutes, and mean blood loss was 706.9±254.3mL. Blood loss was significantly higher in completion pneumonectomy patients as compared to lobectomy patients, whereas operative time was not different between the operations. There was no perioperative mortality, but intraoperative complications were seen in 4 cases (14.8%), which were 2 pulmonary artery injury, superior venous cava injury and azygos vein injury. Perioperative morbidity was seen in 8 cases (29.6%), and postoperative bronchopleural fistula occurred in one case. Fourteen patients had Pathological stage IA disease, 6 had IB, and 5 stage II or over. As clinical outcome, 5-year overall survival rate was 71.1%. **Conclusion:** Pulmonary lobectomy or completion pneumonectomy for ipsilateral lung cancer after radical resection were performed in 27 patients without perioperative mortality. Our results strongly suggests that this strategy is a meaningful option for new or recurrent ipsilateral lung cancer.

Keywords: completion pneumonectomy, reoperation, ipsilateral

EP1.18-09 ANALYSIS OF THE ROLE OF POSTOPERATIVE RADIOTHERAPY IN PATHOLOGICAL N2 NON-SMALL CELL LUNG CANCER WITH PROPENSITY SCORE MATCHING

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Background: N2 non-small cell lung cancer (NSCLC) is a heterogeneous disease. For operable patients with postoperative N2 non-small cell lung cancer, the optimum adjuvant treatment strategy is still in dispute. Our aim was to assess the efficacy of conbine postoperative chemoradiotherapy (POCRT) or postoperative chemotherapy(PCT)alone following surgery in pathological N2 non-small cell lung cancer using propensity score matching, and to explore the factors influencing the prognosis. **Method:** Between 2004 and 2014, a total of 175 patients fulfilled the inclusion criteria. The initiation of PCT started later than 2 weeks after the operation. The regimens of PCT in the present study included a cisplatin-based regimen and were administered for at least 2 cycles. POCRT was executed sequentially or sandwiched with PCT with three-dimensional conformal radiotherapy(3D-CRT) or intensity-modulated radiotherapy technique(IMRT). The prescription dose to clinical target volume (CTV) was 50 (range 44-60) Gy, Data were analyzed using SPSS version 24.0. Survival curves were produced using the Kaplan-Meier estimator method and compared with the log-rank test. Univariable and multivariable analyses of clinical characteristics. All available patient and tumor variables were compared using the $\chi 2$ test. Propensity score matching (PSM) analyses were used to compensate for differences in baseline characteristics between the POCRT and PCT groups to confirm the survival difference. The survival of the two groups was followed up and the effect of postoperative radiotherapy was analyzed. **Result:** The median survival time was 57 vs 40 months in the POCRT and PCT groups, and the 1, 3 and 5-year OS rates in the POCRT and pCT groups were 98.3 vs. 86.1%, 71.7 vs.53.0% and 45.7 vs. 39.0%, respectively (P=0.019). Exploratory subgroup analysis found that compared with PCT, POCRT improved OS in patients with squamous cell subtype (P=0.010), no lymphovascular invasion (P=0.006), pN2a (P=0.006) or total number of metastatic lymph nodes ≤7 (P=0.016). Following PSM, a total of 113 events were identified in both the POCRT and PCT groups, with 60 and 53 patients in each group, respectively. There was no significant difference in the general clinical data between the two groups after matching. The median survival time was 57 vs 63 months in the POCRT and PCT groups after matching, and the 1, 3 and 5-year OS rates in the POCRT and PCT groups were 98.3 vs. 92.5%, 71.7 vs. 64.2% 和 45.7 vs. 50.7% respectively, with no significant difference (P=0.463). Following PSM, the survival differences between POCRT and PCT in the various subgroups were not statistically significant, except in patients with squamous cell lung cancer (P=0.010), there was also a trend toward an increase in the overall survival of pN2-NSCLC with pN2a (P = 0.196) or total number of metastatic lymph nodes ≤7 (P=0.367). **Conclusion:** Univariate and multivariate analyses indicated that T stage, total number of MLNs and POCRT were independent factors affecting OS. POCRT following complete resection clearly demonstrated superior survival compared with pCT. And POCRT may be specifically recommended to N2 patients with squamous cell lung cancer, particularly those with limited nodal involvement and T4 disease.

Keywords: non-small-cell lung cancer, N2 Lymph Node Metastasis, Propensity Score Matching

EP1.18-10 BILATERAL MEDIASTINAL LYMPHADENECTOMY IS ASSOCIATED WITH BETTER SURVIVAL IN STAGE IA-IIIB NON-SMALL CELL LUNG CANCER

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Background: Studies have shown that, mediastinal lymph node dissection improves survival in non-small cell lung cancer. However, the role of bilateral lymph node dissection is yet to be elucidated. The aim of this study was to analyze the impact of bilateral mediastinal lymphadenectomy on survival in operable and inoperable non small-cell lung cancer (NSCLC) patients. **Method:** Between May Between March 2010 and December 2017, 1344 patients with potentially operable non-small cell lung cancer were evaluated. Of those 560 patients(41.7%) underwent video-assisted mediastinoscopic bilateral mediastinal lymphadenectomy(VAMLA) including removal of upper paratreacheal, lower paratracheal, subcarinal lymph node dissection via cervical incision, As the preference of surgeon, 510 patients(37.9%) underwent mediastinoscopic biopsy before planned operation. Of 1344 patients, 801(59.6%) were found to have no mediastinal lymph nodal involvement after bilateral lymphadenectomy or mediastinoscopy. Of those, 690 patients(51.3%) underwent anatomical lung resection. The patients who had negative VAMLA/mediastinoscopy results underwent anatomic pulmonary resection and systematic lymph node dissection/systematic sampling. **Result:** The 5-year survival rate in all patients was 44% for bilateral lymphadenectomy patients and 35.1% for patients who had unilateral mediastinal lymphadenectomy patients(p=0.001). Among the patients who had pulmonary resection (pstage IA-IIIA), The 5-year survival was 88% for BML patients and 61% for patients who had mediastinal lymph node sampling(P=0.02). By multivariable analysis, BML was associated with better survival (odds ratio, 0.64; 95% confidence interval, 0.27-0.83; P=0.02). After propensity matching of two groups, BML provided independently better survival (odds ratio; 95% confidence interval, 0.34-0.82; P=0.03) **Conclusion:** ML was associated with improved survival in resectable (pIA-IIIA) or non-resectable (pIIIA-IIIB) NSCLC patients.

Keywords: Survival, bilateral lymph node dissection, video assisted mediastinoscopic lymphadenectomy

EP1.18-11 PANCOST TUMOR: FEASIBILITY OF MINIMALLY INVASIVE APPROACH

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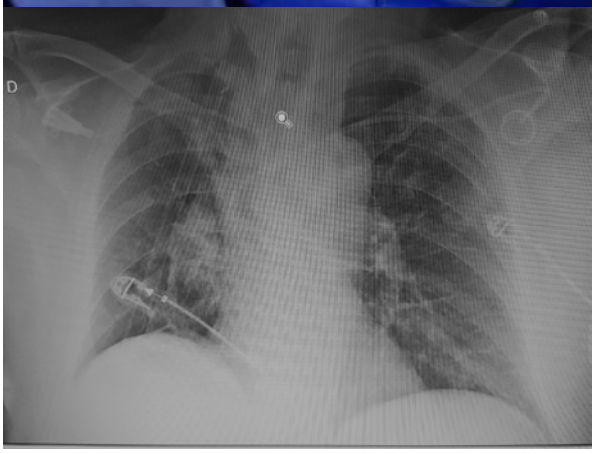
Background: Surgery for Pancoast tumors is one of the most challenging procedures in thoracic oncology. Completeness of resection and preservation of vital structures plays major role in survival and post operative quality of life. Classical posterior approach (Shaw-Paulson) and anterior (Dartevelle) are well defined

in literature, offers excellent exposure, and have been used for many decades, but is there a safe and less invasive surgical procedure for these patients? **Method:** Patient information and surgical notes of patients treated by our group with a hybrid-minimmaly-invasive approach were reviewed. **Result:** We performed two hybrid-minimally invasive pancost tumor resection in 2019. One patient was male. Both had squamous cell carcinoma at the rigth upper lobe with invasion the first two ribs, shoulder/arm pain and Horner syndrome. One was treated with induction chemoradiotherapy and other had upfront surgery. Procedure has been carried out with 4 incisions: A) posterior 10cm vertical incision betwen the medial border of scapula and spine, from fourth rib up to the base of the neck; B) anterior 3cm over the 4th intercostal space; C) 12mm trocar at 7th anterior axillary line for camera; D) 12mm trocar at 8th posterior axillary line for stapling. VATS rigth upper lobectomy with lymphadenectomy was performed by sequential stapling of upper lobe vein, arterial branches, bronchus and fissure at last. Then the chest wall resection "en bloc" with rigth upper lobe, first and second ribs, ligation of the T1 root of brachial plexus, scalene muscles insertions and soft tissues below the C 8 root and subclavian artery adventicia. Mean operative time was 270'. Frozen sections from surrounding margins were negative. Patients had uneventfull recoveries and were discharged on 5th and 6th post operative days with oral analgesics.



Conclusion: The Hybrid-minimally invasive approach is feasible and offer the advantage of less surgical trauma and probably earlier recovery.

Keywords: VATS, pancoast, surgery

EP1.18-12 THE NEUTROPHIL AND PLATELET TO LYMPHOCYTE RATIOS AND GLASGOW PROGNOSTIC SCORE AS A PREDICTOR FOR RELAPSE AFTER STEREOTACTIC RADIATION FOR LUNG CANCER

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Background: Chronic inflammation plays an important role in lung carcinogenesis. The neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratios (PLR) and modified Glasgow Prognostic Score (mGPS) have been associated with overall mortality and PLR greater than 250 with non-local failures in non-small cell lung cancer (NSCLC) patients. We hypothesised that NLR, PLR and mGPS were higher in patients developing non-local failures within the first year after stereotactic body radiation therapy (SBRT) than in those without non-local failures. **Method:** Medically inoperable stage I NSCLC patients were included in a prospective, observational, single centre study from February 2014 until December 2017. Follow up included physical examination, CT scans and blood samples at baseline, 6 weeks, 3, 6, 9 and 12 months after SBRT. Most patients took baseline blood samples within mean 7 days before treatment. Differences in NLP, PLR and mGPS between the groups (with and without non-local failures) were calculated using Mann-Whitney-Wilcoxon U-test. **Result:** We included 46 patients with median age 75 years, of which 67% were men. Comorbidities were common, and 80% had chronic obstructive pulmonary disease (COPD). Six patients were diagnosed with non-local failures within the first year of follow-up. Multiple metastases were identified in the mediastinum (2 patients), contralateral lung (2 patients) and in the liver and bone (2 patients).

Marker	Non-local failures (n=6)	Without non-local failures (n=40)	P-value
NLR	3.3	3.5	0.83
PLR	246	158	0.35
mGPS	0.67	0.33	0.27

Conclusion: Our study found no statistically significant association between increased NLR, PLR, mGPS and the identification of non-local failures within the first year after SBRT. This is a relatively small cohort of patients, and the patients suffered from serious chronic medical comorbidities such as COPD, chronical renal and cardiac disease. These medical conditions can also influence NLR, PLR, mGPS and can explain our finding.

Keywords: Non–small-cell lung cancer, Stereotactic radiation, inflammation

EP1.18-13 REVIEW OF PREOPERATIVE EXAMINATION

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Background: Before lung resection, it is necessary to perform various preoperative examinations to determine the indication for surgery. In our department, lung blood flow scintigraphy is performed on all cases scheduled for lung resection, and predicted post operation (ppo)%FEV1 and ppo%DLCO, are calculated based on lung function tests and scheduled surgery. Both have a cut-off value of 40%, and if the case has less than 40%, change to surgery with less lung volume loss. However, the large number of cases have no difference between left and right lung blood flow ratios. Even if the difference is large, almost all cases have organic lung abnormalities which are detected by CT easily. In addition, even if there is a large dissociation in the left-right difference in pulmonary blood flow, it is very rare that the predicted value after surgery is less than 40% in normal respiratory function patients. In recent years, most institutions do not perform pulmonary blood flow scintigraphy as preoperative examination, and it may be necessary to examine the significance of lung blood flow scintigraphy as preoperative examination. **Method:** Of the cases in which lung blood flow scintigraphy was performed as a preoperative examination for lung resection in our department from January 2010 to December 2018, we selected the cases who has the blood flow ratio between the left and right lungs has more than doubled difference and doesn't have detectable organic abnormality and history of lung resection. **Result:** Nineteen out of 1570 cases were extracted. The blood flow of the right lung was more than twice that of the left lung in 18 cases. 19 cases have 12 men and the average age is 73.6 ± 6.9. There were 13 cases undergoing planned surgery, 3 cases that could not be resected due to the progress of the tumor, 1 case refusing the operation, and only 2 cases changed treatment based on the result of scintigraphy. One case treated by radiation therapy and another was treated by PDT. **Conclusion:** It is suggested that lung blood flow scintigraphy may not be necessary in cases who have normal pulmonary function and have no organic abnormalities.

Keywords: preoperative examination, lung blood flow scintigraphy

EP1.18-14 ALGORITHM FOR DECIDING RADIOTHERAPY TECHNIQUE IN STAGE III NON-SMALL CELL LUNG CANCER

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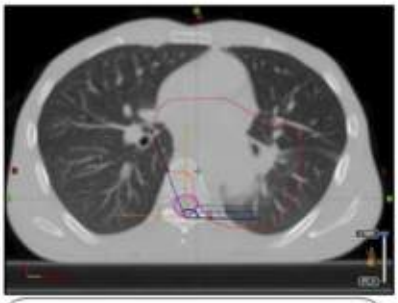
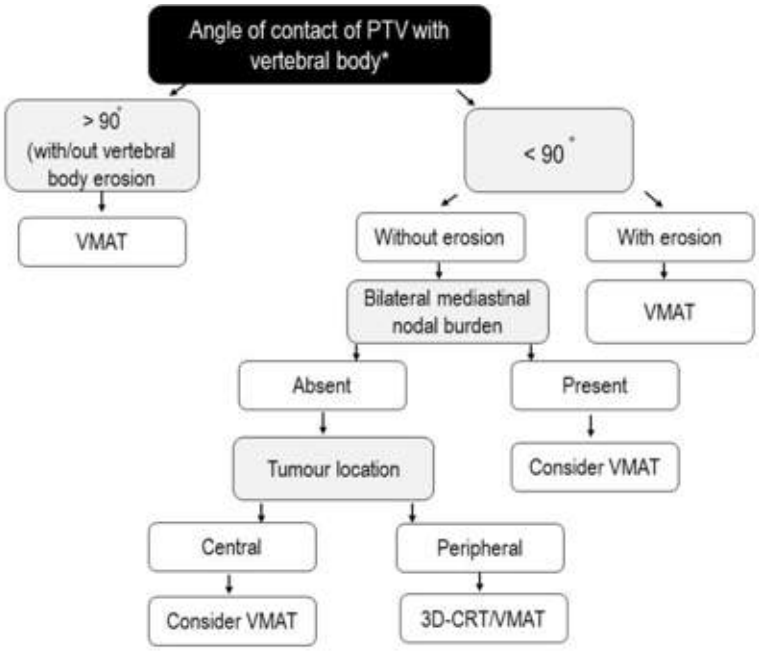
Background: Concurrent chemoradiotherapy has shown superior survival outcomes in inoperable, Stage III non-small cell lung cancer (NSCLC) with good performance status. Usage of 3-dimensional conformal radiotherapy (3D-CRT) technique is commonest with intensity modulated radiotherapy (IMRT) gaining popularity owing to its ability to spare normal tissues. In our study we analysed the tumour and nodal characteristics of patients to predict which technique maybe beneficial by generating optimised plans of both 3D-CRT and volumetric modulated arc radiotherapy (VMAT), a type of IMRT. **Method:** A total of 27 Stage III NSCLC patients underwent PET-CT (in the treatment position) co-registered treatment planning using either 3D-CRT or VMAT. The total prescription dose was 60 Gy in 30 fractions over 6 weeks with concurrent cisplatin based chemotherapy. Retrospectively alternate treatment plans were generated to obtain two sets of plans (3D-CRT and VMAT) of each patient for dosimetric comparison. The tumour and nodal characteristics and treatment technique were analysed to identify predictive factors limiting total dose delivery. The angle of contact of the PTV with the circumference of the vertebral body was calculated for patients where the tumour or nodal mass was in contact with the vertebral body (Figure 1).

Figure 1



*Angle of contact: angle subtended by the lines joining the extreme extents of the PTV on the vertebral body to the midpoint of a horizontal line joining the transverse process . Here angle of contact >90 degrees



Result: Of the 27 patients enrolled, 6 patients could not be planned to the complete dose of 60 Gy in a single phase by 3D-CRT. Dose limiting factors were high spinal cord doses due to vertebral body erosion (2 out of 6) and bilateral bulky mediastinal lymphadenopathy (4 out of 6). Alternate VMAT plans for these patients could achieve the dose constraints in all but the two patients with vertebral body erosion. Differences in the normal tissue doses of bilateral normal lungs, esophagus, heart and spinal cord were compared between both techniques to ascertain statistical significance. **Conclusion:** The spatial location of the tumour and nodal burden rather than the volume limited the maximum dose delivered. For tumours with vertebral body contact of more than 90 degrees, VMAT should be used. With gross vertebral body erosion, even VMAT falls short if the PTV includes the spinal cord. In view of high patient volume and limited resources, VMAT is not an economical option for all patients. A simple clinical algorithm is outlined (Figure 1) which will help select patients who will best benefit from VMAT.

Keywords: NSCLC, Treatment algorithm, 3D-CRT versus IMRT

EP1.18-15 SURGICAL RESULTS OF PRIMARY MUCOEPIDERMOID CARCINOMA OF LUNGS: A 9 YEARS' EXPERIENCE

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Background: Pulmonary mucoepidermoid carcinoma is a rare salivary-gland type lung cancer and accounts for 0.1%–0.2% of all primary lung malignancies. The optimal treatment of pulmonary mucoepidermoid carcinoma is not well determined. The aim of this study was to examine the surgical outcomes for the pulmonary mucoepidermoid carcinoma in our institution. **Method:** From January 2010 to December 2018, we performed a retrospective review including all patients with primary pulmonary mucoepidermoid carcinoma of lung who underwent pulmonary resections in our institutions. The patients'demographic, clinical, and survival data were analyzed. **Result:** A total of 3124 primary lung cancer patients underwent surgical resections by the same surgical team during the 8-year study period. 8 cases (0.25%) patients who were diagnosed with primary mucoepidermoid carcinoma of the lung were analyzed in this study. The patients' characteristics are shown in Table 1. The median age of all patients was 57 year-old (range: 22-75 year-old). Cough is the most common symptom (5 cases, 62.5%). 7 cases had a low-grade tumor, and all the cases were completely resected thoracoscopically. Two cases were resected by wedge resection because peripherally located, and two cases required bronchial reconstruction. There was no adverse effect after the operation. One case recived adjuvent chemotherapy due to nodal invasion. However, this case had disease progression with patella bone metastasis 5 months after opeartion. The other cases were free of malignancy with a median follow-up of 27.2 months.

Table 1. Patients' demographic's data.

Age	Sex	Tumor Size (cm)	pTMN	p-Stage	Grade	Tumor Location	Surgical Procedure	Outcome
22	F	2	T1aN0M0	IA	Low	RLL, peri bronchial	Lobectomy	Disease Free
72	M	2.8	T2aN0M0	IB	Low	LLL, peripheral	Wedge	Died of cardiac disease 5 years after surgery
27	M	2.5	T1bN0M0	IA	Low	LLL, endobronchial	Lobectomy	Disease Free
75	F	1	T1aN0M0	IA	Low	LLL, peripheral	Wedge	Disease Free
53	F	2.8	T2aN0M0	IB	Low	LLL, bronchial	Sleeve Lobectomy	Disease Free
67	F	3.6	T2aN1M0	IIA	High	RUL, peri bronchial	Sleeve Lobectomy	Died due to bone metastasis 5 months after surgery
49	F	2.2	T1bN0M0	IA	Low	RUL, peri bronchial	Lobectomy	Disease Free
49	M	2.2	T1bN0M0	IA	Low	LLL, endobronchial	Lobectomy	Disease Free

Conclusion: Complete surgical resection of a mucoepidermoid carcinoma of lungs can be atributed to a long-term survival in patients. For an elederly patient with a peripherally located tumor, wedge rsection with mediastinal lymphnode dissection could be an alternative treatment.

Keywords: Mucoepidermoid carcinoma of lung, video-assisted thoracoscopic surgery, Non-Small Cell Lung Cancer

EP1.18-16 SURGERY FOR LOCALLY ADVANCED LUNG CANCER INVADING THE SPINE AFTER CHEMORADIOTHERAPY

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Background: Treatment for locally-advanced lung cancer invading the spine remains challenging, and multimodality treatment should be considered. The aim of this study was to clarify surgical outcomes following induction chemoradiotherapy (CRT) for lung cancer invading the spine following chemoradiotherapy. **Method:** We retrospectively reviewed clinical and pathological data of locally-advanced lung cancer patients with vertebral invasion, in who we have performed total or partial vertebrectomy after induction CRT between 2011 and 2017. **Result:** A total of 4 patients were extracted. All patients were diagnosed as cT4N0M0 disease based on chest computed tomography (CT) and positron emission tomography (PET)-CT, and vertebral invasion was evaluated by chest computed tomography (CT) and magnetic resonance imaging. The histologic type included adenocarcinoma in 3 patients and squamous cell carcinoma in one patient, respectively. Average dose of radiation was 50 Gy. Total vertebrectomy was performed in 3 patients and transverse-process resection in one patient. Average Median operation time and blood loss were 800 minutes and 878 ml, respectively. In all 4 cases, complete R0 resection was performed. There was no perioperative and in-hospital death, and complication occurred in one patient. Median follow-up period was 39 months (range, 16-63 months), and median overall survival time and relapse free survival time were 39 months (range, 16-63 months) and 29months (range, 7-63 months). **Conclusion:** The current preliminary result indicated that lung cancer surgery combined with vertebrectomy after induction CRT was feasible. Although our series were small, this multimodal treatment strategy might be a option for cT4N0M0 lung cancer invading to the spine. Further study should be conducted to confirm the current result with a large sample size.

Keywords: locally advanced lung cancer, surgery after chemoradiotherapy, invading the spine

EP1.18-17 PRE-RADICAL RADIOTHERAPY PLASMA EGFR DNA LEVELS IN LUNG CANCER PATIENTS MAY PREDICT FOR EARLY DISEASE PROGRESSION

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National Cancer Centre Singapore, Singapore/Singapore

Background: Circulating cell-free tumour DNA is an alternative method to detect for and monitor sensitising EGFR mutations in metastatic lung adenocarcinoma. The clinical utility of plasma EGFR (pEGFR) DNA is increasing but there is limited data for its use in early stage patients. We performed a pilot prospective study to test for and monitor pEGFR DNA in lung cancer patients planned for radical lung radiotherapy (RT). **Method:** Patients with biopsy proven lung adenocarcinoma harbouring sensitising EGFR mutations that were referred for radical lung RT were recruited in our centre. Patients who tested positive on baseline plasma (Pre-RT) sample would be monitored at 1 month post-RT. Detection of pEGFR p.E746_A750del, p.L858R and p.T790M was performed by mutation-specific quantitative PCR. The protocol was later updated to allow the use of next-generation sequencing, LiquidMARK™ Lung assay. Patients baseline characteristics, tumour and treatment details were recorded. Follow-up data was collected prospectively. **Result:** From April 2017 to August 2018 a total of 9 patients (3 Stage IA/B, 1 IIB, 3 IIIA and 2 IIIC) were enrolled. All were PET staged. 8 underwent radical lung radiotherapy (3 SBRT, 5 chemo-radiotherapy). 3 patients had detectable baseline pEGFR. These patients had stage IIIA/C disease at diagnosis. None of the 4 Stage I/II patients had a detectable pEGFR DNA. Gross tumour volume did not correlate with pEGFR detection rate (GTV range 9.1cc - 124.9cc). Median follow-up was 300 days (range 196-404 days). Of the 3 patients with positive pEGFR DNA mutations, 1 defaulted treatment, 1 had a positive post-RT blood test and 1 refused 2nd blood test. These patients had distal metastatic relapse shortly after RT while patients with an undetectable baseline pEGFR DNA remained disease free on last follow-up. On analysis, a positive baseline pEGFR DNA predicted for early disease progression (Median time to progression 99.5 days vs NR, p=0.004). **Conclusion:** Our study was terminated due to poor recruitment. In early stage I/II lung cancers, pEGFR DNA was not detectable suggesting limited utility of this test in these patients. Detection rate was higher in stage III patients. Detection of baseline pEGFR DNA in patients with treatable lung cancers appears to have a negative prognostic value and could suggest evidence of micro-metastatic disease. This test may be a useful biomarker to guide treatment and follow-up in locally advanced patients and should be explored in larger studies.

Keywords: Plasma EGFR DNA, prognostic, Locally advanced Lung adenocarcinoma

EP1.18-18 BODY SHAPE AND TISSUE COMPOSITION INFLUENCES UNIFORM DISTRIBUTION OF TUMOR TREATING FIELDS INTENSITY DELIVERED TO THE LUNGS

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Background: Tumor Treating Fields (TTFields) are low intensity, alternating electric fields in the intermediate frequency range that disrupt mitosis. TTFields are approved for the treatment of glioblastoma. A Phase 3 study investigating the efficacy of TTFields in Non-Small Cell Lung Cancer is ongoing [LUNAR NCT02973789]. TTFields are delivered through two pairs of transducer arrays placed on the patient's skin. Since the efficacy of TTFields increases with intensity, identifying factors that influence field intensity in the lungs is beneficial to understand how body shape and tissue composition influence the field intensity. We present a computer-simulation-based study investigating the effect of body size, shape, and composition on TTFields distribution in the lungs. **Method:** This study was performed using the Sim4Life software package and realistic computational phantoms: female (ELLA), male (DUKE), and obese male (FATS). Various array layouts were placed on the models, and the distribution of TTFields within their lungs were calculated and compared. **Result:** For all models, uniform field distributions within the lungs were obtained when the arrays were axially-aligned with the parenchyma as much as anatomically possible. The layouts that generated the highest average field intensities were those in which one pair of arrays delivered an electric field from the anterolateral to the posterior-contralateral aspect of the patient and the second pair inducing the field from the anterior-contralateral to the posterolateral aspect of the patient. In all models, these layouts led to average field intensities in the lungs above the therapeutic threshold (>1 V/cm). The highest field intensities were seen in DUKE's lungs and the lowest field intensities in FATS's lungs. Analysis suggests that field attenuation was caused primarily by layers of fat. Hence, the lower field intensities in the lungs of ELLA and FATS can be largely attributed to the thick layers of fat present in FATS and the fatty tissue in ELLA's breasts. **Conclusion:** This study provides insights into how TTFields distribution in the lungs is influenced by body composition. These findings will help to optimize the placement and design of transducer array placement for the treatment of lung cancers.

Keywords: Tumor Treating Fields, Body Shape, Tissue Composition

EP1.18-19 PATIENTS WITH UNRESECTABLE STAGE III NON-SMALL CELL LUNG CANCER ELIGIBLE TO RECEIVE DURVALUMAB IN CLINICAL PRACTICE

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Background: Durvalumab has been reported to significantly prolong progression-free survival and overall survival in patients with stage III unresectable non-small cell lung cancer (NSCLC) after chemoradiotherapy, compared with placebo. The aim of this retrospective study is to evaluate the eligibility of patients with unresectable stage III NSCLC able to receive consolidation therapy with durvalumab in clinical practice based on the PACIFIC study criteria. **Method:** From January 2011 to May 2018, electronic data were collected from patients diagnosed with unresectable stage III NSCLC treated with definitive chemoradiotherapy. A total of 81 patients were identified. Of these, 73 were treated with platinum-based chemotherapy based on the criteria of the PACIFIC study. **Result:** Radiation pneumonitis of any grade occurred in 54 patients (73.9%) who received definitive chemoradiotherapy. Of these, 12 (16.4%) developed radiation pneumonitis of grade 2 or more within 42 days after chemoradiotherapy and would be excluded from durvalumab treatment. Two patients (2.7%) developed other pneumonitis, 7 patients (9.6%) showed poor performance status, and 3 patients (4.1%) displayed disease progression at initial assessment. After considering overlapping cases mentioned above, 22 patients (30.1%) were ineligible to receive durvalumab by the criteria utilized in the PACIFIC study. **Conclusion:** In clinical practice, approximately 70% of patients with unresectable stage III NSCLC would be eligible to receive consolidation therapy with durvalumab.

Keywords: chemoradiotherapy, durvalumab, Non-Small Cell Lung Cancer

EP1.18-20 SLEEVE LOBECTOMY FOR CENTRALLY LOCATED NON-SMALL CELL LUNG CANCER: INITIAL SHORT-TERM RESULTS FROM A SINGLE INSTITUTE IN NORTHEAST CHINA

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Background: To evaluate the feasibility and short-term outcome of sleeve lobectomy for centrally located non-small cell lung cancer in Northeast China. **Method:** Clinical data of 69 patients who underwent sleeve lobectomy in the Department of Thoracic Surgery of Liaoning Cancer Hospital & Institute from November 2016 to February 2019, were retrospectively collected. Operative strategies, duration of postoperative drainage, postoperative hospital stay, complications and follow-up data were recorded. Simple bronchoplasty or angioplasty without any sleeve resection was excluded in this study. **Result:** 14 of the 69 patients received neoadjuvant chemotherapy because of N2 disease. Nine underwent bronchial and arterial sleeve lobectomy (double sleeve resection), 6 bronchial sleeve resection and partial resection of pulmonary arterial wall (angioplasty), 2 arterial sleeve resection and partial resection of bronchial wall (bronchoplasty), 2 arterial sleeve resection only, 50 bronchial sleeve resection only., Simple sleeve resection was achieved in 57 cases,

and extended sleeve resection in 12 cases. Of the extended cases, two were classified as Okada type B, 2 Okada type C, 5 Okada type D, 2 with complex anastomosis between left main stem bronchus with superior and basal bronchus, 1 with anastomosis between trachea and right middle lobe bronchus. There was 1 perioperative death (1.4%), which was highly suspected of myocardial infarction. There was neither anastomotic fistula nor symptomatic stricture, which needed treatment thereof. Surgical margin status was R0 in 50 patients (72.5%), R1 in 18 patients (26.1%), and R2 in 1 patient (1.5%). The median time of postoperative drainage was 7 days (3-33 days), median time of postoperative hospital stay was 11 days (6-39 days). Major complications occurred in 14 patients (21.5%), including 2 with chylothorax, 7 pneumonia, 3 pleural effusion, 1 air leak, 1 heart failure. Atelectasis necessitated endoscopic sputum clearance in 16 patients. Pathology showed squamous cell carcinoma in 50 patients, adenocarcinoma in 16, adenosquamous carcinoma in 2, and large cell carcinoma in 1 patient. Two patients were in stage IA2, 2 in stage IA3, 12 stage IB, 2 stage IIA, 34 stage IIB, 12 stage IIIA,and 5 stage IIIB. The median follow-up duration was 14 months (0-25months), with the follow-up rate of 97.1%. All patients are alive except for one death. The local-recurrent rate was 1.4% (1/69), and the distant metastasis rate was 7.2% (5/69). **Conclusion:** Sleeve lobectomy is a safe and reasonable procedure for surgical treatment of centrally located non-small-cell lung cancer. It has the advantages of expanding operation indication, avoiding pneumonectomy, preserving more pulmonary function, and improving postoperative quality of life.

Keywords: sleeve lobectomy, bronchoplasty, arterioplasty

EP1.18-21 SURGICAL TREATMENT FOR LUNG CANCER IN TWO PATIENTS WITH SITUS INVERSUS

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Background: Situs inversus is congenital recessive condition with a prevalence of 1to 2 in 10000 people. All organs of chest and abdomen locate at opposite side. Cardiac and vascular anomalies are frequent in patients with situs inversus compared to the general population. There are few reports of resected cases of lung cancer with situs inversus. In such cases, additional technical difficulties during operation should be expected. The risk of situs peri-operative cardiovascular complications in patients with situs inversus is higher. We report two cases of lung cancer in patients with situs inversus who underwent video assisted thoracoscopic surgery. **Method:** Case 1. A medical check showed abnormal shadow in left lower lobe in 72-year-old man. Chest CT revealed tumor, 3.5cm diameter, in left lower lobe and situs inversus. Squamous cell carcinoma was confirmed by transbronchial biopsy. Chest three-dimensional computed tomography showed that pulmonary artery corresponded to the usual right side pattern. Left lower lobectomy was performed successfully after induction chemotherapy. Case 2. A medical check showed abnormal shadow in left upper lobe in 70-year-old woman. Chest CT revealed tumor, 1.5cm diameter, in left upper lobe and situs inversus. Chest three-dimensional computed tomography showed that pulmonary artery corresponded to the usual right side pattern. Thoracoscopic surgery was performed. Upper pulmonary vein was injured during dissecting procedure of hilar. Left upper lobectomy was completed after repair of upper pulmonary vein. Adenocarcinoma was confirmed by postoperative pathological examination. **Result:** We performed operation for lung cancer in two patients with situs inversus successfully. Diagnosis of situs inversus can be confirmed using chest three-dimensional computed tomography. **Conclusion:** Anatomical resection is optimal surgical treatment for lung cancer. However anatomical resection of lung is associated with an increased risk of peri-operative complications in such patients who have stractual anomalies of lung, heart and mediastinum. Situs inversus is rare. Pre and intraoperative attention should be paid for vascular anomalies to avoid intraoperative injuries and complications. Chest three-dimensional computed tomography should be performed before surgery to detect anomalies of pulmonary artery and vein.

EP1.18-22 A RANDOMIZED PROSPECTIVE STUDY COMPARING CONCOMITANT CRT USING PACLITAXEL-CARBOPLATIN AND ETOPOSIDE-CISPLATIN IN LOCALLY ADVANCED NSCLC

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Background: Several randomized trials and meta-analyses have established that the best survival can be achieved in patients with locally advanced NSCLC with concurrent CRT instead of the sequential approach. Most of the studies used cisplatin based regime along with radiation. However, due to the higher toxicity of this treatment, this is generally given to patients with minimal or no comorbidities, and who are relatively young. In this study, we have compared different CCT regime along with RT in inoperable locally advanced non-metastatic NSCLC. **Method:** In this study, 36 patients were enrolled. In study arm patients were treated with concomitant CCT using Injection cisplatin 20 mg/m2/day iv days 1-5 & days 29-33 and Injection etoposide 50 mg/m2/day iv days 1-5 & days 29-33 along with EBRT to a total dose of 60 Gy in 30#, starting day 1 of chemotherapy, @ 2Gy/# & 5#/week using CO-60 machine. In study arm patients were treated with concomitant CCT using Injection paclitaxel 50mg/m2 i/v every Monday and Injection carboplatin AUC2 i/v every Monday along with EBRT to a total dose of 60 Gy in 30# starting day 1 @ 2Gy/# & 5#/week using CO-60 machine. In both the arms spinal cord off was done after 44Gy. QOL was evaluated and recorded weekly using the EORTC QLQ–LC13 questionnaire. Improvement/deterioration in any scale was analysed between the baseline score and the score at treatment completion or 1st follow-up, whichever was higher. **Result:** When the response rates at 1st follow-up were assessed, CR was obtained in 2 patients in the control and 2 patients in the study arm. PR was obtained in 11 patients in the control arm(61.1%) and 13 patients in the study arm(72.2%). There were 2 patients in the control arm and 1 in the study arm who were found to have disease progression at 1st follow up and they were statistically insignificant. When grade >III toxicities are analysed, the total number of events in the control arm were 3(16.7%) and in the study arm were 5(27.8%), which is statistically insignificant and the OS was similar. Both, the improvement in the 5 major symptoms and worsening / appearance of 4 symptoms, shows equal quality of life in both control and study arm Both, the improvement in the 5 major symptoms and worsening / appearance of 4 symptoms, shows equal quality of life in both control and study arm **Conclusion:** This study has attempted to address the topic of different chemotherapeutic agents in combination with radiotherapy for the definitive treatment of stage III_A and III_B (unresectable) non-small cell lung cancer. The response rates, disease progression and overall survival are similar between study and the control arm. The other two endpoints namely the toxicity profile and quality of life are also similar between the two arms. Since we are not only treating the disease but treating the patient as a whole, due consideration must be given to toxicities as well as quality of life. However larger study with longer follow up are needed to establish the comparability of these two regimens.

Keywords: concurrent chemoradiotherapy, Non-Small Cell Lung Cancer, Quality of life

EP1.18-23 IS SALVAGE LUNG RESECTION NECESSARY AFTER DEFINITIVE CHEMORADIATION THERAPY FOR STAGE IIIA(N2) NON-SMALL CELL LUNG CANCER?

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Background: A combination of platinum-based chemotherapy and definitive radiotherapy is the standard of care for Stage III (N2) NSCLC patients who have single or multiple lymph node metastasis. However, the role of salvage lung resection in patients with residual disease without lymph node metastasis is yet to be identified. **Method:** Between January 2011 and December 2018 103 eligible patients who had pathologically proven in two university hospital clinics, stage IIIA/N2 non-small-cell lung cancer and were prospectively recorded. Those in the chemoradiotherapy group

received three cycles of neoadjuvant chemotherapy (AUCx2 carboplatin and docetaxel 85 mg/m[2] docetaxel) and concurrent radiotherapy with 61.2-64.0 Gy in 34 fractions over 3 weeks followed by surgical resection. Also, a group of patients who had definitive chemoradiotherapy who did not undergo surgery was compared with the surgical group. **Result:** A total of 103 patients were analyzed, of whom 75(72.8%) received chemoradiotherapy followed by surgical resection and 28(27.2) had chemoradiotherapy only. Median overall survival was 49 months (95% CI 8.0–58.0) in the chemoradiotherapy + surgery group and 33.0 months (95% CI:7.5–90.4) in the chemotherapy group (p=0.423). One patients died in the surgery group within 30 days(0.9%) after surgery. Complication rate in all patients and the patients who underwent pneumonectomy after chemoradiation were not statistically significantly different compared to those who had undergone resectional surgery without oncological therapy(p=0.321, p=0.08 respectively) **Conclusion:** Pulmonary salvage resection after definitive chemoradiotherapy is safe and surgical resection after chemoradiotherapy did not seem to provide better survival in histologically proven N2 stage IIIA non-small cell lung cancer.

Keywords: stage IIIA, definitive chemoradiotherapy, salvage resection

EP1.18-24 NOVEL TECHNIQUE - MINI PORT THORACOSCOPIC APPROACH AND ENHANCED RECOVERY AFTER SURGERY FOR TREATMENT OF LUNG CANCER

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Background: In the last two decades, thoracic minimal invasive surgical approaches gain in the treatment of lung cancer. Mainly, because they are less invasive and they provide shortened hospital stay. With new anesthesia protocols which are incoporated in Enhanced Recovery After Surgery (ERAS) protocol, they are one of the most important points in the treatment of lung cancer. New mini video-assisted thoracoscopic surgical approach and enhanced recovery after surgery approach are safe for the patients and decreases hospital stay of the patients.

Method: In our study were inroled 100 patients who undergone surgery for lung cancer. All of them were treated with a new minimal invasive approach - mini Video Assisted Thoracic Surgery (VATS). The approach is less traumatic of all other previous described and used minimal invasive thoracoscopic procedures because it consists of only two small ports (mini ports), 1cm each. One port we use for the camera and the other port for applying the instruments in the thoracic cavity. We didn't use additional ports. Also, this minimal invasive approach is more cosmetic than all other previosly used minimal invasive thoracic approaches which is important for most of the patients. All of the patients undergone general anesthesia with endotracheal double-lumen tube. They all had lobectomy (or segmentectomy) with locoregional lymphadenectomy. Twenty to fifty minutes after extubation all of the patients were doing some easy exercises in the operating room (OR) and were walking from the OR to their room in the Department. **Result:** Because of the new minimal invasive surgical approach, less-invasive surgical treatment and anesthesiology protocol incorporated in ERAS protocol, none of the patients who undergone this type of treatment had complications in the postoperative period. Also, all of the patients were discharged on the 2nd (some of them 3rd) postoperative day. Their recovery was faster, they had shorter hospital stay, without any complications, and they had less needs for analgesics in the postoperative period. **Conclusion:** Our new multimodal approach (anesthesiological and surgical) showed that described less invasive surgical approach as well as treatment, and adequate anesthesiologic technique incorporated in ERAS protocol are the key for adequate treatment as well as early recovery of the patients treated for lung cancer. Also, postoperative complications and hospital stay were decreased a lot. Also, the patients were more satisfied in the postoperative period because of their extremely early recovery after surgery as well as shortened hospital stay.

Keywords: mini port VATS, ERAS, lung cancer

EP1.18-25 DEFINITIVE RADIOTHERAPY IN LUNG CANCER – A GLIMPSE OVER THE NARROW WINDOW

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Background: Lung cancer is one of the leading global malignancies. Locally advanced NSCLC (LA-NSCLC) comprises of a significant proportion of patient burden. Despite advances in the treatment definitive radiotherapy is delivered only to a small proportion of patients. The current study was carried out to analyze various factors associated with change of curative treatment plan to palliative treatment at a tertiary cancer Centre **Method:** Medical records of patients of LA-NSCLC lung cancer treated between June 2016 to June 2018 were evaluated. Clinical presentation, evaluation, treatment details and outcome were recorded. Patients who were not eligible for radical treatment were excluded. All patients were taken for radical treatment but could not receive definitive radiotherapy were analyzed **Result:** Of 67 patients of LA-NSCLC 8 patients that were non metastastic were planned for upfront palliative intent.25 patients needed change in their treatment plan to palliative treatment. Majority of them were ≥ 65years. Median number of chemotherapy cycles was 2 (0-6). Patients were assessed after 2 cycles of chemotherapy for concurrent chemoradiation as our institute practice. Patients were assessed at the end of 2nd chemotherapy. Reasons for ineligibility was noted and categorized into patient, tumor and treatment factors. Factors for change in treatment plan were divided as (i) Patient related factors included, treatment defaults, poor compliance, financial and social reasons, ECOG performance status at the end of chemotherapy, comorbidities, which accounted for 30.3%. (ii)Tumor related factors included, disease progression, poor response to chemotherapy, which accounted for 54.5%. (iii)Treatment factors included ,risk of toxicity due to large volume disease, volume not able to cover in one radiotherapy portal, poor respiratory reserve, which added up for remaining 15.2% of patients. Palliative radiotherapy to primary tumor alone was delivered in 25 patients, 5 patients received palliative radiotherapy to primary and brain2 patients received palliative radiotherapy to bone and I received radiation to brain alone. The median time to diagnose and stage was 0.65months (0.06 to 3.6 months). Median time to start chemotherapy was 0.8 months (0.16 to 7.3 months). **Conclusion:** Eligibility for definitive radiotherapy is a dynamic decision which need to be reviewed at every stage of treatment. Timely radical intervention need not necessarily translate into radical radiotherapy. Feasibility of definitive radiotherapy pass through a narrow window and multiple factors play pivotal role in it.

Keywords: Advanced lung cancer, treatment patterns, Non small cell lung cancer

EP1.18-26 TREATMENT PATTERNS AND CLINICAL OUTCOMES IN LOCALLY ADVANCED NON SMALL CELL LUNG CANCER: EXPERIENCE FROM TERTIARY CARE CENTRE

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Background: Lung Cancer comprises a significant global cancer burden.About two-thirds patients with non small cell lung cancer, present in advanced/metastatic stage, of which the locally advanced group account for 30%.Combined modality approach with definitive chemoradiation is feasible in only a small proportion of patients. Several factors play a role in deciding the treatment and outcome In developing countries access to cancer centres and waiting period for oncological intervention and radiation therapy also significantly affect the management.The current study evaluates the demographic profile, treatment pattern, outcome and Radiotherapy practice and patient care at a tertiary care academic medical institution. **Method:** Archives patients of locally advanced Non Small Cell lung cancer(LA-NSCLC) treated at our centre between, June 2016-June 2018 were included in our study. Clinical, demographic characteristics, treatment patterns, outcomes was recorded. Radiotherpy practice and patient care process including integration of radiation therapy with other specilities,waiting time, compliance to treatment was documented. Case records with incomplete work up or treatment was excluded. Univariate and multivariate analysis of factors on survival and overall survival was analysed. **Result:** 174 patients were treated during the study period. The distribution as

per histology include Squamous cell carcinoma 54, Adenocarcinoma 108, Others (adenosquamous,poorly differentiated) 12. The median age was 57 years(35-84) with male preponderance .Only 67 patients belonged to locally advanced group and remaining 107 presented with metastastic disease. 59 patients of LA-NSCLC group were planned for definitive chemoradiation comprising of two cycles of induction chemotherapy followed by concurrent chemoradiation. 34 patients eventually underwent the planned treatment.The reason for conversion to palliative radiotherapy included disease progression during induction chemotherapy(18),poor performance status(7),large volume disease and risk of toxicity with radical dose ,defaulters(3). Median follow up was 11 months (range 0.7-29), overall survival 9.4 months(range 1.7-44.8). Median overall treatment time was 44 days.Progression free survival 8.9 months(range 1.6-28.6). Time to start any oncological intervention was 1 month(0.1-4.3) and time to start radiotherapy was 2.1 months(0.1-5.4). Adherence to treatment was 91.2%.Age ≥65 and performance status ≥2 were significant for overall survival in univariate analysis but did not confer any significance in multivariate analysis. **Conclusion:** The study concludes that more than 60%of patients with Non small cell lung cancer present with metastatic disease. Only about a third are suitable for definitive chemoradiation and eventually only 20% undergo the planned treatment. Adherence to treatment is good in definitive setting

Keywords: Non small cell lung cancer, treatment patterns, overall time

EP1.18-27 STUDY OF FIVE CASES RESECTED PULMONARY PLEOMORPHIC CARCINOMA - IMMUNE CHECKPOINT INHIBITORS ARE IMPROVED THE PROGNOSIS?

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Background: Pulmonary pleomorphic carcinomas are rare malignant tumors, poor prognosis, and no standard treatments have been established. A previous study reported that pulmonary pleomorphic carcinomas expressed high levels of programmed death ligand-1 (PD-L1), suggesting the potential efficacy of immune checkpoint inhibitors in these tumors. **Method:** We retrospectively reviewed the clinical records of 5 patients with pulmonary pleomorphic carcinoma who had a surgical resection from January 2014 to December 2018 at our institution. The characteristics, histological parameters, PD-L1 expressions, treatment and outcome of 5 patients were studied. **Result:** There were 4 male and 1 female. The average ages were 77.4 years (range, 69-84 years). At pathologic analysis, one of 5 was stage IA3, one was IIB, two were IIIA, and one was IVA. PD-L1 was highly expressed in all patients (70-90%). Three patients of 5 relapsed within one year after surgery. Two patients (case 3, 4) were no recurrence and were alive for 39 months, 24 months after surgery. Case 1 was confirmed mediastinal lymphnode recurrence at 3 months after surgery and performed radiation therapy. This case is alive for 53 months after recurrence. Case 2 was confirmed pleural dissemination and chest wall recurrence at 10 months after surgery and was treated with cisplatin, docetaxel plus bevacizumab at first line treatment, carboplatin, gemcitabine plus bevacizumab at second line, and nivolumab at third line. This case is alive for 51 months after recurrence. Case 5 was confirmed multiple liver metastasis and chest wall recurrence at one month after surgery and was treated with pembrolizumab at first line treatment. This case is alive for three months after recurrence.

case	1	2	3	4	5
sex	male	male	male	female	male
age	82	69	79	73	84
pstage	IVA	IIB	IA3	IIIA	IIIA
PD-L1 (22C3)	90	90	70	80	90
recurrence	yes	yes	no	no	yes

Conclusion: We thought that immune checkpoint inhibitors are improved the prognosis of pulmonary pleomorphic carcinoma.

Keywords: pulumonary pleomorphic carcinoma, PD-L1, immune checkpoint inhibitors

EP1.18-28 NEOADJUVANT THERAPY AMONG PATIENTS UNDERGOING RESECTION FOR NON-SMALL-CELL LUNG CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background: Lung cancer is the leading cause of cancer deaths worldwide. Surgery alone results in poor overall survival in patients with stage III non-small cell lung cancer (NSCLC). Neoadjuvant therapy offers the ability to treat micrometastatic tumor cell dissemination preoperatively and increased resectability due to tumor regression. The aim of this study is to analyze the experience of our center and to identify clinical and pathological characteristics related to greater relapse-free survival (RFS). **Method:** We conducted a retrospective study, which included all patients with NSCLC treated with neoadjuvant therapy follow by surgery in a tertiary referral hospital from April 2013 to March 2019. Data regarding clinical and pathological characteristics, treatment response, type of surgery and survival were collected. **Result:** We selected 10 patients. Table 1 summarizes the main sociodemographic characteristics, the histological subtype, the stage, the regimens of neoadjuvant therapy and the types of surgery.

Table 1	**Nº (%)**
Sex: Male/Female	6 (60%) / 4 (40%)
Age (years):	62 (44 – 77)
Performance status: – 0 – 1	6 (60%) 4 (40%)
Smoking: – No – Yes	1 (10%) 9 (90%)
Weight loss before diagnosis: – High (≥5%) – Low (<5%)	1 (10%) 9 (90%)
Histology: – Squamous cell carcinoma – Adenocarcinoma – Large-cell cancer	3 (30%) 6 (60%) 1 (10%)
Stage: – Stage IIIA – Stage IIIB	6 (60%) 4 (40%)
Node status: – N0 – N1 – N2	3 (30%) 1 (10%) 6 (60%)
ALK translocation: – No – Yes – Unknown	8 (80%) 0 (0%) 2 (20%)
EGFR mutation: – No – Yes – Unknow	8 (80%) 0 (0%) 2 (20%)
Percentage of PD-L1 at diagnosis: – < 1% – 1 – 49% – ≥ 50% – Unknow	5 (50%) 1 (10%) 2 (20%) 2 (20%)
Neoadjuvant therapy regimens: – Platinum – pemetrexed – Platinum – vinorelbine – Platinum – paclitaxel – bevicizumab – Platinum – vinorelbine – gemcitabine – Platinum – paclitaxel – nivolumab	5 (50%) 1 (10%) 1 (10%) 1 (10%) 2 (20%)
Types of surgery: – Lobectomy – Bilobectomy – Pneumonectomy	6 (60%) 1 (10%) 3 (30%)
Percentage of PD-L1 after neoadjuvant therapy: – < 1% – 1 – 49% – ≥ 50% – Pathological complete remission – Unknow	2 (20%) 1 (10%) 4 (40%) 2 (20%) 1 (10%)

Regarding tumour response rates after neoadjuvant chemotherapy, 2 (20%) of 10 patients achieved a complete response and 8 (80%) achieved a partial response. Furthermore, 5 (71%) of 7 patients with mediastinal lymph node involvement achieved a nodal downstaging. Using the Wilcoxon signed-rank test, there are statistically significant differences in the stage of the patients before and after the neoadjuvant chemotherapy (Z: -2,82, p:0,005). After a median follow-up duration of 38 months, 5 (50%) patients had relapsed. The median RFS was 22 months (IC95%: 2–41). We did a *multivariate logistic regression analysis, in which* no statistically significant associations were found between clinical and pathological characteristics studied and the RFS (p>0,05). **Conclusion:** Neoadjuvant therapy followed by surgery should be considered as standard treatment for a selective group of patients with stage III of NSCLC, in our sample all patients yielded excellent results. In the *multivariate analysis* no statistically significant associations were found due to the small size of our sample.

Keywords: non-small cell lung cancer, neoadjuvant therapy.

EP1.18-29 SURVIVAL OF PATIENTS WITH NON-SMALL CELL LUNG CANCER THAT HAS SINGLE STATION LYMPH NODE METASTASIS OF 4R OR 10R AFTER SURGICAL TREATMENT

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Background: The effect of single station 4R or 10R lymph node metastasis on survival in patients that had right upper lobectomy because of non-small cell lung cancer is investigated. **Method:** The survival of patients that were operated on due to non-small cell lung cancer that were applied right upper lobectomy between November 20076 and March 2018 and had single station 4R or 10R lymph node metastasis are compared. The patients with perioperative mortality and incomplete resection are excluded. **Result:** There were a total of 30 patients (25 men and 5 women) with a mean age of 60,5±8,9 (range 47-77) in the study population Ten patients had preoperative chemotherapy and/or radiotherapy. Seven-teen patients had single station 4R and 13 patients had single station 10R metastasis. The 5-year survival of patients with 4R and 10R metastasis were 39.8% and 53.8% respectively (p=0.33). **Conclusion:** Altough patients with right upper lobectomy that had single station 10R lymph node metastasis has a relatively better survival than patients with 4R metastasis the difference is not statistically significant. Surgeons should name the lypmh node stations 10R and 4R during lymph node dissection carefully that can sometimes be very challenging because of the localization of the lymph nodes.

Keywords: metastasis, 4R, 10R

EP1.18-30 A CASE OF RESECTED PRIMARY LUNG CANCER WITH INTERLOBAR DISSEMINATION

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Background: Primary lung cancer with pleural dissemination is at least diagnosed as Stage IVa, and it is considered that there are no surgical indications. This is because the presence of pleural dissemination indicates that the cancer cells exist in the entire pleural cavity, and radical resection is impossible. However, if pleural dissemination is observed in a limited space, we could consider the case as one of locally advanced lung cancer and perform radical resection as an exception of the current staging system. **Method:**

A 71-year-old man was referred to our hospital because of an abnormal shadow on chest radiography. He was diagnosed with adenocarcinoma of the right upper lobe and cT2aN0M0 stage IB (Union for International Cancer Control (UICC) 8th edition). We planned to perform right upper lobectomy. There were sporadic trabecular adhesions in the right pleural cavity. Although lobulation was relatively favorable, we could not recognize the interlober surface between the upper and middle lobes until after interlobar adhesilolysis. In other words, the interlober space was packed. There were diffuse nodules between the upper and middle lobes suspected of interlobar disseminations. Intraoperative frozen-section diagnosis yielded a pathological diagnosis of pleural dissemination. The pleural effusion cytology showed negative findings. Therefore, we considered the diagnosis to be of locally advanced lung cancer, and upper and middle lobectomy was performed. **Result:** Pathologically, the patient was finally diagnosed with papillary invasive adenocarcinoma and pT2aN0M1a Stage IVa (UICC 8th edition), and subsequently, we administered adjuvant chemotherapy, which is in progress. **Conclusion:** We performed radical right upper and middle lobectomy for locally advanced lung cancer, which showed interlobar pleural dissemination. This kind of dissemination could be treated like interlobar T3.

Keywords: Lung cancer, local advanced, interlobar dissemination

EP1.18-31 MINIPORT VIDEO-ASSISTED THORACIC SURGERY TECHNIQUE - A NEW MINIMAL INVASIVE APPROACH FOR TREATMENT OF LUNG CANCER: CASE REPORT

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Background: When multiportal VATS lobectomy was first developed in the 1990s, it has been changed through years. Since the first VATS anatomical resection (lobectomy) for lung cancer 20 years ago, the approach has been modified from approach with four ports, three ports, two ports and one additional and uniportal approach which skin incision is about 3-5 cm long. After all these modified approaches, we modified an approach which is least invasive of all the others mentioned above and most cosmetic. In this article we will describe our approach with use of only two small ports and steps for performing lobectomy of the left uper lobe for lung cancer with lymphadenectomy. **Method:** Patient is positioned in a right lateral decubitus position. The hands are placed in the almost "prayer" position and the left arm is slightly supported on an arm holder. As soon as the double lumen endotracheal tube is confirmed to be in the correct position, ventilation is switched to the contralateral lung to optimize deflation of the lung that is going to be operated. Suction can be used if the lung does not deflate. The respiratory rate can also be increased to 20 breaths/min or more in order to reduce the tidal volume and hence the degree of the of mediastinal excursion due to ventilation which provides more stable operating field. The surgeon and the assistant stand in the front part of the patient (the surgeon on the cranial part and the assistant on the caudal part, on the right side of the surgeon) with the screen directly across them and the scrub nurse stands obliquely opposite. Incision: only two small (mini) ports are used in this approach. The skin incisions of the ports are not bigger than 1 cm. The incision of the first port is located in the 8th intercostal space at the posterior axillary line. This port we will use to insert the 30 degree camera. After the incision is done by electrocautery, we place the camera in the left chest cavity. By that, we can explore the chest cavity and see where is the best location for the second port. The second port's incision is done on the 4th intercostal space in the posterior axillary line. After the incision is done and intercostal muscle is devided by electrocautery, we place the wound retractor. Afterwards, we try to localise the tumor using the suction tube or sometimes grasper. The disection starts from the anterior side **Result:** With this type of approach any type of lung resection is feasible. **Conclusion:** This approch is safe, less traumatic and more cosmetic for the patients comparing to other approaches.

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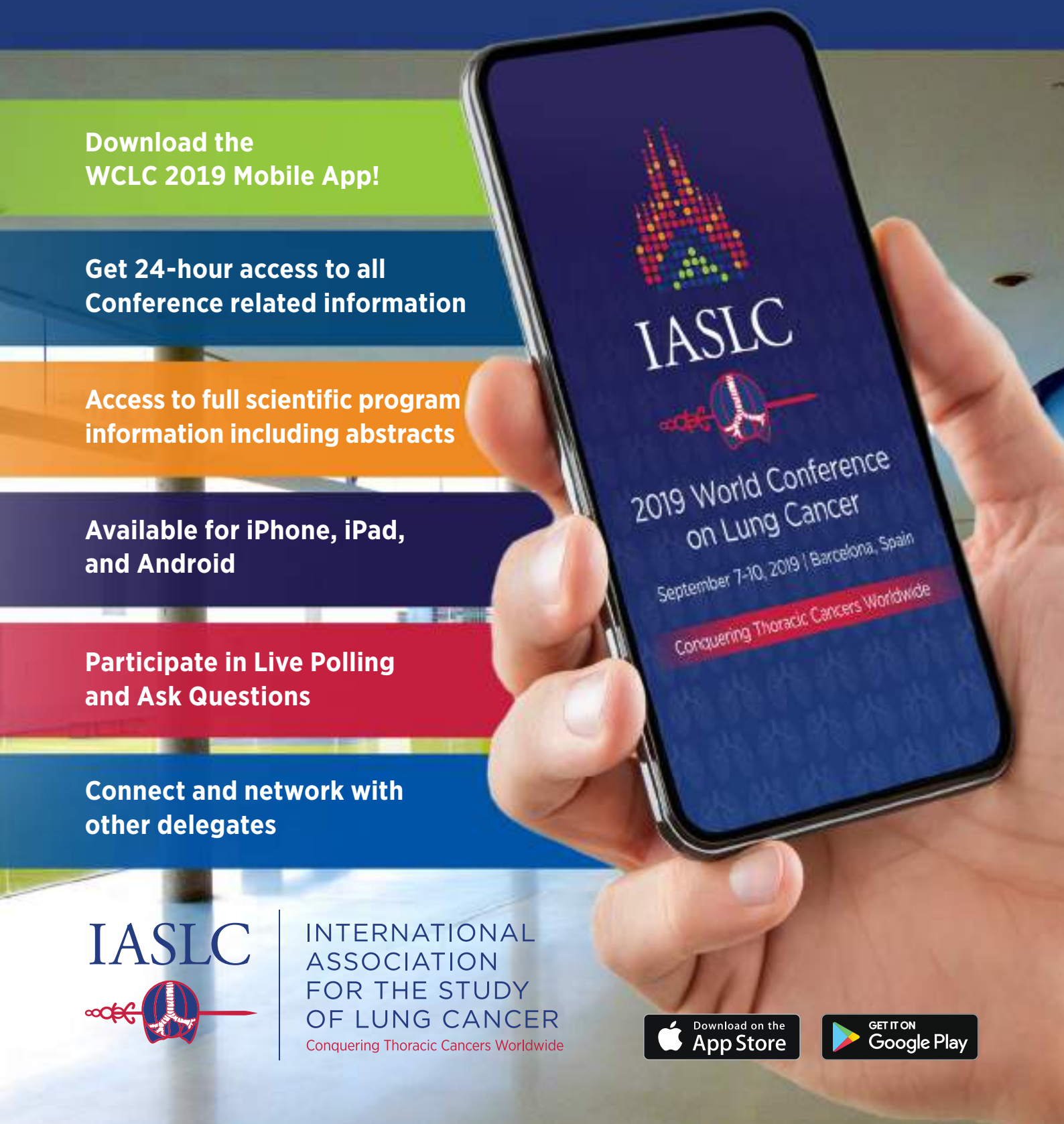

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